ABSTRACTS COLLECTION

The 49th Annual Meeting of the European Society for Blood and Marrow Transplantation: Physicians – Poster Session (P001-P708)

Bone Marrow Transplantation (2023) 58:153–627; https://doi.org/10.1038/s41409-023-02056-7

23 – 26 April, 2023 ● Hybrid Meeting

Sponsorship Statement: Publication of this supplement is sponsored by the European Society for Blood and Marrow Transplantation. All content was reviewed and approved by the EBMT Committee, which held full responsibility for the abstract selections.

19 - Acute Leukaemia

P001

CORD BLOOD TRANSPLANTATION FOR AML: COMPARABLE LFS IN PATIENTS WITH DE NOVO VERSUS SECONDARY AML

Frederic Baron[1], Arnon Nagler[2], Jacques-Emmanuel Galimard[3], Jaime Sanz[4], A.E.C. Broers[5], Edouard Forcade[6], Patrice Chevalier[7], Anne Sirvent[8], Emma Nicholson[9], Jürgen Kuball[10], Sabine Furst[11], Alessandro Rambaldi[12], Jorge Sierra[13], Peter A. von dem Borne[14], Maria Pilar Gallego Hernanz[15], Thomas Cluzeau[16], Stephen Robinson[17], Anna Maria Raiola[18], Hélène Labussière-Wallet[19], Jenny L. Byrne[20], Jean-Valère Malfuson[21], Annalisa Ruggeri[22], Mohamad Mohty[23], Fabio Ciceri[22]

[1]University of Liege, Liege, Belgium, [2]The Chaim Sheba Medical Center, Tel Hashomer, Israel, [3]EBMT Paris Office, Paris, France, [4]University Hospital La Fe, Valancia, Spain, [5]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [6]CHU Bordeaux, Pessac, France, [7]CHU Nantes, Nantes, France, [8]CHU Montpellie1,0r, Montpellier, France, [9]Royal Marsden Hospital, London, United Kingdom, [10]University Medical Centre, Dept. of Haematology – Utrecht, Utrecht, Netherlands, [11]Institut Paoli Calmettes, Marseille, France, [12]ASST Papa Giovanni XXIII, Bergamo, Italy, [13]Hospital Santa Creu i Sant Pau, Barcelona, Spain, [14]Leiden University, Leiden, Netherlands, [15]Hopital La Miletrie, Poitiers, France, [16]CHU Nice, Nice, France, [17]Bristol Royal Hospital for Children, Bristol, United Kingdom, [18]IRCCS Ospedale San Martino, Genova, Italy, [19]CHU Lyon, Lyon, France, [20]Nottingham University, Nottingham, United Kingdom, [21]Hôpital D'Instruction des Armées (HIA) PERCY, Clamart, France, [22]Ospedale San Raffaele s.r.l., Milano, Italy, [23]Hôpital Saint-Antoine, Sorbonne University, INSERM UMRs 938, Paris, France

Background: We previously reported inferior leukemia-free survival (LFS) following allogeneic hematopoietic stem cell transplantation (allo-HCT) for secondary versus de novo acute myeloid leukemia (AML) in first complete remission (CR1) among patients given grafts from either HLA-identical sibling, unrelated donor or HLA-haploidentical donor[1]. Given that unrelated cord blood transplantation (CBT) has been associated with high graft-versus-leukemia effects[2] and with good transplantation outcomes in secondary AML (sAML)[3], we investigated whether secondary versus de novo AML would be also a risk factor for poor outcomes in adult AML patients in CR1 receiving unrelated CBT.

Methods: This is a retrospective study from the acute leukemia working party (ALWP) of the EBMT. Inclusion criteria included adult at first allo-HCT between 2000 and 2021, unrelated single or double unit CBT, AML in CR1, no ex vivo T-cell depletion and no post-transplant cyclophosphamide. The primary endpoint of the study was leukemia-free survival (LFS). Multivariate Cox models were adjusted for cytogenetic risk, single versus double CBT, anti-thymocte globuline (ATG) or not, TBI or not, myeloablative versus reduced-intensity (RIC) conditioning, age at CBT, time from diagnosis to transplantation and year of transplantation.

Results: A total of 879 patients with de novo (n = 696) or secondary (n = 183) AML met the inclusion criteria. In comparison with de novo AML patients, those with sAML were older (55 versus 47 years old, P < 0.001), were transplanted sooner after diagnosis (median of 5 months versus 5.6 months, P = 0.003), received more frequently double CBT (62 versus 47%, P < 0.001) and were transplanted more frequently following RIC (63% versus 50%, P = 0.002). Two-year LFS in de novo versus secondary AML patients were 48 (95% CI: 44-52%) and 44 (95% CI: 36-51%), respectively. In multivariable analyses, sAML patients had non significantly different LFS (HR = 0.98, P = 0.86), overall survival (HR = 1.07, P = 0.58), relapse incidence (HR = 0.74, P = 0.09) and incidence of nonrelapse mortality (HR = 1.26, P = 0.13) than those with de novo AML. Factors associated with worse LFS in multivariate analysis included poor risk cytogenetic (HR = 1.43, P = 0.002), the use of ATG(HR = 1.5, P = 0.007), and older age at transplantation (HR per ten-year increment = 1.11, P = 0.008).

Conclusions: Our results demonstrate comparable LFS following CBT in adult patients with secondary versus de novo AML. A potential negative impact on LFS of ATG emerged in this specific disease context.

Clinical Trial Registry: References:

1. Schmaelter A-K, Labopin M, Socié G, Itälä-Remes M, Blaise D, Yakoub-Agha I et al. Inferior outcome of allogeneic stem cell transplantation for secondary acute myeloid leukemia in first

complete remission as compared to de novo acute myeloid leukemia. *Blood Cancer J* 2020; **10**: 26.

2. Milano F, Gooley T, Wood B, Woolfrey A, Flowers ME, Doney K et al. Cord-Blood Transplantation in Patients with Minimal Residual Disease. *N Engl J Med* 2016; **375**: 944–953.

3. Baron F, Labopin M, Ruggeri A, Volt F, Mohty M, Blaise D et al. Cord blood transplantation is associated with good outcomes in secondary Acute Myeloid Leukaemia in first remission. *J Intern Med* 2019; **285**: 446–454.

*FB and AN contributed equally to this abstract

Disclosure: No COI to report

19 - Acute Leukaemia

P002

SECOND ALLOGENEIC STEM CELL TRANSPLANTATION (HSCT2) FOR PRIMARY GRAFT FAILURE IN PATIENTS WITH ACUTE LEUKEMIA IN REMISSION: ON BEHALF OF THE ALWP OF THE EBMT

Arnon Nagler[1], Myriam Labopin[2], Aleksandr Kulagin[3], Andrea Velardi[4], Jaime Sanz[5], Hélène Labussière-Wallet[6], Victoria Potter[7], Jürgen Kuball[8], Simona Sica[9], Elena Parovichnikova[10], Wolfgang Bethge[11], Xavier Leleu[12], Uwe Platzbecker[13], Friedrich Stölzel[14], Fabio Ciceri[15], Mohamad Mohty[2]

[1]Sheba MC, Ramat-Gan, Israel, [2]Hôpital Saint-Antoine, Paris, France, [3]First State Pavlov Medical University of St. Petersburg, Raisa Gorbacheva Memorial Research Institute for Paediatric Oncology, Hematology, and Transplantation, St Petersburg, Russian Federation, [4]Università di Perugia, Ospedale Santa Maria della, Perugia, Italy, [5]University Hospital La Fe, Valencia, Spain, [6]Centre Hospitalier Lyon Sud, Lyon, France, [7]Kings College Hospital NHS Foundation Trust, London, United Kingdom, [8]University Medical Centre, Utrecht, Netherlands, [9]Universita Cattolica S. Cuore, Rome, Italy, [10]National Research Center for Hematology, Moscow, Russian Federation, [11]Universitaet Tuebingen, Medizinische Klinik, Tuebingen, Germany, [12]Hopital La Miletrie, Poitiers, France, [13]Medical Clinic and Policinic 1, Hematology and Cellular Therapy, University hospital Leipzig, Leipzig, Germany, [14]Universitaetsklinikum Dresden, Medizinische Klinik und Poliklinik I, Dresden, Germany, [15]Ospedale San Raffaele s.r.l. Haematology and BMT, Milano, Italy

Background: Primary graft failure (GF) is a devastating complication of allogeneic transplantation (HSCT). Second transplantation (HSCT2) is a potential treatment.

Methods: We assessed the outcome of adult patients (pts) with acute leukemia failing to engraft (ANC < 0.5 x 10^9/L) ≥ day 28 after the first transplant (HSCT1) and received a second transplant between 2000 and 2021.

Results: 243 pts were included: 182 (74.9%) with AML and 61(25.1%) with ALL. Median age was 44.8 (range, 18.4-75.2) years, 71.6% and 28.4% of pts were in CR1 and CR2, respectively. Donors of HSCT1 were matched siblings in 9.1%, unrelated in 39.9%, haploidentical in 35%, and cord blood in 16%. At HSCT1, conditioning was myeloablative (MAC) in 58.4% of the cases. GVHD prophylaxis was mainly calcineurin inhibitor (CNI)-based (70.9%). 46.1% and 14.8% of the HSCTs were with in vivo and ex vivo T-cell depletion, respectively. The time from first to second transplantation was 48 (range, 28-120) days. Donors at HSCT2 were the same as in HSCT1 in 49% while they differ in 51%. Engraftment post HSCT2 was achieved by 78.6% vs. 59% of the pts with AML and ALL, respectively ($p = 0.034$.) Incidence of acute (a) GVHD II-IV and III-IV was 23.2% and 8.2%, and 5-year total and extensive chronic (c) GVHD was 22.3%, and 10.1%, respectively. The 5-year NRM was 51.6% with infections being the main cause. The 5 -year RI, LFS, OS and GRFS were 18.8%, 29.6%, 30.7% and 22.4%, respectively. Being transplanted at CR2 vs. CR1, increased age (per 10-years), lower KPS (< 90) at HSCT2 and receiving MAC at HSCT1 were adverse prognostic factors for NRM, LFS and OS. Hazard ratio (HRs) for NRM were 2.26 (95% CI 1.41-3.63, $p = 0.0007$), HR = 1.31 (95% CI 1.09-1.54, $p = 0.005$), HR = 2.17 (95% CI 1.30-3.70, $p = 0.003$) and HR = 2.63 (95% CI 1.52-4.55, $p = 0.0006$), respectively. HRs for LFS were 2.21 (95% CI 1.43-3.33, $p = 0.0002$), HR = 1.2 (95% CI 1.03-1.41, $p = 0.02$), HR = 1.92 (95% CI 1.23-3.03, $p = 0.004$) and HR = 2.0 (95% CI 1.27-3.13, $p = 0.003$), respectively. HRs for OS were 2.38 (95% CI 1.57-3.6, $p < 0.0001$), HR = 1.26 (95% CI 1.07-1.48, $p = 0.005$), HR = 2.04 (95% CI 1.30-3.23, $p = 0.002$) and HR = 2.38 (95% CI 1.47-3.85, $p = 0.0003$), respectively. Being transplanted at CR2 vs CR1, lower KPS (< 90) and receiving MAC at HSCT1 were adverse prognostic factors for GRFS with HR of 1.82 (95% CI 1.23-2.71, $p = 0.003$), HR = 1.49 (95% CI 1-2.22, $p = 0.047$), and HR = 1.59 (95% CI 1.02-2.5, $p = 0.039$), respectively. In AML patients, adverse cytogenetics was an adverse prognostic factor for RI, LFS, OS, GRFS, and aGVHD II-IV with a HR of 8.22 (95% CI 3.01-22.46, $p < 0.0001$), HR = 2.48 (95% CI 1.43-4.31, $p = 0.001$), HR = 2.06 (95% CI 1.16-3.65, $p = 0.014$), HR = 2.34 (95% CI 1.38-3.97, $p = 0.002$) and HR = 3.32 (95% CI 1.36-8.13, $p = 0.008$), respectively.

Conclusions: HSCT2 can rescue about a third of AL pts with GF. However, transplant-related mortality is very high with a 5–year mortality of about 50%. The outcomes of HSCT2 for GF in AML and ALL are similar. A different donor at HSCT2 seems not to improve results. GF remains a grave complication of transplantation that awaits novel ideas and strategies.

Disclosure: Nothing to declare

19 - Acute Leukaemia

P003

AUTOLOGOUS VERSUS HAPLOIDENTICAL DONOR STEM CELL TRANSPLANTATION IN ADULT PATIENTS WITH AML IN FIRST COMPLETE REMISSION WITH UNDETECTABLE MRD: A GLOBAL REAL WORLD STUDY

Jia Chen[1], Myriam Labopin[2], Michael Daskalakis[3], Xi Zhang[4], Erlie Jiang[5], Alessandra Tucci[6], A.E.C Broers[7], Ellen Meijer[8], Emmanuelle Polge[2], Irma Khevelidze[2], Depei Wu[1], Mohamad Mohty[2], Norbert-Claude Gorin[2]

[1]National Clinical Research Center for Hematologic Diseases, the First Affiliated Hospital of Soochow University, Suzhou, China, [2]Saint-Antoine Hospital, AP-HP, Sorbonne University, Paris, France, [3]University Hospital Bern, Bern, Switzerland, [4]Xinqiao Hospital of Army Medical University, Chongqing, China, [5]Institute of Hematology, Chinese Academy of Medical Sciences, Tianjin, China, [6]Spedali Civili – Brescia, Brescia, Italy, [7]Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, Netherlands, [8]VU University Medical Center, Amsterdam, Netherlands

Background: For intermediate-risk AML patients in CR1, the optimal choice of consolidation therapy is still questioned. Recent Existing data have demonstrated the value of autologous stem cell transplantation (ASCT) in CR1 patients with undetectable MRD (uMRD). However allogeneic stem cell transplantation is the standard approach for the majority of transplant teams, including the use of haploidentical donor transplants (HAPLO) in the absence of a matched donor. There are presently no comparative data on transplant outcomes following a HAPLO or an ASCT for AML patients in CR1 with uMRD.

Methods: The retrospective study was conducted by the Global Committee and the ALWP of the EBMT. All patients reported to the EBMT registry, older than 18 years of age, diagnosed as intermediate-risk AML according to the ELN 2010 classification, and underwent a first auto or haplo-HCT while in CR1 with uMRD in the period of 2010-2021 were included. The endpoints were overall survival (OS), leukemia-free survival (LFS), relapse incidence (RI) and Non relapse Mortality (NRM). A particular attention was devoted to molecular markers to enable detailed stratification.

Results: 1122 patients from 196 centers were recruited, including 547 patients who received a ASCT and 575 patients receiving a HAPLO (Table 1). When compared to HAPLO, ASCT patients were older and transplanted earlier. ASCT patients less frequently carried a FLT3-ITD mutation and more frequently a NPM1 mutation. Besides, they had inconspicuously shorter interval from diagnosis and better performance status at transplant.

Table 1 Comparison of characteristics of enrolled patients

		Auto-HCT (n = 547)	Haplo-HCT (n = 575)	P value
Patient age	median years (range)	53.8 (18.7-77.4)	49.1 (18.1-78.7)	<0.0001
Patient sex	Male	278 (50.8%)	328 (57%)	0.037
	Female	269 (49.2%)	247 (43%)	
Year of HCT	median (range)	2016 (2010-2021)	2018 (2010-2021)	<0.0001
FLT3-ITD mutation	FLT3-wt	418 (76.4%)	325 (56.5%)	<0.0001
	FLT3-ITD	129 (23.6%)	250 (43.5%)	
NPM1 mutation	NPM1 absent	210 (39.3%)	327 (63.5%)	<0.0001
	NPM1 presence	324 (60.7%)	188 (36.5%)	
	missing	13	60	
Patient CMV	Pat. CMV neg.	64 (36.8%)	209 (37.9%)	0.8
	Pat. CMV pos	110 (63.2%)	343 (62.1%)	
	missing	373	23	
Karnofsky score	<90	82 (15.9%)	188 (35.9%)	<0.0001
	≥90	433 (84.1%)	335 (64.1%)	
	missing	32	52	
Time from diagnosis to HCT	median months (range)	4.7 (1.2-52.6)	5.2 (1.4-61.4) [4-6.8]	0.0003

The median follow-up was 37.5 months. All survival events were censored at 3 years. Due to a significant interaction between the FLT3-ITD status and the type of transplant, comparisons were performed separately for patients with wild type FLT3 (FLT3-wt) and those bearing a FLT3-ITD mutation (FLT3-ITD).

For FLT3-wt patients, the RI was lower in HAPLO than in ASCT (16.9% versus 32.6%; HR = 0.40 [95% CI: 0.27-0.60], P < 0.001), but contrarily the NRM was higher (17.2% vs 3.5%; HR = 7.02 [95% CI: 3.26-15.08, p < 0.001). Although no significant difference for LFS (65.9% vs 63.8%; HR = 0.86 [95% CI: 0.62-1.2], p = 0.37), the OS was significantly lower following HAPLO (73.2% vs 80.6%; HR = 1.69 [95% CI: 1.09-2.61], p = 0.018).

For FLT3-ITD patients, HAPLO was associated with a lower RI (8.2% vs 47.8%; HR = 0.14 [95% CI: 0.07-0.28], p < 0.001) and a higher NRM (20.2% vs 5.6%; HR = 3.43 [95% CI: 1.55-7.61], p = 0.002). The LFS was better (71.5% vs 46.6%; HR = 0.53 [95% CI: 0.34-0.85], p = 0.007) for HAPLO, but OS was comparable (73.5% vs 61.9%; HR = 0.83 [95% CI: 0.52-1.33], p = 0.44). Of note, more ASCT patients received a subsequent allogeneic HCT (25.2% vs 3.3%, P < 0.0001).

In both the FLT3-wt and FLT3-ITD group, NPM1 mutation was identified as a favorable factor for RI, LFS and OS.

Conclusions: For intermediate-risk AML patients without FLT3-ITD, ASCT is a valid consolidation option in CR1 with uMRD. In patients with FLT3-ITD, results of HAPLO could be better. In these patients, the role of maintenance with targeted agents post-transplant deserves further investigation.

Clinical Trial Registry: N.A.

Disclosure: No conflict to disclose.

19 - Acute Leukaemia

P004

NON MYELOABLATIVE VERSUS REDUCED INTENSITY CONDITIONING FOR ALLO-HCT FROM SIBLING OR UNRELATED DONORS IN PATIENTS WITH AML ≥ 65YEARS. A STUDY FROM THE EBMT ALWP

Alexandros Kanellopoulos[1,2], Myriam Labopin[3], Alexandros Spyridonidis[4], Emmanouil Nikolousis[5], Uwe Platzbecker[6], Didier Blaise[7], Henrik Sengeloev[8], David Burns[5], Thomas Schroeder[9], Goda Choi[10], Eleni Tholouli[11], Peter Dreger[12], Victoria Potter[13], Régis Peffault de Latour[14], AEC Broers[15], Jakob Passweg[16], Matthias Eder[17], Gitte Olesen[18], Jean-Henri Bourhis[19], Gwendolyn Van Gorkom[20], Matthias Stelljes[21], Jacques-Olivier Bay[22], J.L. Byrne[23], Anne Sirvent[24], JA Snowden[25], Eolia Brissot[3], Fabio Ciceri[26], Arnon Nagler[27], Mohamad Mohty[3]

[1]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, [2]University of Sheffield, Sheffield, United Kingdom, [3]Hôpital Saint Antoine, Sorbonne University and INSERM UMRs 938, Paris, France, [4]University of Patras, Patras, Greece, [5]University Hospitals Birmingham, Birmingham, United Kingdom, [6]University hospital Leipzig, Leipzig, Germany, [7]Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, Marseille, France, [8]National University Hospital, Copenhagen, Denmark, [9]University Hospital, Essen, Germany, [10]University Medical Center Groningen (UMCG), Groningen, Netherlands, [11]Manchester Royal Infirmary, Manchester, United Kingdom, [12]University of Heidelberg, Heidelberg, Germany, [13]Kings College Hospital, London, United Kingdom, [14]Hopital St. Louis, Paris, France, [15]Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, Netherlands, [16]University Hospital, Basel, Switzerland, [17]Hannover Medical School, Hannover, Germany, [18]Aarhus University Hospital, Aarhus, Denmark, [19]Gustave Roussy Cancer Campus, Villejuif, France, [20]University Hospital Maastricht, Maastricht, Netherlands, [21]University of Muenster, Muenster, Germany, [22]Chu Estaing, Clermont, France, [23]Nottingham University, Nottingham, United Kingdom, [24]CHU Lapeyronie, Montpellier, France, [25]Sheffield Teaching Hospitals NHS Foundation trust, Sheffield, United Kingdom, [26]Ospedale San Raffaele, Milano, Italy, [27]Sheba Medical Center, Tel Aviv, Israel

Background: Acute myeloid leukemia patients ≥65 years old have higher transplant failure risks and should be considered for reduced intensity (RIC) or non-myeloablative (NMA) conditioning. The optimal type of conditioning in allogeneic hematopoietic stem cell transplantation (allo-HCT) for elderly AML remains unknown. The aim of this study was to compare NMA versus RIC allo-HCT outcomes in AML patients aged ≥65 years.

Methods: Retrospective analysis of transplant outcomes for AML patients ≥65 years old (n = 2900) who had first allo-HCT in first or second complete remission (CR1/CR2) between years 2004-2021 from either matched sibling, HLA-10/10 or HLA-9/10 matched unrelated, or haploidentical unrelated donor receiving RIC Fludarabine/Busulfan iv 6.4mg/kg (Flu/Bu2) (35.6%, n = 1033), or Fludarabine/Melphalan 110-140mg/m^2(Flu/Mel) (22.2%, n = 643), or Fludarabine/Treosulfan 30g/m^2(Flu/Treo) (10.8%, n = 313), versus NMA Fludarabine/Total Body Irradiation 2Gy

(Flu/TBI2Gy) (31.4%, n = 911). Patients who had cord blood units or ex vivo T cell depletion (TCD) were excluded.

Results: Median age of NMA and RIC cohorts was 68.6 and 68.0 years respectively (p < 0.0001). The RIC arm had more Karnofsky score ≥90 (70% vs 63.4%, p < 0.0006), female donor to male recipient combination (44.7% vs 16.6%, p < 0.0001), and in vivo T cell depletion (82.5% vs 10.2%, p,0.0001) whereas NMA patients more frequently received a haploidentical graft (19.9% vs 4.3%, p < 0.0001), bone marrow graft (6.4% vs 3.1%, p < 0.0001), and post-transplant cyclophosphamide (23.8% vs 7.3%, p < 0.0001). Secondary AML incidence, recipient sex, cytogenetic risk group, pre-transplant measurable residual disease (MRD), and FLT3/NPM1 status were not statistically different between the two arms. With a median follow-up 35.6 and 50.4 months for RIC and NMA (p < 0.0001) respectively, overall survival (OS), leukemia free survival (LFS) and non-relapse mortality (NRM) at 2 years was 53.4% v 56.5% (HR 0.87, p = 0.19), 51% vs 50.7% (HR 0.97, p = 0.78) and 23.8% vs 20.7% (HR 0.97, p = 0.83) respectively. Despite higher cumulative incidence (CI) of grade II-IV graft versus host disease (GVHD) for RIC (26.3% vs 25.5%, HR = 1.45, p = 0.01), the NMA arm had higher CI of chronic extensive GVHD (25.3% vs 12.9%, HR = 1.59, p = 0.02) whilst GVHD-free/relapse free survival (GRFS) was equivalent [HR (RIC vs NMA) = 0.94, p = 0.46] between both arms. Adverse factors for OS were HLA-9/10 donors (HR 1.5, p = 0.002), secondary AML (HR 1.19, p = 0.01), and complex cytogenetics (HR 1.64, p = 0.014). KPS ≥ 90 (HR 0.84, P = 0.006) and use of peripheral blood stem cell over bone marrow grafts (HR 0.66, p = 0.001), exerted a favourable OS effect.

Subgroup sensitivity analysis between NMA n = 242 and RIC n = 737 patients with known MRD pre-transplant, demonstrated no significant benefit of RIC over NMA, in terms of LFS (HR 0.95, p = 0.74), relapse (HR 0.88, p = 0.58) and OS (HR 0.85, p = 0.38).

Conclusions: We conclude that conditioning intensity (NMA vs RIC) did not impact on 2-year NRM, LFS and OS in elderly (≥ 65 years) AML. Higher risk of acute gr II-IV GVHD and lower risk of extensive chronic GVHD using RIC compared to NMA was identified. Subgroup sensitivity analysis did not reveal significant interaction between conditioning intensity and pre-transplant MRD status in terms of transplant outcomes.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P005

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT IN ADULT PATIENTS WITH IDH MUTATED AML AND MDS: A STUDY FROM THE GRUPO ESPAÑOL DE TRASPLANTE HEMATOPOYÉTICO Y TERAPIA CELULAR

Ana Pérez-González[1], Víctor Navarro[2], Manuel Guerreiro[3], Izarbe Delgado[4], Ana Pilar González[5], Alejandro Avendaño[6], Alberto Musseti[7], Mi Kwon[8], Irene García Cadenas[9], María Teresa Zudaire Ripa[10], Oriana Lopez Godino[11], David Valcárcel Ferreiras[1], Guillermo Ortí Pascual[1]

[1]University Hospital Vall d'Hebron, Barcelona, Spain, [2]Oncology Data Science (ODysSey) Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [3]University Hospital La Fe, Valencia, Spain, [4]University Hospital Arnau de Vilanova, Lleida, Spain, [5]University Hospital of Cabueñes, Gijón, Spain, [6]University Hospital of Salamanca, Salamanca, Spain, [7]Institut Catalá d'Oncologia, Hospital Duran i Reynals, Barcelona, Spain, [8]University Hospital Gregorio Marañón, Madrid, Spain, [9]University Hospital Santa Creu i Sant Pau, Barcelona, Spain, [10]Complejo Hospitalario de Navarra, Pamplona, Spain, [11]University Hospital Morales Meseguer, Murcia, Spain

Background: Data regarding the prognostic relevance of IDH mutations (IDHm) in AML and MDS patients undergoing allogeneic hematopoietic cell transplant (allo-HCT) are limited. We sought to investigate the outcomes and prognostic factors of these patients in a retrospective manner.

Methods: This was a multicentre, retrospective study approved by Grupo Español de Trasplante Hematopoyético y Terapia Celular (GETH-TC) and by the Vall d'Hebron University Hospital ethics committee. Inclusion criteria were: 1) diagnosis of AML/MDS as per WHO criteria in patients >18 years; 2) mutation of IDH1/IDH2 detected by Sanger, PCR or NGS; and 3) undergoing first allo-HCT with MRD/MMRD/MUD/MMUD and myeloablative/reduced-intensity conditioning. The primary endpoint was overall survival. Secondary endpoints were PFS, NRM, cumulative incidence of relapse and GRFS.

Results: A total of 101 patients allografted from 2012 to 2021 in 9 GETH-TC institutions were identified and constitute the objective of this analysis; 88 (87.1%) and 13 (12.9%) patients were diagnosed with AML and MDS, respectively. Clinical and allo-HCT characteristics are shown in table 1. Of note, only one patient with IDH1m-AML received an IDH-inhibitor prior to allo-HCT in our cohort. Normal karyotype was observed in 66 patients (71%). The vast majority of patients (99%) carried additional mutations, with 43 patients (43%) harbouring ≥2 mutations. The most frequent co-mutations comprised NPM1 (31%) and DNMT3A (27%); FLT3-ITD mutations (12%) and TP53 (2%) were less represented.

With a median follow up of 21.2 months (CI95% 17.5 - 29.6), the estimated 2-year OS was 73% (IQR 63-84); 2-year OS was 77% and 70% in IDH1 and IDH2 cohorts, respectively ($p = 0.76$). In univariate analysis non-intensive treatment ($p = 0.03$) was associated with lower OS and MRD positivity ($p = 0.07$) showed a trend towards impaired outcomes. The 2-year PFS was 70% (IQR 61-81), with 2-year PFS of 71% and 69% in IDH1 and IDH2 cohorts, respectively ($p = 0.86$). MVA showed that non-intensive induction treatment ($p = 0.05$) and FLT3 mutations ($p = 0.01$) were associated with a lower PFS. The 2-year RI was 16% and 23% in IDH1 and IDH2 cohorts, respectively ($p = 0.7$). In the MVA, active disease at allo-HCT ($p = 0.1$) and detectable MRD ($p = 0,08$) showed a trend towards a higher RI. The 2-year NRM was 12% (95% CI 4-19), with no differences between IDH1 and IDH2 cohorts.

The 100-day CI of aGVHD was 39% (IQR 29-48); with grade III-IV of 9% (IQR 2-12). In univariate analysis, IDH1m patients showed a trend to a higher CI of 100-day grade I-IV/grade III-IV aGVHD compared to IDH2m patients, 46.1%/12% vs 32.6%/5%, respectively ($p = 0.06$ / $p = 0.1$). The 1-year CI of cGVHD was 31% (IQR 20-41) with no differences between IDH1 and IDH2 cohorts. The 1-year GRFS was 54% (40-65%), with 1-year GRFS 31% for IDH1 and 58% for IDH2 cohort ($p = 0.08$).

Table 1. Patients' characteristics

Variables	Total (n = 101)	IDH1 (n = 46)	IDH2 (n = 54)
Median age (range)	55 (23 - 69)	56 (27 - 69)	55 (23 - 70)
Male gender, *n* (%)	70 (69%)	34 (74%)	35 (65%)
Diagnosis AML/MDS, *n* (%)	88 (87%)/13 (13%)	41 (89%)/5 (11%)	46 (85%)/8 (15%)
Abnormal cytogenetics, *n* (%)	27 (29%)	10 (24%)	16 (32%)
ELN 2017 cytogenetic risk in AML (n = 88), *n* (%)			
Favourable	20 (23%)	9 (22%)	11 (24%)
Intermediate	46 (52%)	23 (56%)	23 (50%)
Adverse	22 (25%)	9 (22%)	12 (26%)
Treatment prior to allo-HCT, *n* (%)			
Intensive/	83 (82%)/	36 (78%)/	46 (85%)/

Variables	Total (n = 101)	IDH1 (n = 46)	IDH2 (n = 54)
hypomethylating & other non-intensive treatments	18 (18%)	10 (22%)	8 (15%)
Disease status at allo-HCT (CR+CRi) CR1/CR2, *n* (%)	66 (65%)/20 (20%)	28 (61%)/13 (28%)	37 (69)/7 (13)
Conditioning, MAC/RIC *n* (%)	41 (41%)/60 (60%)	13 (28%)/33 (72%)	28 (52%)/26 (48%)
Type of donor, *n* (%)			
MRD/MUD	38 (38%)/37 (37%)	21 (46%)/15 (33)	16 (30%)/22 (40%)
Haplo	26 (26%)	10 (22%)	16 (30%)
GvHD prophylaxis, *n* (%)			
CNI-based/ PT-Cy	37 (37%)/54 (53%)	18 (39%)/25 (54%)	18 (33%)/29 (54%)
None (TCD ex-vivo)	10 (10%)	3 (7%)	7 (13%)

N number, AML acute myeloid leukemia, MDS myelodysplastic syndrome, ELN European Leukemia Net, CR1 first complete response, CR2 second complete response, CRi complete response without haematological recovery, MAC myeloablative conditioning, RIC reduced intensity conditioning, MRD matched related donor, MUD matched unrelated donor, Haplo haploidentical donor, GVHD graft-versus-host disease, CNI-based calcineurin inhibitor based, PT-Cy Post-Transplant Cyclophosphamide, TCD ex-vivo *T-cell depleted* ex-vivo.

Conclusions: In this cohort, the prognosis of IDH1 and IDH2m patients undergoing allo-HCT is comparable, with a 2-year OS exceeding 70% in both cohorts. FLT3 mutation was an independent prognostic factor for PFS. Studies on post allo-HCT maintenance with FLT3 or IDH inhibitors in this setting are warranted.

Disclosure: Nothing to declare

19 - Acute Leukaemia

P006

COMBINATION OF BENDAMUSTINE AND CYCLOPHOSPHOMIDE FOR GRAFT-VERSUS-HOST DISEASE PROPHYLAXIS IN REFRACTORY MYELOID NEOPLASMS

Ivan Moiseev[1], Yulia Vlasova[1], Elena Morozova[1], Olga Epifanovskaya[1], Ksenia Afanasyeva[1], Anastasia Beynarovich[1], Dmitrii Zhogolev[1], Mikhail Kanunnikov[1], Yulia Rogacheva[1], Tatyana Rudakova[1], Nikita Volkov[1], Sergey Bondarenko[1], Alexander Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation

Background: Efficacy of salvage allogeinic hematopoietic stem cell transplantation (HSCT) in myeloid neoplasms not responding to chemotherapy and targeted therapies remains limited. Our group have recently demonstrated augmented graft-versus-leukemia (GVL) effect with substituting cyclophosphamide with bendamustine in graft-versus-host disease (GVHD) prophylaxis regimen (Moiseev et al., TCT, 2021), but significant toxicity due to poorly controlled cytokine release syndrome (CRS). To overcome this limitation we conducted a pilot single-center study of GVHD prophylaxis with a combination of cyclophosphamide with bendamustine in refractory myeloid neoplasms.

Methods: The prospective (NCT04943757) Phase I/II single-arm study evaluated GVHD prophylaxis regimen consisting of bendamustine 50 mg/kg/day on days +3, +4, cyclophosphamide 25 mg/kg/day on days +3, +4 (PTCBCy), tacrolimus 0.03 mg/kg from day+5 to day+100 and mycophenolate mofetil 30 mg/kg/day on days 5-35. Patients received reduced intensity FB2 or FB3 conditioning according to performance status. Forty patients evaluable for response were included into the interim safety and efficacy analysis. Median age was 43 years (range 18-69). AML was an indication for HSCT in 29, MDS in 9 and 2 patients had CML and aCML. All patients had >5% of blasts in a bone marrow at the time of conditioning. Donors were matched related siblings in 23%, matched unrelated for 50% and haploidentical for 27% of patients. None of the patients received DLI for relapse prevention.

Results: Engraftment with hematological complete remission was documented in 85% of patients. No detectable minimal residual disease after engraftment was documented in 75%. Median time to engraftment was 17 days (range 12-35). One-year overall survival was 47% (95%CI 24-67%), while event-free survival (EFS, including graft failure as event) was 24% (95%CI 6-48%). Disease progression or relapse was the major cause of failure and was documented in 71% of patients (95%CI 47-86%). The only predictor of better EFS was either unrelated or haploidentical donor compared to matched related (36% vs 11%, p = 0.0060). On the other hand non-relapse mortality was very low (7.5%, 95%CI 2-18%) as well as the incidence of other complications. Cumulative incidence of Grade II-IV acute GVHD was 10%, moderate and severe chronic GVHD – 19%. CRS was documented in 27% of patients and only in 2 it was grade 4-5. Most common manifestations of CRS involved liver (in 25%) and skin (7%). CRS was effectively controlled by tocilizumab, ruxolitinib and high dose steroids in all, but one patient. All CRS cases were associated with increased serum ferritin (median 15541 ng/ml, range 6150-206500). Preliminary flow cytometry analysis demonstrated the same pattern of early immunological recovery, preservation of memory T-cells and induction of tolerance by PD-1L positive monocytes as in the single-agent bendamustine study.

Conclusions: This pilot trial demonstrated that PTBCy combination prophylaxis provides the level of safety compared to conventional GVHD prophylaxis regimens with maintenance of GVL patterns. Optimal type of donor and post-transplant relapse prevention are still to be determined.

Clinical Trial Registry: NCT04943757, clinicaltrials.gov

Disclosure: The authors declare no conflicts of interest. The study was supported by RSF grant 23-15-00327.

19 - Acute Leukaemia

P007

OUTCOMES IN PATIENTS WITH B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA WHO RECEIVED INOTUZUMAB OZOGAMICIN AND PROCEEDED TO HEMATOPOIETIC STEM CELL TRANSPLANTATION: A REGISTRY-BASED, OBSERVATIONAL STUDY

David Marks[1], Marcos de Lima[2], Partow Kebriaei[3], Francesco Lanza[4], Christina Cho[5], Gizelle Popradi[6], Mei-Jie Zhang[7], Fan Zhang[8], Verna Welch[9], Saara Tikka[10], Erik Vandendries[11], Matthias Stelljes[12], Wael Saber[7]

[1]University Hospitals Bristol NHS Trust, Bristol, United Kingdom, [2]Ohio State University, Blood and Marrow and Cellular Therapy Program, Columbus, United States, [3]MD Anderson Cancer Center, Houston, United States, [4]Ospedale di Ravenna, Ravenna, Italy, [5]Memorial Sloan Kettering Cancer Center, New York, United States, [6]McGill University Health Centre, Montreal, Canada, [7]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, United States, [8]Pfizer Inc, Shanghai, China, [9]Pfizer Inc, New York, United States, [10]Pfizer Oy, Helsinki, Finland,

[11]Pfizer Inc, Cambridge, United States, [12]Universitätsklinikum Münster, Münster, Germany

Background: Inotuzumab ozogamicin (InO) is a CD22-directed antibody–drug conjugate indicated for the treatment of relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL). This study examined outcomes following hematopoietic stem cell transplantation (HSCT) in patients who received InO prior to HSCT.

Methods: We report outcomes in patients (aged ≥18 years) with ALL and R/R ALL who received InO and proceeded to first allogeneic HSCT (United States observational, post-authorization safety study). Outcomes included disease status, overall survival, non-relapse (transplant-related) mortality (NRM), non-transplant-related mortality, and adverse events (AEs) of interest, including veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS). Multivariate analyses examined prognostic factors of NRM at 1 year and VOD/SOS incidence at 100 days post HSCT. This analysis is based on 4-year interim data.

Results: In total, 196 adults (median age 39 years, 54% male, 75% White) received InO and proceeded to first allogeneic HSCT: 32% in first complete remission (CR1), 46% in CR2, 12% in CR ≥ 3, 5% in first relapse, 2% in third or subsequent relapse, and 3% with primary induction failure. Prior to HSCT, 32%, 45%, and 17% received 1, 2, and ≥3 cycles of InO, respectively. Post HSCT outcomes were analyzed in 177 adults with ALL and 120 adults with R/R ALL. The most common causes of NRM at 12 months were VOD/SOS (10/35; 29%) and graft-versus-host disease (GVHD; 8/35; 23%). AEs occurring in ≥30% of patients ≤100 days post HSCT were bacterial infection (46%), viral infection (41%), and acute GVHD (grades II–IV, 38%). VOD/SOS incidence ≤100 days post HSCT was 15% and 19% in patients with ALL and R/R ALL; corresponding mortality rates were 38% and 36% in patients who developed VOD/SOS ≤ 100 days (6% and 7% as a percentage of all patients). Median (range) time from HSCT to VOD/SOS was 0.4 (0.2–2.6) months in both groups. Of 26 adults with ALL who developed VOD/SOS, 10 cases were mild, 16 severe; 5/26 patients received prophylactic defibrotide; 12/26 patients received defibrotide treatment alone or in combination. In those who died, median (range) time to death was 4.5 (0.4–39.2) months.

In total, 143 adults with ALL (alive at last contact and reported ≥1 year of follow-up or who died at any time after HSCT) were included in multivariate analyses. Total serum bilirubin ≥ the upper limit of normal before HSCT (hazard ratio [HR], 5.72; $P = 0.0001$) and 4 cycles of InO (HR, 6.81; $P = 0.0009$) were negative prognostic factors for NRM at 1 year. A conditioning regimen containing dual alkylators was the only negative prognostic factor for VOD/SOS incidence at 100 days (odds ratio, 8.3; $P = 0.0033$).

Conclusions: In this real-world population of adults with ALL who received InO before HSCT, including heavily pretreated patients, the incidence of VOD/SOS after HSCT was similar to that observed in INO-VATE (phase 3 study) and a pooled analysis of 2 clinical trials of InO-treated patients with R/R ALL. Although the VOD/SOS mortality rate was higher (36% vs 26%), NRM at 12 months was lower (24% vs 38%) here vs the pooled clinical trial population.

Disclosure: David Marks: consultancy at Kite and Pfizer, honoraria from Amgen, Kite, Novartis, and Pfizer, and speakers bureau with Kite, Novartis, and Pfizer; Marcos de Lima: consultancy at Amgen, Celgene, Incyte, and Pfizer, and research funding from Celgene and Pfizer; Partow Kebriaei: consultancy at Jazz, Kite, and Pfizer, and research funding from Amgen and Ziopharm; Francesco Lanza: consultancy at AbbVie, Alexion, and Amgen, and research funding from Pfizer; Christina Cho: consultancy at AlloVir; Gizelle Popradi: consultancy at, and honoraria from, AbbVie, Kite, Gilead, Kyowa Kirin, Merck, Novartis, Pfizer, Servier, Seattle Genetics, and Taiho, research funding from Jazz, Novartis, and Syndax Pharmaceutical, and speakers bureau with AbbVie, Gilead, Jazz, Kyoma Kirin, Merck, Novartis, PeerVoice, Pfizer, Servier, and Seattle Genetics; Mei-Jie Zhang: nothing to declare; Fan Zhang: employment at Pfizer; Verna Welch, Saara Tikka, and Erik Vandendries: employment and equity ownership at Pfizer; Matthias Stelljes: consultancy at, speakers bureau with, and research funding and honoraria from, Pfizer; Wael Saber: nothing to declare.

19 - Acute Leukaemia

P008

ACUTE LYMPHOBLASTIC LEUKEMIA PH POSITIVE VS PH NEGATIVE - REAL WORLD EXPERIENCE WITH ALLOGENEIC HCT OUTCOME ON BEHALF OF POLISH ADULT LEUKEMIA GROUP (PALG)

Jarosław Dybko[1], Agnieszka Piekarska[2], Alicja Sadowska-Klasa[2], Anna Płotka[3], Beata Piątkowska-Jakubas[4], Donata Urbaniak-Kujda[5], Małgorzata Sobczyk-Kruszelnicka[6], Sebastian Giebel[6], Lidia Gil[3]

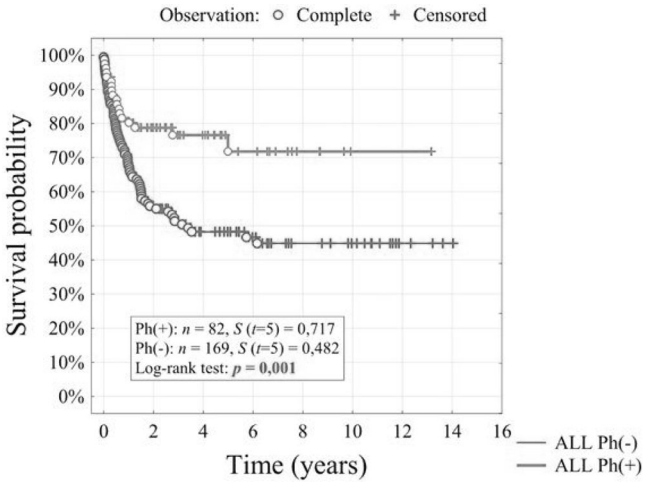
Lower Silesian Oncology Center, Wrocław, Poland, University Clinical Center, Medical University of Gdańsk, Gdańsk, Poland, Poznań University of Medical Sciences, Poznań, Poland, Jagiellonian University Hospital, Kraków, Poland, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University,, Wrocław, Poland, Maria Skłodowska-Curie National Research Institute of Oncology (MSCNRIO), Gliwice, Poland

Background: Patients with acute lymphoblastic leukemia Philadelphia positive (ALL Ph+) have been reported to have a better transplant outcome comparing to Ph negative cases (ALL Ph-). The routine pretransplant and posttransplant use of tyrosine kinase inhibitors (TKIs) has improved outcomes in Ph+ cases but the optimal conditioning regimen, donor type, and TKI remain undefined although the role of pre-transplant positive minimal residual disease (MRD) has beem established. We analyzed retrospective PALG data of 256 ALL patients to compare this outcome in Polish population.

Methods: We analyzed a "historic" group from pre-antibodies (anti-CD19 and anti-CD22) era. The whole cohort consisted of 82 Ph+ and 169 Ph- cases. The Ph+ group was older (median age 40 vs 29, $p < 0.001$) but there were no differences in sex or demographics. Majority of Ph+ patients expressed B-cell phenotype (95.1% vs 76.9% in Ph-, $p < 0.001$) and most of them in both groups were transplanted in CR1 (87.8% vs 78.1, p = NS) from matched unrelated donor (61.2% vs 52.0%, p = NS; only 10 haploidentical transplants in Ph- group, all the rest transplanted form matched sibling donors) based on MAC conditioning (80.5% vs 89.3%, p = NS). In Ph+ group 66 patients were treated with imatinib, 16 - with dasatinib before alloHCT, 50 and 9 after transplantation, respectively.

Results: Patienst were transplanted form matched unrelated and sibling donors in Ph+ group (50 and 32, respectively) and from matched unrelated, sibling and haplidentical donors in Ph- group (89, 71 and 10, respectively) with no signifcant difference between groups. MAC/RIC conditioning ratio was 66/16 in Ph+ and 151/18 in Ph- negative group. There were no differences in CMV staus of patients and donors and median number of CD34+ cells transplanted. Acute GvHD rate was 46.3% vs 41.4% (p=NS), chronic GvHD - 65.9% vs 66.9% (p=NS) with no difference for higher grades. The only significant difference was for liver acute

GvHD with Ph- group domination (3.7% vs 13.0%, p = 0.02). The survival rate was significantly higher for Ph+ group (78.0% vs 52.1%, p < 0.001, Fig.1) with no difference between groups for non relapse mortality. The relapse rate was significantly lower in Ph+ group (9.7% vs 20.1%, p < 0.01).



Conclusions: Our historic data confirmed better survival rate in Ph+ group with no significant differences in NRM or GvHD but significantly higher relapse rate in Ph- group. These results are just another voice in discussion on precise control of minimal residual disease in pre- and post-transplant setting in ALL patients and modern therapies with bispecific antibodies and antibody-drug conjugates as new tools to eliminate MRD are of course another chapter.

Clinical Trial Registry: No

Disclosure: Nothing to declare

19 - Acute Leukaemia

P009

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA: OUTCOMES AT THE NATIONAL CANCER CENTER HOSPITAL (NCCH) OF JAPAN

Masanori Sakata[1], Mizuki Watanabe[1], Sung Won Kim[1], Asako Usui[1], Wataru Takeda[1], Takashi Tanaka[1], Ayumu Ito[1], Yoshihiro Inamoto[1], Takahiro Fukuda[1]

[1]National Cancer Center Hospital, Tokyo, Japan

Background: There are limited data on outcomes and prognostic factors in allogeneic hematopoietic stem cell transplantation (allo-HSCT) for T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL). Herein, we retrospectively examined the clinical outcomes of patients with T-ALL/T-LBL receiving allo-HSCT at National Cancer Center Hospital of Japan.

Methods: Between 2000 and 2022, 54 patients received a first allo-HSCT for T-ALL(n = 24) and T-LBL(n = 30). Overall survival (OS) and relapse free survival (RFS) were assessed using the Cox proportional hazard model and progression and transplant-related mortality (TRM) were assessed using Fine and Gray's proportional subhazards model. Variables selected manually in the preceding univariate analysis with P < 0.05 were put in the multivariate models.

Results: Median age at transplantation was 31 years (range, 7-64) and median follow-up for survivors was 3 years. Disease status at allo-HSCT was 1st complete remission (CR) in 19 patients, 2nd CR in 12 patients and not in remission (NIR) in 23 patients. Myeloablative conditioning (MAC) regimens utilizing total body irradiation (TBI) ≥ 12Gy was used in 37 patients, non TBI-MAC regimens in 5 and reduced intensity conditioning (RIC) regimens in 12. A total of 16 patients (T-ALL, n = 3; T-LBL, n = 13) had received focal irradiation at mediastinal or sanctuary involvements prior to allo-HSCT. Twelve patients were with early T-cell precursor type, and other subtypes were pre-T in 21, cortical-T in 9, mature-T in 5, and pro-T in 2. Three-years overall survival (OS) was 46.9% and 3-years relapse/progression-free survival (RFS) was 37.8 %. Cumulative incidence of relapse/progression and non-relapse mortality (NRM) at 3 years was 54.3 % and 7.9 %, respectively, In multivariable analysis, status of NIR at allo-HSCT was significantly associated with inferior outcomes (1st CR vs NIR: OS, HR 3.33, P = 0.038; PFS, HR 4.72, P = 0.006) with higher relapse/progression risk (1st CR vs NIR: relapse, HR 3.37, P = 0.01), whereas patients with 2nd CR and 1st CR showed comparable outcomes (1st CR vs 2nd CR : OS, HR 0.826, P = 0.795; PFS, HR 1.07, P = 0.919; relapse/progression, HR 1.02, P = 0.97). ETP type was associated with inferior OS (HR 4.97, P = 0.0038). TBI-MAC had no superior outcomes compared to non TBI-MAC (OS, HR 1.42, P = 0.68; PFS, HR 0.55, P = 0.479) and RIC (OS, HR 1.07, P = 0.899; PFS, HR 0.52, P = 0.224). Conditioning regimen showed no impact on NRM, either (P = 0.138, in univariable analysis).

Conclusions: In our analysis, no difference was observed among the conditioning groups, contrary to the previous reports. Although our study was a retrospective analysis in a small cohort, it suggested that conditioning regimens other than TBI-MAC potentially could be taken into consideration in certain situations. We observed no difference in clinical outcomes between patients with 1st and 2nd CR at transplantation, although NIR status significantly affected the outcomes. Patients who achieved 2nd CR might be good candidates for allo-HSCT. Overall, high frequency of relapse after transplant remains a major issue, especially in those at NIR (3-year relapse: 65.2%), where efforts to achieve better remission before transplantation should be made.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P010

EARLY LYMPHOCYTE IMMUNE RECONSTITUTION AS PREDICTOR FOR OUTCOMES AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR MALIGNANT INDICATIONS: A TRI-INSTITUTIONAL ANALYSIS

Alexandre Troullioud Lucas[1,2], Caroline Lindemans[2,3], Senthil Velan Bhoopalan[4], Rana Dandis[2], Susan Prockop[5], Swati Naik[4], Dinesh Keerthi[4], Coco de Koning[3], Akshay Sharma[4], Stefan Nierkens[2,3], Jaap Jan Boelens[1]

[1]Memorial Sloan Kettering Cancer Center, New York, United States, [2]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, [3]University Medical Center Utrecht, Utrecht, Netherlands, [4]St. Jude Children's Research Hospital, Memphis, United States, [5]Boston Children's Hospital/Dana-Farber Cancer Institute, Boston, United States

Background: Early CD4 immune reconstitution (IR) after allogeneic hematopoietic cell transplant (allo-HCT) correlates with lower non-relapse mortality (NRM) and a cutoff of >50/mL CD4+ cells has been found to be a good predictor for reduced NRM. The impact of CD4 and other lymphocyte IR on relapse of malignancy is less clear, especially in children.

To study the correlation of CD4, CD8 and natural killer (NK) cell IR with NRM and relapse in a large cohort of children and young adults after HCT for malignant indications.

Methods: We retrospectively analyzed data from consecutive patients receiving their first allo-HCT for a malignant indication at three large academic institutions between 2008-2019. Immune phenotyping analyses were performed regularly as standard of care after HCT in these centers. Statistical analyses involved linearity evaluation using martingale residuals plots. Cox proportional hazard models were used to study correlations where linearity assumptions were met. In case of non-linearity, maximally selected log-rank statistics were used to identify cutoffs related to outcomes. Fine-Gray competing risk methods were used to calculate cumulative incidence. All statistical analyses were done using R statistical software, version 4.2.1.

Results: Up to 503 patients were included in our analyses, median age 11.9 years (range 0.5 – 32.2). Diagnoses included acute lymphoblastic leukemia (n = 219), acute myeloid leukemia (n = 186), myelodysplastic syndrome (n = 42), non-Hodgkin lymphoma (n = 17), mixed phenotype acute leukemia (n = 11), and others (n = 28). There was non-linearity between maximum CD4 cell count before day 100 after HCT and NRM n = 503). Log-rank statistics demonstrated a CD4 count of 57 cells/μL as the best cut-off to discriminate for risk of NRM (hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.17-0.44, $P < 0.001$). There was linear correlation between maximum CD8 and NK cell counts within 100 days and NRM, but Cox proportional hazard models did not reveal any clinically relevant association (CD8: hazard ratio [HR] 0.999, 95% CI 0.998–1, $P = 0.046$, n = 491; NK: HR 0.9997, 95% CI 0.999 – 1, $P = 0.381$, n = 481). We found linear correlation between CD4, CD8 and NK cells within 100 days and relapse, but once again Cox proportional hazard models showed no statistical correlation (CD4: HR 1, 95% CI 0.9996–1.001, $P = 0.407$, n = 503; CD8: HR 1, 95% CI 0.9997–1, $P = 0.943$, n = 491; NK: HR 1, 95% CI 0.9996–1, $P = 0.926$, n = 481).

Conclusions: We confirm the strong association between early CD4 IR (of ~50/mL) and decreased NRM, but did not find an association between early CD8 or NK cell IR and NRM. Also, no component of IR (CD4, CD8 or NK cell) correlated with relapse in this analysis. To further elucidate cellular anti-leukemic effects of allo-HCT, more detailed studies on reconstitution of more specific lymphocyte subsets after allo-HCT need to be performed.

Disclosure: Caroline Lindemans reports honoraria for a lecture from Genzyme and on a data safety monitoring board of ExCellThera (related to this topic).

Susan Prockop reports support for the conduct of clinical trials: Jasper, Atara, AlloVir, Consulting/Advisory Board Participation CellEvolve, Smart Immune, Regeneron, and IP related to VSTs licensed to Atara with all rights assigned to MSKCC.

Akshay Sharma has received consultant fee from Spotlight Therapeutics, Medexus Inc. and Vertex Pharmaceuticals. He has also received research funding from CRISPR Therapeutics and honoraria from Vindico Medical Education. Akshay Sharma is the St. Jude Children's Research Hospital site principal investigator of clinical trials for genome editing of sickle cell disease sponsored by Vertex Pharmaceuticals/CRISPR Therapeutics, Novartis Pharmaceuticals and Beam Therapeutics. The industry sponsors provide funding for the clinical trial, which includes salary support paid to his institution. Akshay Sharma has no direct financial interest in these therapies. None of these conflicts are related to the work presented here.

Jaap Jan Boelens reports honoraria from Avrobio, BlueRock, Bluebird Bio, Sanofi, Sobi, SmartImmune, Advanced Clinical consulting (not related to this topic).

All other authors report no conflicts of interest.

19 - Acute Leukaemia

P011

FREQUENCY AND IMPACT OF PRE-TRANSPLANT SOMATIC MUTATIONS ON CLINICAL OUTCOMES OF AML PATIENTS RECEIVING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Khalid Halahleh[1], Eman Alnaimi[1], Ebtisam Danoun[1], Isra Muradi[2], Malek Horani[1], Mohammad Makoseh[1], Iyad Sultan[1], Waleed Da'na[1]

[1]King Hussein Cancer Center, Amman, Jordan, [2]Al-Ahliyya Amman University, Amman, Jordan

Background: Acute myelogenous leukemia is characterized by recurrent somatic variants that have implications in management algorithm. ELN-AML 2022 included ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2 and TP53 mutations. In the context allo-HSCT, the frequency and prognostic value of different gene-gene interactions has not been studied. We aim to assess the frequency and impact of different somatic mutations, either alone or in combination, on prediction of relapse and survival in patients receiving allo-HSCT regardless of MRD status.

Methods: This is a retrospective, single center KHCC registry-based analysis. Adult patients aged ≥18 years with a diagnosis of AML who received an allo-HSCT, Jan 2018- dec 2021 with an available pre-transplant genetic profile by next generation sequencing (NGS) were included.

Results: 149 patients were identified. 133 patients had de novo AML (89%). 94 patients (63%) were males, median age of 41 y (range: 18-78 y). 134 patients (90%) had pathogenetic mutation, -2 VUS (1.5%), and 13 (8.5%) had no detectable mutations. The most frequent mutations were DNMT3A (20%), NPM1 (20%), FLT3 (16%), NRAS (13.5%), TET2(9%), TP53(7.5%), SRSF2(7%), IDH1(6%), RUNX1, IDH2, KIT, and KRAS (5.4%); GATA2, ASXL1, CEBPA (5%). By multiple correspondence analysis, two independent groups of co-occurring mutations were identified, group 1 includes DNMT3A, NPM1 and FLT3, group 2 includes ASXL1, SRSF2, RUNX1.

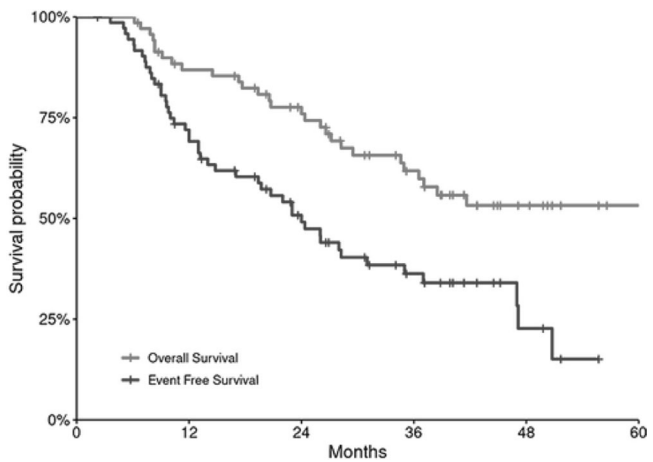
Outcome analysis was performed on the subset of 74 patients allografted with available data for the six genes.29 subjects had de novo AML (39%), median age 41y (range:18-65 y). 53 patients (35.6%) received myeloablative conditioning, blood grafts (100%) from MRD 63(42.3%), MMRD 1 (0.7%), and haplo-donors 10(6.7%). 35 patients (47%) were in CR1, and 39(53%) ≥ CR2. 16/35 patients classified as intermediate and 19 as adverse risk.

Median follow up calculated by reverse Kaplan-Meier 38.4 mo(2-78 mo). Median LFS was 29mo (18.5-42.5mo) and OS 25 mo (17-34mo) with 2-year LFS and OS of 54% and 50%. The 2-year LFS and OS were 70%, and 82%, respectively, for patients with DNMT3 mutation; 44% and 68% with NPM1 mutation; 44% and 67% with FLT-3 mutation, 100% and 100 % with ASXL mutation; 67% and 67% with RUNX1 mutation; 25% and 25 % with TP53 mutation; 75% and 74% with SRSF2 mutation; 50%, and 67% with NRAS; 67% and 100% with KRAS; 50% and 74% with TET2; 67% and 67% with IDH1; 80%, and 80% for patients with C-KIT mutation. When mutations were investigated in groups, the 2-year LFS and OS for group 1 and 2

were 50%, and 42.5% compared with 60%, and 29% respectively. 2-year LFS and OS for patients in CR1 84% and 84% compared with 22% and 69% allografted in CR2. 2-year LFS according to ELN-AML-2022, were 44%,43%, 61% and 90%,76% and 68% for OS.

Tale-1: Description of most frequent mutations (N-12)

Gene	Frequency (N)	Frequency (%)	Median VAF	Max VAF	Min FAV
DNMT3A	30	20%	40.0%	80.0%	3.0%
NPM1	30	20%	39.5%	69.0%	5.0%
FLT-3	24	16%	22.5%	56.0%	1.4%
NRAS	13	13.5%	28.0%	52.0%	3.0%
TET2	`3	9%	43.5%	81.0%	3.0%
TP53	11	7.5%	45.0%	92.0%	6.0%
SRSF2	10	7%	49.0%	77.0%	5.0%
IDH1	9	6%	42.0%	55.0%	16.0%
IDH2	8	5.4%	41.0%	45.0%	9.0%
C-KIT	8	5.4%	28.5%	53.0%	7.0%
RUNX1	8	5.4%	29.5%	67.0%	7.0%
KRAS	8	5.4%	23.0%	36.0%	7.0%



LFS and OS for allografted patients(N-74)

Conclusions: Next generation sequencing is a pivotal important too for risk stratification of patients with AML receiving allo-HSCT and determining post-transplant consolidation.

Disclosure: All authers have nothing to disclose

19 - Acute Leukaemia

P012

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION SUB-ANALYSIS OF THE GIMEMA AML1310, A RISK ADAPTED, MRD-DIRECTED THERAPY FOR YOUNG ADULTS WITH AML

Francesca Bonifazi[1], Alfonso Piciocchi[2], Valentina Arena[2], Enrico Maffini[1], Anna Candoni[3], Giovanni Martinelli[4], Valeria Calafiore[5], Lorella Melillo[6], Paolo de Fabritiis[7], Maria Paola Martelli[8], Francesco Fabbiano[9], Roberto Cairoli[10], Prassede Salutari[11], Agostino Tafuri[12], Saveria Capria[13], Mario Luppi[14], Francesco Buccisano[15], Maria Ilaria Del Principe[15], Luca Maurillo[15], Paola Fazi[16], Marco Vignetti[16], Fabio Ciceri[17], Adriano Venditti[15]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [2]GIMEMA Foundation, Roma, Italy, [3]Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy, [4]Istituto Tumori della Romagna, Meldola, Italy, [5]Ospedale Ferrarotto, Catania, Italy, [6]Fondazione IRCCS Casa Sollievo della Sofferenza, UO di Ematologia, San Giovanni Rotondo, Italy, [7]Ospedale S. Eugenio, Roma, Italy, [8]Ospedale S. Maria della Misericordia, Perugia, Italy, [9]Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy, [10]Ospedale Niguarda Ca Granda, Milano, Italy, [11]Azienda USL di Pescara, Pescara, Italy, [12]Azienda Ospedaliera Sant' Andrea, Roma, Italy, [13]Università degli Studi di Roma Sapienza, Roma, Italy, [14]Università degli Studi di Modena e Reggio Emilia, Modena, Italy, Università di Tor Vergata, Roma, Italy, [16]GIMEMA Foundation Rome, Roma, Italy, [17]University Vita-Salute San Raffaele, Milano, Italy

Background: GIMEMA AML1310 was a prospective, MRD-driven clinical trial, designed to offer a risk-adapted treatment strategy for de novo young adults with acute myeloid leukemia (AML), including allogeneic hematopoietic cell transplantation (HCT) for patients with significant disease relapse risk.

Methods: The aim of this specific sub-analysis was to describe post-HCT outcomes of the patients included in the study who underwent allogeneic HCT. In the original protocol, patients with high-risk cytogenetics/genetics and those belonging to the intermediate-risk (IR) category with a MRD positive status after the first consolidation, were candidate to HCT.

Results: A total of 142 patients (median age 45 years, range 18-61) underwent an allogeneic HCT and were included in the analysis. Sixty-three percent of patients belong to HR group. Median follow-up for the entire population was 6.6 years. Donors were HLA-matched sibling (MSD) (n = 40), unrelated donors (UD) (n = 68), and haploidentical donors (n = 34). Graft source was peripheral blood in 56%, and bone marrow in the remaining patients. Most of the patients (91%) received myeloablative regimens. Patients' characteristics stratified by donor type were superimposable across the cohorts. The overall 6-year rates of overall survival (OS) and disease-free survival (DFS) were: 50.6% (95% CI 43.0 - 59.5) and 43.7% (95% CI 35.7 – 53.3) respectively, for the entire population. The cumulative incidence of disease relapse (RI) and non-relapse mortality (NRM) were 33.9% (95% CI 25.4 - 42.4) and 22.3% (95% CI 14.9 – 29.8) respectively. There was a statistically not significant trend for better survival rates for IR respect to HR patients (6-year OS 58.4% vs. 46.6%, $p = 0.16$). Patients transplanted from haploidentical donors (24.1%, 95% CI 8.1 – 40.1) and UD (27.4%, 95% CI 15.4 – 39.3) showed a lower RI in comparison to MSD (51.4%, 95% CI 34.9 – 67.8). Conversely, patients grafted from MSD experienced lower rates of NRM (5.6%, 95% CI 2.1 – 13.3) opposed to UD (30.9%, 95% CI 18.5 – 43.3) and haploidentical (27.6%, 95% CI 11 – 44.2). Six-year OS was superimposable between MSD (54.8%, 95% CI 41.3 – 72.7) haploidentical (52.9%, 95% CI 38.6 – 72.7) and UD (47.1%, 95% CI 36.6 – 60.6). The analysis failed to demonstrate any influence of MRD on relapse incidence and survival outcomes. The univariate analysis did not identify sufficient statistically significant variables, to perform a multivariate analysis.

Conclusions: The protective effect of an allogeneic HCT observed among recipients of UD and haploidentical donors, respect to MSD, was offset by higher rates of NRM, nullifying the relative advantage and making survival outcomes superimposable between different donors. Although the original AML1310 was not conceived as a transplantation study, MRD was not informative respect to clinical outcomes.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P013

EFFICACY OF FLAG-MITOXANTRONE (M) COMBINED TO

SHORT-ADMNINISTRATION OF VENETOCLAX (VEN) FOLLOWED BY ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT) IN RELAPSED/REFRACTORY (R/R) ACUTE MYELOBLASTIC LEUKEMIA (AML)

Ahmad Ibrahim[1], Abir Harmouch[1], Ahmad Khalil[1], Pamela Sfeir[1], Kamal Zahran[1], Charbel Khalil[1], Rima Moghnieh[1], Ali Youssef[1], Tamima Jisr[1]

[1]Lebanese University, Middle East Institute of Health, Beirut Arab University, Makassed Hospital, Beirut, Lebanon

Background: Ven combined with FLAG-Ida (G-CSF, Fludarabine, Cytarabine, Idarubicin) represents an effective therapy for R/R AML patients (pts), associated with deep remissions and high rate of transition to successful AHSCT. Lowering the cytarabine dose (to 1.5g/m^2/d for 5 d) and shortening the duration of Ven (to 14 days) led to lower toxicities (DiNardo, JCO 2021). FLAG -M is highly effective and well tolerated salvage regimen for R/R AML (Hassan, Int. J. Hematol. 2018). We report the results of salvage regimen combining shortened duration of Ven (7d) and dose reduced FLAG-M followed by AHSCT when feasible in R/R AML pts aged ≥ 18y.

Methods: This is a pilot study conducted between 7/2020 and 7/2022. Salvage therapy combined G-CSF d1-7, Fludarabine (30mg/m^2/d IV) and Cytarabine (1.5g/m^2/d IV) d2-5, M (12mg/m^2/d IV) d2,4 and Ven (100mg PO daily) given with voriconazole d2-8. Anti-FLT3 therapy was included in 3 pts. For refractory pts after 1 cycle, no more cycles were given. Pts planned for AHSCT received 2 cycles of salvage and responsive pts not planned for AHSCT received 3 more cycles as consolidation. The objectives included rate of composite CR (CRc: CR,CRh,Cri), OS and RFS after salvage, and safety. Safety profile will not presented in this report.

Results: Median age at relapse was 40 y (25-67). There were 13 females and 7 males. First line therapy was 7 + 3 in 12 pts followed by AHSCT in 4, FLAG-Ida in 6 pts followed by AHSCT in 2, and 5-azacytidine+Ven in 2 pts. Anti FLT3 therapy was included in 3 pts. Median interval between first induction and salvage was 27.5m (2-175). Salvage therapy was given at a median of 2 cycles (1-4). Sixteen pts (80%) obtained CRc. Eleven pts (55%) underwent AHSCT in 2nd CR. Median follow up after salvage was 7m (1-34). Of the 20 pts, 8(40 %) are alive in CR between 4 and 34m, 2 are alive with AML, 8 died of AML and 2 pts died of infection in CR after AHSCT. The 3y-OS and 3y-RFS were 35% and 40%, respectively. Of the 9 pts who did not undergo AHSCT, only 1 pt is alive in CR at 4m, 1 pt is alive with AML at 14m, and 7 pts died of AML. The 3y-OS and 3y-RFS for these pts were 20% and 25%, respectively. Of the 11 pts who underwent AHSCT, 7 (64%) are alive in CR between 5 and 34m, 1 pt is alive with AML, 1 pt died of AML, and 2 pts died of infection at 1 and 5m of AHSCT. The 3y-OS and 3y-RFS for these pts were 70% and 85%, respectively, significantly higher than those for the pts who did not undergo AHSCT ($p = 0.025$ and $p = 0.002$,respectively).

Conclusions: Reduced dose FLAG- M with shortened duration of Ven (7d) is an active regimen in R/R AML capable of producing high remission rate and enabling transition to AHSCT when appropriate, with significant improvement in survival.

Disclosure: Nothing to declare

19 - Acute Leukaemia

P014

VOLATILE PROFILING USING AN ENOSE ALLOWS DIFFERENTIATION OF HEALTHY AND LEUKEMIC BREATH SAMPLES

Tobias Baudrexler[1], Tobias Boeselt[2], Micheal Atzler[1], Anne Hartz[1], Ursel Boas[2], Christoph Schmid[3], Andreas Rank[3], Jörg Schmohl[4], Rembert Koczulla[2], Helga Schmetzer[1]

[1]Ludwig-Maximilians-University, Munich, Germany, [2]Phillipps-University of Marburg, Marburg, Germany, [3]University Hospital of Augsburg, Augsburg, Germany, Diaconia Hospital Stuttgart, Stuttgart, Germany

Background: Volatile organic compounds (VOCs) reflecting the human metabolism can be collected easily in a noninvasive matter, directly measured by electronical nose (eNose) and might qualify as a systemic tool to monitor biomarkers related to disease. Myeloid leukemic blasts can be transformed into leukemia derived dendritic cells (DC_{leu}) being able to improve (anti-leukemic) immune responses.

Methods: 3 therapy refractory AML were treated with/without rescue therapy (for 2-4 weeks) using Kit M (Granulocyte macrophage colony stimulating factor and Prostaglandin E1: GM-CSF and PGE_1) (in consensus the local Ethic Committee of LMU in Munich, Vote-No 339-05). The impact of Kit-M on several immune cells and blasts (control vs. Kit-M treatment) was evaluated by culturing patients' blood cells ex vivo (dendritic cell-culture (DC), mixed lymphocyte-culture (MLC), functional assays (cytokine secretion- (CSA), intracellular- (InCyt) and cytotoxicity-assay (CTX)). Patients were monitored clinically, hematologically and immunologically over the whole treatment phase. VOC monitoring: VOCs were collected with earloop masks containing exhaled air from AML patients in the course of the disease and from healthy probands (n = 15) and were measured by eNose. To profile the immunological changes in acute myeloid leukemia (AML) patients, we correlated clinical- and immunological- with the VOC results of breath samples collected in the course of the disease. Clinical and immunological monitoring: 3 refractory AML patients were observed in the course of the disease with different therapies: P1511 received chemotherapy and served as a control. P1482 and P1601 were treated with Kit-M (GM-CSF and PGE_1) for 2-4 weeks. These patients were monitored clinically, hematologically and immunologically over the whole treatment phase. Blood samples were taken in the course of the observation time to monitor (leukemia specific) immune cells (flowcytometry, CSA, InCyt).

Results: Ex vivo: Kit-M was shown to give rise to DC/DC_{leu} as well as to improve antileukemic functionality after (T cell enriched) mixed lymphocyte culture with Kit-M treated blood. In vivo: Patients' treatment with Kit-M was shown to be safe, to improve clinical parameters (neutrophils, thrombocytes, and blast counts) and to induce (leukemia specific) immune activation, although effects decreased after discontinuation of Kit-M treatment. Healthy and leukemic VOC results from P1511, P1482 and P1601 could be differentiated during the whole observation time. Moreover, VOC profiles collected from healthy vs. AML breath donors (%sensitivity: 100; %specificity: 100; p = .0001) and VOC prints during chemotherapy vs. during Kit-M therapy (%sensitivity: 100; %specificity: 100; p = .0006) were significantly different.

Conclusions: Kit-M was a safe clinical drug, that produced DC/DC_{leu} and improved anti-leukemic responses with an activating effect on adaptive and innate (leukemia specific) immunoreactive cells ex vivo and in vivo in patients with AML. Breath profiling using an eNose might qualify as a diagnostic tool to detect residual disease and to deduce a VOC based, disease-related monitoring strategy- without need of collecting VOCs directly via eNose.

Disclosure: Modiblast Pharma GmbH (Oberhaching, Germany) holds the European Patent 15 801 987.7-1118 and US Patent 15-

517627 'Use of immunomodulatory effective compositions for the immunotherapeutic treatment of patients suffering from myeloid leukemias', with whom H.M.S. is involved with.

19 - Acute Leukaemia

P015

VENETOCLAX AND HYPOMETHYLATING AGENTS FOLLOWED BY ALLOGENEIC STEM CELL TRANSPLANTATION IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

Christina Rautenberg[1], Matthias Stelljes[2], Fabian Acker[3], Udo Holtick[4], Edgar Jost[5], Christoph Schliemann[2], Anja Ragette[1], Jennifer Kaivers[1], Nina Neuendorff[1], Maher Hanoun[1], Laura K. Schmalbrock[6], Krishan Braitsch[7], Mareike Verbeek[7], Katharina Goetze[7], Gesine Bug[3], Christian Reinhardt[1], Nicolaus Kröger[8], Thomas Schroeder[1]

[1]University Hospital Essen, Essen, Germany, [2]University Hospital Muenster, Muenster, Germany, [3]University Hospital Frankfurt, Frankfurt, Germany, [4]University Hospital Cologne, Cologne, Germany, [5]University Hospital Aachen, Aachen, Germany, [6]Charite Berlin, Berlin, Germany, [7]TU Munich, Munich, Germany, [8]University Hospital Hamburg, Hamburg, Germany

Background: So far, it was a treatment paradigm to induce remission in patients with either newly diagnosed (ND) or relapsed/refractory (R/R) AML prior allo-SCT using intensive therapies with anthracyclins in combination with low- or intermediate to high-dose cytarabine. For AML patients ineligible for intensive therapy, the combination of HMA and Venetoclax (VEN) has become the new treatment standard due to high and rapidly achieved remission rates and a favorable toxicity profile. These properties make this combination also attractive for frontline induction of ND-AML or as salvage therapy in R/R-AML patients with borderline fitness to tolerate and/or limited chance to achieve remission by intensive therapy. Considering the limited evidence from the literature so far, we here report our multi-center experience of allo-SCT after HMA/VEN-based therapy.

Methods: We retrospectively analyzed ND and R/R AML patients, who had received HMA/VEN therapy followed by first allo-SCT at 8 German centers from 2021 to 2022, regarding outcome after transplant. The study was approved by the ethics committee of University Duisburg/Essen (approval number: 22-10708-BO) and all patients gave written informed consent for scientific use of their data.

Results: Eigthy-six patients (median 64 years, 15 to 76) with ND (n = 33, 38%) or R/R (n = 53, 62%) AML (ELN 2022 genetic risk int/adv 86%) were treated with a median of 2 cycles HMA/VEN (1 to 5). Overall response rate (CR/CRi, MLFS) in the entire cohort was 69% with no difference between patients with ND and R/R AML (76% vs. 63%, p = 0.22). MRD was not detectable prior transplant in 50% of responders. Allo-SCT using PBSC (n = 83, 99%) or BM (n = 1, 1% missing n = 2) from related (n = 14, 17%), unrelated (n = 56, 66%) or haploidentical donor (n = 14, 17%, missing n = 2) was performed in median 88 days (17 to 481) after start of HMA/VEN. RIC was used in 91% including 24% receiving sequential conditioning. Median follow-up from start of HMA/VEN was 15 months and from allo-SCT 11 months, respectively. The estimated 1-year-OS probability after allo-SCT is 60% with no significant difference between patients with ND and those with R/R AML (50% vs. 67%, p = .54). However, 1-year-OS after transplant was significantly higher in patients transplanted in remission (72% vs. 33%, p = .001), mainly driven by R/R patients achieving remission prior transplant (1-year-OS 92%). In patients with remission prior transplant OS did not differ between MRD negative and positive patients (85% vs. 71%, p = .98). A total of 25 patients (29%) relapsed after allo-SCT and a total of 31 patients (36%) have died due to relapse (n = 21) or treatment-related toxicity (n = 10). The estimated 1-year-RFS probability was 54% with no significant difference between ND and R/R patients (46% vs. 60%, p = 0.46). Again, RFS significantly differed between patients in remission and with active disease at transplant (66% vs. 28%, p = 0.002), but not between MRD negative and positive patients (73% vs. 66%, p = 0.69).

Conclusions: Treatment with HMA/VEN either as induction or salvage therapy in ND or R/R AML leads to reasonable remission rates facilitating allo-SCT with promising survival in this elderly high-risk population. This warrants confirmatory prospective investigation in larger cohorts with longer follow-up.

Clinical Trial Registry: not applicable

Disclosure: no COI

19 - Acute Leukaemia

P016

OUTCOMES OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT IN PATIENTS WITH *WT1* MUTATED MYELOID NEOPLASMS

Anmol Baranwal[1], Rami Basmaci[1], Rong He[1], David Viswanatha[1], Patricia Greipp[1], James Foran[2], Jeanne Palmer[3], William Hogan[1], Mark Litzow[1], Abhishek Mangaonkar[1], Mithun Shah[1], Aref Al-Kali[1], Hassan Alkhateeb[1]

[1]Mayo Clinic, Rochester, United States, [2]Mayo Clinic, Jacksonville, United States, [3]Mayo Clinic, Phoenix, United States

Background: Mutation in *Wilms' Tumor 1* (*WT1*) gene in patients with acute myeloid leukemia (AML) has been associated with a poor prognosis. The primary objective of this study was to describe allogeneic stem cell transplant (alloSCT) outcomes and assess prognostic factors in patients with *WT1* mutated (m*WT1*) myeloid neoplasms.

Methods: We retrospectively reviewed patients with m*WT1* myeloid neoplasms who underwent alloSCT. Kaplan–Meier and log-rank tests were used to estimate OS. Post-transplant non-relapse mortality (NRM) and relapse incidence (RI) was calculated using competing risk analysis. Factors with $P < 0.10$ in univariate analysis were included in multivariate analysis. Genes/co-mutations were analyzed if they were present in at least 10% ($n \approx 3$) patients. R 4.2.0 (R Foundation for Statistical Computing) was used for statistical analyses.

Results: Thirty-two patients (24 (75%) AML, 3 (9.4%) MDS and 5 (15.6%) others) were evaluated. Median age at alloSCT was 45 years (IQR 33-62 years). Among patients with AML, 4 (16.7%) were favorable, 9 (37.5%) intermediate, and 11 (45.8%) adverse risk disease. Twelve (37.5%) patients had multiple WT1 mutations (mm*WT1*). Two hotspots in exon 4 were found: 1. codons 301-303 [7 (21.9%) patients], and 2. codons 312-314 [13 (40.6%) patients]. Compared to single m*WT1*, a higher proportion of patients with mm*WT1* had a mutation in one of the hotspot regions (35% *vs*. 91.7%, $P = 0.006$): 6 (50%) had mutation among codons 301-303 ($P = 0.01$), while 5 (41.7%) had mutation among codons 312-314 ($P = 0.23$). Median *WT1* VAF was 31% (IQR 12-42%).

The cumulative incidence of NRM was 6.3% at 100 days, 13.2% at 1 year and 17.9% at 3 years after alloSCT. Cumulative RI was 18.8% at 100 days, 49.2% at 1 year and 55.8% at 3 years after alloSCT.

Patients with mm*WT1* had higher RI at 100 days (33.3% *vs*. 10%, $P = 0.12$), 1 year (75% *vs*. 35.6%, $P = 0.04$) and 3-years (87.5% *vs*. 35.6%, $P = 0.01$) post-transplant. Multivariate analysis showed that mm*WT1* was associated with increased risk of post-transplant relapse (HR 6.12, 95% CI 2.03-18.4, $P = 0.001$). Among the 9 patients with mm*WT1* who relapsed, 2 were alive at 3-years post-alloSCT (**Table 1**).

OS at 3-years post-transplant was similar among patients with AML *vs*. other, non-AML, diseases (median OS 1.45 *vs*. 1.20 years, $P = 0.59$). Among the patients with mutations in codons 312-314, 3-year RI was 61.5%, compared to 53.9% for the rest of the cohort ($P = 0.64$). However, all the patients with codon 312-314 mutations who relapsed, died within 3 years of alloSCT, and codon 312-314 mutations were associated with worse 3-year post-alloSCT survival (median 0.8 *vs*. 1.9 years, $P = 0.03$). Multivariate analysis identified the presence of a m*WT1* in codons 312-314 as an independent risk factor for 3-year post-alloSCT OS (HR 4.15, 95%CI 1.43-12.01, $P = 0.009$).

Table 1. Characteristics and outcomes of patients with *WT1* mutated myeloid neoplasms.

Variable	Multi-mutated WT1 (mmWT1)		P-value
	No (N = 20)	Yes (N = 12)	
Complete remission at alloSCT			
No	2 (10.0%)	2 (16.7%)	1
Yes	17 (85.0%)	10 (83.3%)	
Conditioning intensity			
MAC	12 (60.0%)	7 (58.3%)	1
RIC	7 (35.0%)	5 (41.7%)	
Grade 2-4 acute GVHD			
No	17 (85.0%)	10 (83.3%)	1
Yes	3 (15.0%)	2 (16.7%)	
Grade 3-4 acute GVHD			
No	13 (65.0%)	12 (100%)	0.06
Yes	7 (35.0%)	0 (0%)	
Chronic GVHD			
None	17 (85.0%)	10 (83.3%)	0.83
Mild	1 (5.0%)	0 (0%)	
Moderate	1 (5.0%)	1 (8.3%)	
Severe	1 (5.0%)	1 (8.3%)	

Conclusions: m*WT1* MN is associated with high risk of relapse post-transplant, especially in patients with multi-m*WT1*. Moreover, patients with mutations in hotspot codon 312-314 of exon 4 have inferior survival post-alloSCT. Further studies are needed to validate these findings.

Disclosure: Nothing to declare

19 - Acute Leukaemia

P017

VENETOCLAX COMBINED WITH LOW DOSE CYTARABINE AND ACTINOMYCIN D FOR RELAPSED ACUTE MYELOID LEUKEMIA OR MYELODYSPLASTIC SYNDROME WITH EXCESS BLASTS-2 AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

Andrius Žučenka[1], Dominika Vasilevska[1], Vilmantė Vaitekėnaitė[1], Igoris Trociukas[1], Regina Pileckytė[1], Rita Čekauskienė[1], Valdas Pečeliūnas[1], Artūras Slobinas[1], Renata Jucaitienė[1], Inga Šlepikienė[1], Linas Davainis[1], Adomas Bukauskas[1], Mindaugas Stoškus[1], Eglė Gineikienė[1], Vaidas Dirsė[1], Rimvydas Norvilas[1], Ugnė Ringelevičiūtė[1], Kazimieras Maneikis[1], Lukas Kevličius[1], Birutė Davainienė[1], Rūta Čepulytė[1], Roberta Petrauskaitė[1], Agnė Šiaudinienė[1], Tomas Daukšas[1], Karolis Šablauskas[1], Emilė Žučenkienė[1], Rūta Semaškevičienė[1], Indrė Klimienė[1], Andrius Degulys[1], Skirmantė Černauskienė[1], Austėja Dapkevičiūtė-Purlienė[1], Sima Pakštytė-Danėlienė[1], Ilma Tavorienė[1], Lina Kryžauskaitė[1], Guoda Daukėlaitė[1], Laimonas Griškevičius[1]

[1]*Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania*

Background: Despite the recent advancement in acute myeloid leukemia (AML) therapy, almost half of the allotransplanted patients relapse and face poor prognosis. Promising results of various Venetoclax-based salvage therapies for relapsed AML or Myelodysplastic Syndrome with Excess Blasts-2 (MDS-EB2) in the post-allogeneic stem cell transplantation (alloSCT) setting have been published. However, the highest response rates and improved survival were demonstrated mainly after intensive chemotherapy and Venetoclax combination regimens which are highly myelosuppressive and can result in excessive toxicity, especially in the post-alloSCT patients.

Methods: We performed an observational, retrospective, single-center study. The patients were older than 18 years of age and had a morphologically relapsed AML or MDS-EB2 post-alloSCT. The salvage ACTIVE regimen consisted of either 1 or 2 cycles of Venetoclax 600mg/d from D1 up to D28 + Cytarabine 20mg/m^2 D1-10 + Actinomycin D 12.5mcg/kg D1-3. The number of Venetoclax days per cycle was adapted individually based on the early bone marrow evaluations and toxicity but could not exceed 28 days per cycle. Concomitant Gilteritinib or Trametinib was administered in 2 cases harboring *FLT3* or *KRAS* mutations. Responders proceeded to either second alloSCT or continued maintenance therapy with Venetoclax 600mg/d (D1-D14), Cytarabine 20mg/m^2 (D1-5, or D1-10), and concomitant DLI in the absence of GVHD. We evaluated patients' characteristics, composite CR (CRc = CR + CRi + CRp), overall response (ORR = CRc + MLFS), measurable disease negativity (MRD) rates, overall survival (OS), relapse-free survival (RFS) for responders, Grade 4-5 CTCAE v5.0 non-hematological toxicity, mortality rates within 60 days.

Results: 27 patients had been enrolled of whom 24 (89%) had AML, whereas 3 (11%) had MDS-EB2. 52% (14/27) were male, the median age was 59 (20-74) years and the median ECOG was 1 (0-3). 59% (16/27) of patients had secondary AML or MDS-EB2. 78% (21/27) of patients had been stratified to the adverse ELN2022 risk group. 41% (11/27) of cases had adverse cytogenetics of which 26% (7/27) were identified as complex-monosomal karyotypes. 81% (22/27) of patients had received intensive chemotherapy, 15% (4/27) had prior HMA exposure, and 19% (5/27) had previously received Venetoclax. The median number of previous therapy lines was 1 (1-5). RIC was used in 85% (23/27) of patients. The median time from alloSCT to relapse was 203 days (48-1215). The ORR of the ACTIVE regimen was 70% (19/27). The CRc rate was 67% (18/27), and the CR rate was 59% (16/27). MRD negativity was achieved in 56% (10/18) of CRc cases. 74% (14/19) of responders proceeded to maintenance therapy, 15% (3/19) underwent the second alloSCT, whereas 11% (2/19) relapsed prior to subsequent therapy. The median OS was 10.1 months (Figure 1A), and the median RFS was 8 months (Figure

1B). D30 and D60 mortality rates were 4% (1/27) and 7% (2/27), respectively. Both deaths were related to AML progression. Efficacy and toxicity results are summarized in Table 1.

Figure 1. Overall and relapse-free survival

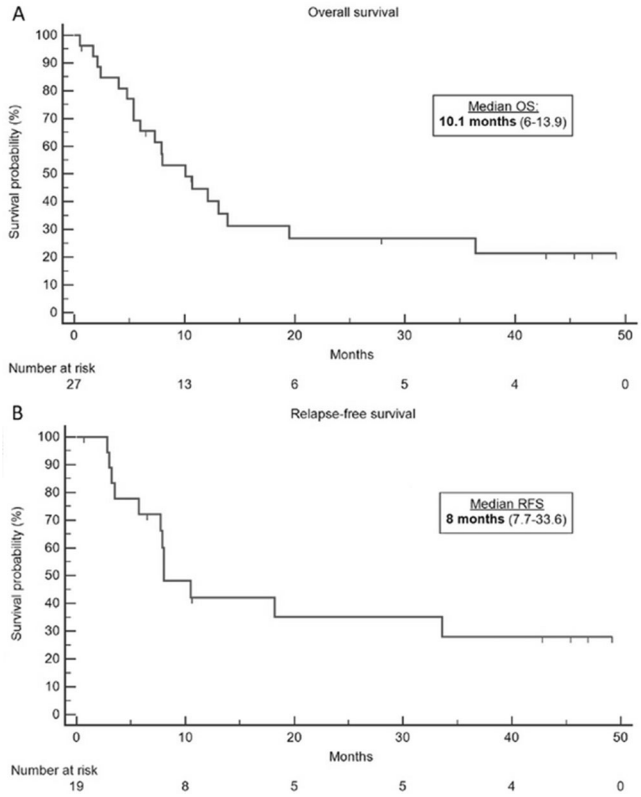


Table 1. Efficacy and toxicity

Response evaluation	
Overall response rate	70% (19/27)
Cumulative CR rate	67% (18/27)
CR	59% (16/27)
CRp	7% (2/27)
MLFS	4% (1/27)
Refractory/progressive disease	30% (8/27)
MRD negativity in CRc patients	56% (10/18)
Toxicity	
Grade 4 non-hematological toxicity	7% (2/27)
Treatment-related deaths	0
Deaths within 60 days due to progressive disease	7% (2/27)

Conclusions: In the real-life setting, the ACTIVE regimen demonstrates promising anti-leukemic efficacy with manageable toxicities in AML and MDS-EB2 patients relapsing post-alloSCT.

Clinical Trial Registry: Observational trial No.2019/2-1088-591 approved by Vilnius Regional Biomedical Research Ethics Committee.

http://bioetika.sam.lt/index.php?1444926469

Disclosure: **Funding:** none.

Disclosures:

Žučenka: *Abbvie:* Consultancy, Honoraria, Travel Expenses; *Astellas:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Travel Expenses; *Pfizer:* Consultancy.

Pileckytė: *Abbvie:* Consultancy, Honoraria, Travel Expenses; Griškevičius: *Miltenyi Biomedicine:* Membership on an entity's Board of Directors or advisory committees.

19 - Acute Leukaemia

P018

INCREASED RELAPSE OF AML WITH HIGHER CYCLOSPORINE-A CONCENTRATION FIRST MONTH AFTER ALLOGENEIC STEM CELL TRANSPLANTATION WHEN COMBINED WITH ANTI-THYMOCYTE GLOBULIN

Mikael Lisak[1], Malin Niklasson[1], Róbert Pálmason[2], Per-Ola Andersson[1], Jan-Erik Johansson[1], Stig Lenhoff[2], Markus Hansson[1]

[1]University of Gothenburg, Gothenburg, Sweden, [2]University of Lund, Lund, Sweden

Background: Cyclosporine-A (CsA) is a well established prophylaxis against acute graft-versus-host disease (aGvHD) after allogeneic stem cell transplantation (HSCT). Higher CsA concentration, especially at time of engraftment, has been shown to reduce presence and severity of aGvHD. Some studies have shown correlation between higher CsA concentration and relapse of hematological malignancies.

There is no consensus on how early CsA concentration affects incidence of relapse of acute myeloid leukemia (AML) when combined with antithymocyte globulin (ATG). European Society for Blood and Marrow transplantation (EBMT) recommends CsA target serum concentration 200-300 µg/L during the first month post-HSCT as aGvHD prophylaxis, without distinction concerning parallell immunosuppressive drugs, e.g. ATG.

The aim of this study was to investigate whether a median CsA concentration the first month post-HSCT of >200 µg/L (CsA_{high}) compared to ≤200 µg/L (CsA_{low}), increases the risk of AML relapse, when combined with ATG.

Methods: We collected data from 157 consecutive patients with AML who underwent HSCT 2010-2016 at three Swedish transplant centers. All patients were transplanted with unrelated donors (URD) and received ATG, besides a a short course of intravenous methotrexate.

CsA exposure was based on median concentration the first month post-HSCT of each patient.

Exclusion criterias were haploidentical donor, cord blood cells, conditioning with total lymphoid irradiation, alemtuzumab in conditioning or CsA treatment shorter than 30 days.

The risk of relapse at transplantation was categorized into low, intermediate or high risk according to the Swedish National Guidelines for AML.

The primary endpoint was the cumulative incidence of relapse at 60 months after HSCT.

Secondary endpoints were acute (aGVHD), chronic GvHD (cGVHD) and OS.

The study was approved by the Regional Ethic Review Board of Gothenburg (Dnr 144-18).

Results: The cumulative incidence of relapse up to 60 months in the $CsA_{high\ and}$ CsA_{low} group was 50% (95% CI, 38 – 62) and 32% (95% CI, 14 – 36; $p = 0.016$), respectively. In univariable analysis, CsA_{high} vs. CsA_{low} ($p = 0.028$), 10-unit increase of CsA as a continuous variable ($p = 0.017$) and high risk disease ($p = 0.003$) were associated with cumulative incidence of relapse up to 60 months. The results remained after adjusting for disease risk. The mean CsA concrentation was lower amongst patients without

relapse compared to those with relapse; 190.5 µg/l vs. 200.9 µg/l, (SE 3.78; 95% CI, -17.86 – -2.93; p = 0.0066).

When analyzing the CsA concentration as a non-linear risk factor, the chosen cut-off, 200 µg/L, seemed to be appropriate.

Relapse as cause of death was more frequent in the CsA_{high} group (p = 0.0051). No significant differences were seen in rates of aGvHD, cGvHD or overall survival. Severe and life threatening aGvHD and GvHD-related deaths were more frequent in the CsA_{low} group, but the numbers to few to render significancy.

Table. Background characteristics (n = 157)

No (%)	CyA conc ≤200µg/L n = 87	CyA conc >200µg/L n = 70	P value
Female gender	38 (44)	32 (46)	*p = 0.80*
Disease risk			
Intermediate risk	26 (30)	21 (30)	*p = 0.99*
High risk	61 (70)	49 (70)	
Stem cell source			
Bone marrow	8 (9)	4 (6)	*p = 0.67*
Peripheral blood stem cells	79 (91)	66 (94)	
HLA ≤ 7/8	8 (9)	7 (10)	*p = 0.88*
CMV IgG-pos recipients	65 (74)	48 (69)	*p = 0.33*
Conditioning			
Reduced conditioning	52 (60)	32 (46)	*p = 0.079*
Myeloablative conditioning	35 (40)	38 (54)	
Age at alloSCT, median (range), yrs	56 (19 – 71)	51.5 (18 – 71)	
Follow-up time, median, months	57.5 (95% CI, 52.9-64.6)		

Conclusions: Our study, only including AML patients, shows that higher CsA exposure the first month post-HSCT is associated with increased relapse incidence, when combined with ATG. This has earlier been shown with alemtuzumab as T-cell depletion. The findings suggest that the EBMT recommendations concerning intended CsA concentration the first month should be nuanced, at least when treating T-cell depleted AML patients.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P019

GENOMIC LANDSCAPE OF MYELOID SARCOMA: A PLEA FOR BETTER MOLECULAR CHARACTERIZATION AND A ROAD MAP FOR TARGETED THERAPIES

Clément Collignon[1], Anne-Béatrice Notarantonio[1], Gabrielle Roth Guepin[1], Caroline Bonmati[1], Maud D'Aveni[1], Arnaud Campidelli[1], Charline Moulin[1], Caroline Jacquet[1], Cécile Pochon[1], Marc Muller[1], Marion Divoux[1], Francesca Ferraro[2], Pierre Feugier[1], Marie Thérèse Rubio[1], Francesco Grimaldi[3], Simona Pagliuca[1]

[1]CHRU de Nancy, Vandœuvre-lès-Nancy, France, [2]Washington University in St. Louis, St. Louis, United States, [3]University Federico II of Naples, Naples, Italy

Background: Myeloid sarcoma (MS) constitutes a rare, high-risk form of acute myeloid leukemia (AML), characterized by infiltration and destruction of otherwise normal tissues by leukemic blasts. This entity could occur de novo or at leukemia relapse, after chemotherapy or allogeneic hematopoietic cell transplantation, and may be isolated or concomitant to bone marrow (BM) infiltration. Small case series exploiting paired high-throughput sequencing of solid lesions vs BM show the presence of complex clonal architectures, sometimes divergent from the genetic structure of BM leukemia and, although some recurrent somatic lesions have been identified, clear genomic correlations are only putative and not investigated in larger cohorts with comparative studies.

Methods: Here we assembled a large metanalytic cohort of 70 patients with paired MS/BM molecularly profiled samples, recruited from our institutions (Nancy University Hospital and Federico II of Naples) and from 10 public studies. https://www.ncbi.nlm.nih.gov/sites/myncbi/simona.pagliuca.1/collections/62441058/public/

Results: In patients with MS, solid lesions, compared to BM, displayed a higher complexity due to an increased mutational burden (average mutational rate of 2.75 vs 1.9, p = 0.011), and a higher variant allele frequency (Median 33 vs 19%, p = 0.008). When paralleled with BM, mutational landscape of MS was characterized by a different configuration of myeloid lesions with enrichment in NPM1 (36 vs 17%), FLT3 (29 vs 15%), NRAS (19 vs 12%) and KRAS (9 vs 2%) mutations. The acquisition of some of these lesions in extramedullary localizations, initially not present in BM, occurred in 53% of the patients and concerned particularly NPM1 and FLT3 mutations. Intriguingly, some patients acquiring NPM1 in MS, presented with a complex karyotype AML, underlying the genomic instability of these disorders as compared to classical NPM1 mutated AML, usually associated with normal cytogenetics.

When comparing this mutational background with an assembled non-MS multi-study AML cohort,https://bit.ly/3hAncqy the enrichment in NPM1 mutations in MS lesions was more evident (p = 0.003). We also noticed a slight increment of co-occurrence of mutations in NPM1 and RAS genes (20% in MS vs 14% in non-MS AML vs 11% in BM of MS patients), while lesions in FLT3 and RAS genes were in all cases mutually exclusives, likely for overlapping deleterious effects on cellular functions.

Since leukemia sanctuaries in solid organs are supposed to exist because of failure of immune control, we reasoned that altered NPM1/FLT3/RAS pathways could share some molecular features prone to tissue invasion and immune escape. We explored this possibility at genomic level, by investigating the patterns of co-mutations in patients with myeloid neoplasms harboring lesions in these genes and profiled with whole exome sequencing (N = 8606). https://bit.ly/3W8CCB8 Gene enrichment analysis of the "altered" vs "unaltered" group showed an increased occurrence of mutations in genes involved in mTOR signaling, interferon alpha and gamma response, hypoxia and unfolded protein response that could play a role in the escape from anti-tumor surveillance in these molecular subsets of AML.

Conclusions: This comparative study sheds light on the unique molecular features of MS, pleading for the need to molecularly characterize all solid lesions occurring in AML context, and to explore targeted therapies in this high-risk category of patients.

Disclosure: No conflict of interest to disclose

19 - Acute Leukaemia

P020

CHIDAMIDE MAINTENANCE THERAPY FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR T CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Xing-Yu Cao[1], De-Yan Liu[1], Yue Lu[1], Jian-Ping Zhang[1], Jia-Rui Zhou[1]

[1]Hebei Yanda Lu Daopei Hospital, Langfang, China

Background: Relapse following allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a major challenge for T cell acute lymphoblastic leukemia (T-ALL) patients. Epigenetic abnormalities are common and histone deacetylase (HDAC)1 and HDAC4 are frequently overexpressed in T-ALL tumor cells compared to normal bone marrow samples. Chidamide, approved in China in 2014, is an HDAC inhibitor that has anti-tumor activity and the ability to enhance immune cell-mediated tumor cell cytotoxicity. Here, we explored whether Chidamide maintenance therapy after allo-HSCT for T-ALL patients is safe, could reduce relapse, and improve survival.

Methods: From June 2017 to May 2020, 12 patients with T-ALL who underwent transplantation at the Hebei Yanda Lu Daopei Hospital and received Chidamide as maintenance therapy post-HSCT were analyzed. Maintenance treatment with Chidamide was initiated when patients met the following criteria: 1) complete remission (CR) status prior to transplantation; 2) post-transplant hematological recovery and minimal residual disease (MRD) negativity.

Results: One patient was female (8.3%) and the median patient age was 14 years (range: 7-37). Five patients (41.7%) had positive fusion genes, including 1 (8.3%) with P2RY8-CRLF2, 1 (8.3%) with SET-CAN and 5 (25%) with STIL-TAL1 fusion genes. Before receiving allo-HSCT, 1 patient (8.3%) was in MRD-positive CR and the other 11 (91.7%) were in MRD-negative CR. Nine patients (75%) received haplo-identical HSCT and the other 3 (25%) underwent sibling-identical HSCT. All patients received total body irradiation (TBI)-based conditioning regimens. The median time of neutrophil and platelet engraftment was 12 days (11-19) and 12 days (7-37), respectively. Post transplantation, the median time to Chidamide administration was 183 days (range: 30-532). The dose of Chidamide ranged from 5 mg once a week to 15 mg twice a week, depending on the patient's weight, hematopoietic functions and other conditions. The median duration of Chidamide therapy was 358 days (range: 74-762). The most common adverse event was a decrease in blood count. The 6-month cumulative relapse incidence (RI) was only 8.3% (95%CI,1.3-54.4%), and the 1-year, 2-year and 5-year RI were 16.7% (95%CI,4.7-59.1%), 25% (95%CI,9.4-66.6%) and 25% (95%CI,9.4-66.6%), respectively. The 2-year overall survival (OS) for all patients was 83.3% (95% CI,58.2-98.1%) and the 5-year OS was 66.7% (95%CI,38.8-89.3%). Two years post-transplant, no relapses occurred. The 2-year and 5-year leukemia free survival (LFS) were 66.7% (95% CI,38.8-89.3%).

The SET-CAN or STIL-TAL1 fusion genes are indicators of poor prognosis based on published papers. The 2 patients with STIL-TAL1 remained leukemia-free up to the last follow-up, and the patient with SET-CAN relapsed on day 389 post-transplant. Four patients died from diffuse alveolar hemorrhage (n = 1) and relapse (n = 3).

Conclusions: Our preliminary study showed that Chidamide maintenance therapy post allo-HSCT was safe for T-ALL patients, which did not increase adverse event frequency. Chidamide has the potential to improve T-ALL patient survival following allo-HSCT. Given the small cohort enrolled, long-term survival follow up is needed as well as additional studies. As we saw an increase in RI after six months and an RI plateau at 2 years after transplantation, we recommend initiation of Chidamide within six months following transplantation.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P021

AUTOLOGOUS STEM CELL TRANSPLANTATION FOR ADULTS WITH PHILADELPHIA-NEGATIVE ACUTE LYMPHOBLASTIC LEUKEMIA IN FIRST COMPLETE REMISSION. A STUDY BY THE ACUTE LEUKEMIA WORKING PARTY OF THE EBMT

Ryszard Swoboda[1], Myriam Labopin[2], Sebastian Giebel[1], Johan Maertens[3], Elena Parovichnikova[4], Annoek E.C. Broers[5], Jane Apperley[6], Grzegorz Helbig[7], Anna Paola Iori[8], Ludek Raida[9], Alessandro Rambaldi[10], Denis Caillot[11], Jiri Mayer[12], Dominik Wolf[13], Mustafa Ozturk[14], Mahmoud Aljurf[15], Marie Thérèse Rubio[16], Norbert Claude Gorin[17], Francesco Lanza[18], Mohamad Mohty[19], Fabio Ciceri[20]

[1]Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland, [2]ALWP of the EBMT Paris Office; Sorbonne University, Saint Antoine Hospital, Paris, France, [3]University Hospital Gasthuisberg, Leuven, Belgium, [4]National Research Center for Hematology, Bone Marrow Transplantation, Moscow, Russian Federation, [5]Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, Netherlands, [6]Imperial College, Hammersmith Hospital, London, United Kingdom, [7]Silesian Medical Academy, Katowice, Poland, [8]Univ. La Sapienza, Rome, Italy, [9]Olomouc University Hospital, Olomouc, Czech Republic, [10]University of Milan and ASST Papa Giovanni XXIII, Bergamo, Italy, [11]Hopital d`Enfants, Dijon, France, [12]University Hospital Brno, Brno, Czech Republic, [13]University Hospital Innsbruck, Innsbruck, Austria, [14]GATA BMT Center, Gülhane Military Medical Academy, Ankara, Turkey, [15]King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, [16]CHRU Nancy, Vandoeuvre les Nancy, Nancy, France, [17]Sorbonne University, Hôpital Saint-Antoine, Paris, France, [18]Romagna Transplant Network, Ravenna, Italy, [19]Sorbonne University, Hospital Saint Antoine, Paris, France, [20]San Raffaele Scientific Institute; Vita-Salute San Raffaele University, Milan, Italy

Background: The role of autologous stem cell transplantation (ASCT) in patients with Philadelphia-negative acute lymphoblastic leukemia (Ph- ALL) remains controversial. According to results of the prospective UKALLXII/ECOG E2993 study, ASCT should not substitute consolidative chemotherapy [Blood 2008:111:1827-33]. However, its role as late intensification in the era of routine testing of minimal residual disease has not been evaluated. The aim of this study was to analyze results of ASCT for adults with ALL and to identify prognostic factors.

Methods: Overall, 700 adult patients with Ph- ALL transplanted in first complete remission (CR1) between years 1999-2020 were included in this retrospective, multicenter study. Comparative analysis was performed between patients transplanted in 1999-2009 (n = 490) and 2010-2020 (n = 210).

Results: In the whole study population median patient age was 31.9 years (68% male). B-ALL and T-ALL was diagnosed in 35% and 65%, respectively. The median time from diagnosis to ASCT was 6.6 months. Total body irradiation (TBI)-based conditioning was used in 43%. Among 190 patients with available data, negative MRD status was reported in 167 (88%) cases.

The graft failure was observed in 1.3% of subjects. The probabilities of overall survival (OS), leukemia-free survival (LFS) at 2 years were 67% and 56%; relapse incidence (RI) and non-relapse mortality (NRM) were 39% and 5%, respectively. The most frequent causes of death were original disease (66%) and infections (13%). T-ALL was associated with lower RI (35% vs. 47%, p = 0.008) and higher LFS (60% vs. 49%, p = 0.01) at 2 years when compared to B-ALL. The older patient age (≥ 32 years) was associated with increased NRM (6.6% vs. 2.9%, p = 0.03) and decreased OS (63% vs. 71%, p = 0.02). In the multivariate analysis, the risk of relapse was reduced for T-ALL compared to B-ALL (hazard ratio (HR) = 0.72, p = 0.02) and with longer interval from diagnosis to ASCT (per month, HR = 0.95, p = 0.03). The risk of NRM was increased with patient age (per 10 years, HR = 1.38, p = 0.01). A chance of LFS was improved with longer interval from diagnosis to ASCT (HR = 0.95, p = 0.02), while a chance of OS was reduced with increasing patient age (HR = 1.14, p = 0.01). No impact of the study period (1999-2009 vs. 2010-2020) as well as the type of conditioning (TBI vs.

chemotherapy alone) could be demonstrated with regard to any of the study end-points. MRD status prior to transplantation could not be included in the analysis due to insufficient data. Better results of T-ALL compared to B-ALL were demonstrated in the analysis restricted to patients treated between years 2010-2020 in terms of reduced risk of relapse (HR = 0.51, p = 0.03) and improved LFS (HR = 0.54, p = 0.02). LFS and OS rates for T-ALL in this period were 68% and 75% at 2 years, respectively.

Conclusions: Results of autologous stem cell transplantation in adults with Ph- ALL, especially for those with T-ALL are encouraging. Late intensification may be a valuable option for T-ALL as no humoral or cellular immunotherapies have been approved so far for this population. The latter, however, requires verification in prospective trials.

Disclosure: Nothing to declare

19 - Acute Leukaemia

P022

POTENTIAL MODIFICATION OF DYSREGULATED EXPRESSIONS OF INHIBITORY CHECKPOINT (ICM) AND THEIR LIGANDS ON T CELLS AND BLASTS IN AML RELAPSES AFTER STEM CELL TRANSPLANTATION (SCT)

Xiaojia Feng[1], Giuliano Filippini Velázquez[2], Sophia Bohlscheid[1], Christoph Schmid[2], Helga Schmetzer[1]

[1]Munich University Hospital, Munich, Germany, [2]Augsburg University Hospital, Augsburg, Germany

Background: Dysregulation of inhibitory checkpoint molecule (ICM) and ICM ligand (ICML) expression on T cells and leukemic blasts may represent a mechanism of immune-escape and clinical relapse of acute myeloid leukemia (AML) blasts after allogeneic stem cell transplantation (SCT). In vitro, culture of AML blasts in the presence of GM-CSF and PGE1 (KitM) can improve presentation of leukemic antigens and blast lysis by generation of dendritic cells of leukemic origin (DCleu). The effect of KitM based DCleu on ICM expression and cellular functions is unknown.

Methods: Flow cytometry analyses of expressions of ICM (PD-1/CTLA-4) and ICML (CD86/PD-L1/PD-L2) were performed on uncultured mononuclear cells (MC) in peripheral blood (PB) and bone marrow (BM) samples of 11 AML-patients at relapse after SCT and from PB of 7 healthy individuals (H).

Dendritic cells (DC) and DCleu were generated in culture in presence or absence of Kit-M (GM-CSF + PGE-1) followed by mixed lymphocyte culture (MLC) with patients' uncultured T-Cells. After MLC, immune-activation and functionality (degranulation, intracellular cytokine production, lysis of the original blasts) were assessed. Clinically, all patients had received hypomethylating agents/Venetoclax (HMA/VEN) as salvage therapy. ICM/ICML expressions on T-cells and blasts were correlated with ex-vivo blast-lysis and patients' clinical response.

Results: **High expressions of ICM/ICML on uncultured blasts and T cells in AML:** Patients presented with varying, but high frequencies of blasts co-expressing CD86/CTLA-4/PD-1(mean% (range): 44 (5.2-72)/49.7(2.73-99.67)/45.7(1.94-97.3)) and high frequencies of T-cells co-expressing CTLA-4/PD-1 (mean%(range): 68.9(47.2-86.7)/54.5(16.5-96.9)), whereas frequencies of PD-L1/PD-L2 co-expressing blasts/T-cells were low. T-cells of H-PB showed low expressions of CTLA-4/PD-1/PD-L1/PD-L2. We observed a negative correlation of ICM-expressions on uncultured patient T-cells with clinical response to HMA/VEN therapy.

Downregulated expressions of ICM on T-cells and improved anti-leukemic activities after MLC with Kit-M pretreated *vs.*untreated PBMC: Whereas there was no difference in the expression of ICM/ICML on blasts/DCs after culture with Kit-M when compared to blasts/DCs cultured without Kit-M, co-cultivation of Kit-M pretreated PBMC enriched with PTs' T-cells resulted in reduced frequencies of ICM-expression on T-cells (CTLA-4 in 8/11 cases) after MLC. Increased leukemia specific degranulation, intracellular IFN production and improved blast lysis was found after MLC with *vs.* without Kit-M-pretreated PBMC. Nevertheless, improvement of anti-leukemic activity was negatively influenced by high CTLA-4/PD-1-expression of uncultured T-cells. Interestingly, this correlation was not observed after MLC with Kit-M-pretreated PBMC.

Conclusions: Uncultured T-cells and blasts of AML-PTs relapsed after SCT regularly co-express ICM (CTLA-4/PD-1). ICM expression on T-cells correlated negatively with PTs' response to HMA/VEN and improvement of blast-lysis in a stimulation-based cell culture. Culture of patients' PBMC with KitM did not alter ICM/ICML expression on blasts, whereas expression of CTLA-4 expression on T cells was downregulated after MLC. Functionally, culture with Kit-M improved specific blast lysis and seemed to overcome the negative influence on cellular immune reaction by ICM/ICML expression on blasts and T-cells.

Disclosure: H.M.S. is involved with Modiblast Pharma GmbH (Oberhaching, Germany) that holds the European Patent 15 801 987.7-1118 and US Patent 15-517627 'Use of immunomodulatory effective compositions for the immunotherapeutic treatment of patients suffering from myeloid leukemias',

19 - Acute Leukaemia

P023

COMPARISON BETWEEN TRANSPLANT OUTCOMES AFTER CPX-351 VS OTHER INDUCTION REGIMENS IN NEWLY DIAGNOSED SECONDARY ACUTE MYELOID LEUKEMIA

Gabriele Facchin[1], Eleonora Toffoletti[1], Marta Lisa Battista[1], Michela Cerno[1], Carla Fili[1], Giulia Battaglia[1], Giuseppe Petruzzellis[1], Martina Pucillo[1], Umberto Pizzano[1], Antonella Geromin[1], Renato Fanin[1], Francesca Patriarca[1]

[1]Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy

Background: Allogeneic transplant (HSCT) remains the only curative therapy for secondary acute myeloid leukemia (sAML). Even if there are many evidence that CPX-351 induction has increased the HSCT rate, less is known regarding the impact of this induction regimen on post-transplant outcome.

Methods: In this study we compared outcome of 26 patients with diagnosis of sAML underwent HSCT after CPX-351 induction with an historical cohort of 27 patients receiving other induction regimen.

Results: Between January 2016 and June 2022, 53 patients with newly diagnosis of sAML underwent HSCT at our Center. Median age at transplant was 63 (23-74) years and the male/female sex ratio was 22/31. According to WHO2016 the sAML subtypes were AML with myelodysplasia-related changes/with prior myelodysplasia-MDS-(69%), AML therapy related (12%) or AML secondary to CMML/MPC (19%). Nine patients (17%) had received prior treatment with hypomethylating agents (HMAs) for MDS. Twenty-six patients (46%) received CPX-351 as induction therapy while 27 other regiments (12/27 fludarabine based, 7/27 HMAs ± venetoclax, 6/27 "3 + 7" standard chemotherapy, 1/27 other regimens). Thirteen (24%) patients received HMAs as bridge to transplant. Most patients received a graft from an unrelated donor (58%) following a myeloablative conditioning (58%). Patient and transplant characteristics were well balanced between CPX-351 and historical cohort except for higher proportion of HCT-CI > 2

(p = 0,0254) and higher median CD3+ infused cells from historical cohort (p = 0,0122). Numerically more patients treated with CPX-351 induction achieve a complete remission (CR) before HSCT (65% vs 44%). With a median follow-up of 11 months for the CPX-351 cohort and 23 months for the historical cohort, the median OS since transplant was not reached in the CPX-351 group while it was 16 months (p = 0.11, HR 2.052, 95% CI 0.8685-4.846) in the historical cohort. The 2-year OS is 73% vs 44% (p = 0,1152), respectively. There are no differences in terms of 2-years-progression free survival-PFS-(51% vs 35%; p = 0,2274), 2-years-transplant relate morality-TRM- (19% vs 16%, P = 0,9140), cumulative incidence of acute GVHD (54% vs 61%, p = 0,6967) and relapse rate (31% vs 55%, p = 0,1621). The most common causes of death were disease relapse (CPX-351: 1/26 [4%] vs 12/27 [44%] other regimens) and GVHD complications (4/26 [15%] vs 3/27 [11%]). Age >65 years, hyperleukocytosis at diagnosis and disease status prior to transplant were the only factors that influence 2-yr-OS in univariate analysis. In multivariate analysis only age and disease status influence survival.

Conclusions: In our real-life experience, 2-yr-OS for HSCT after CPX-351 induction was 73% vs 43% for historical cohort (p = 0,1152). No differences were found also in terms of 2-yr-PFS, TRM, incidence of aGVHD or relapse. We confirm that age and pre-transplant disease status are the main factors that impact on survival after HSCT in sAML. A multicenter real-life study, with a larger number of cases, is necessary to better understand the impact of CPX-351 on transplant outcomes.

Disclosure: no one.

19 - Acute Leukaemia

P024

LONG TERM OUTCOME OF ACUTE LYMPHOBLASTIC LEUKEMIA FOLLOWING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION: A 22 YEARS' SINGLE CENTER EXPERIENCE

Mohammad Vaezi[1], Maryam Barkhordar[1], Tannaz Bahri[1], Mohammad Biglari[1], Soroush Rad[1], Sahar Tavakoli[1], Ardeshir Ghavamzadeh[1]

[1]Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran, Tehran, Iran, Islamic Republic of

Background: Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment for acute lymphoblastic leukemia (ALL). As part of the conditioning regimen for ALL patients receiving allo-HCT, total body irradiation (TBI) has been proposed in particular. However, in many countries with insufficient funding, allo-HSCT patients commonly receive conditioning without TBI. This may cause concern for ALL individuals with a higher recurrence risk following allo-HCT. Therefore, the purpose of this study was to evaluate the outcomes of ALL patients who underwent myeloablative TBI-free allo-HCT throughout the previous two decades.

Methods: We retrospectively analyzed the trends of allo-HCT outcomes in 1120 patients who underwent their first allo-HCT for ALL between 2000 and 2022 at our single high-volume tertiary referral center. All recipients of allo-HCT received the same non-TBI myeloablative conditioning (MAC) regimen consisting of Bu (Busilvex) at 3.2 mg/kg i.v. on days − 6 through − 3, and cyclophosphamide 60 mg/kg on days – 3, – 2, followed by a unmanipulated granulocyte-colony stimulating factor (G-CSF)-mobilized peripheral blood stem cell source. The recipients of Haplo and unrelated allo-HCT received rabbit ATG 2.5 mg/kg (on days − 3, − 2, − 1) as a part of conditioning regimen. Post-transplant cyclophosphamide (PTCy) 40 mg/kg was given on days + 3 and + 4, in the haplo-HSCT. The combining ATG and PTCy with adjusted dosages was employed in haplo-HSCT after 2010.

Results: The period was divided into two intervals of before 2010 (D1) and after 2010 (D2) for analysis. The median follow-up times was 116 and 43.7 months for D1 and D2. Five-year overall survival (OS) improved significantly from 38.0% (95% CI: 33.23-42.69) before 2010 to 48.8% (95% CI: 44.28% to 53.21%) after 2010; (P = 0.0002). The three-year relapse incidence improved over the two decades from 53.5% (45.43% to 63.14%) to 38.9% (33.04% to 45.83%); (P = 0.009). However, we did not find any notable differences in non-relapse mortality (NRM) during the two decades. Additionally, in terms of HLA-match status, there was no statistically significant difference in the five-year OS between full matched (44.81%) and mismatched (33.74%) HCT; P = 0.093. In the first decade, relapse was the main cause of mortality, but in the second decade, infectious complications were the leading reason for death.

Patient characteristics by decade		Before 2010	After 2010	Total
Total (Number,%)		424	696	1120
		37.90%	62.10%	100.00%
Remission status	CR1	260	437	697
		37.30%	62.70%	100.00%
	CR2	107	177	284
		37.70%	62.30%	100.00%
	CR > = 3	57	80	137
		41.60%	58.40%	100.00%
Match status	Full match	408	593	1001
		40.80%	59.20%	100.00%
	Mismatch	16	103	119
		13.40%	86.60%	100.00%
Patients Age	<16	83	175	258
		32.20%	67.80%	100.00%
	16-40	311	424	735
		42.30%	57.70%	100.00%
	> = 40	30	97	127
		23.60%	76.40%	100.00%

Conclusions: We discovered that the whole cohort's 5-year OS, when employing a non-TBI preparative regimen, remained at 44.01% (40.68% to 47.25%), which is within the range of 25 to 50% reported in previous research on the 5-year OS of ALL patients undergoing TBI-based allo-HSCT. Our research showed that the 5-y OS for ALL patients treated with the Bu-based, non-TBI MAC regimen has improved over the past 20 years as a result of a decline in the incidence of relapse. Importantly, to improve NRM and improve outcomes going forward, more efficient infectious complication prevention will likely be needed.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P025

SORAFENIB MAINTENANCE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT FOR FLT3+ ACUTE MYELOID LEUKEMIA: A SINGLE CENTER EXPERIENCE

Giuseppe Sapienza[1], Roberto Bono[1], Stefania Tringali[1], Marta Castronovo[1], Lucia Sbriglio[1], Chiara Russo[2], Giulia Maria Camarda[2], Valeria Calafiore[1], Antonino Mulè[1], Caterina Patti[1], Alessandra Santoro[1], Anna Marfia[1], Cecilia Agueli[1], Valentina Randazzo[1], Luca Castagna[1]

[1]Azienda Ospedaliera Ospedali Riuniti Villa Sofia Cervello, Palermo, Italy, [2]Azienda Ospedaliera Universitaria Policlinico 'Paolo Giaccone', Palermo, Italy

Background: Acute myeloid leukemia (AML) relapse is the main cause of death after allogeneic stem cell transplant (allo-SCT). In AML FLT3+, it was shown that Sorafenib (SOR) used as maintenance therapy after allo-SCT, significantly reduces the risk of relapse and death.

Methods: This is a retrospective analysis aimed to evaluate the feasibility, safety and outcome of maintenance with SOR in patients with FLT3+ AML who underwent allo-SCT. The majority of patients received a myeloablative conditioning regimen and peripheral blood stem cells. Donor types were equally distributed between HLAid sibling MUD and haploidentical donors. SOR was started at different time points after allo-SCT based on hematological reconstitution, performance status, infectious complications and disease evaluation. The starting dose was 400 mg/day. For survival analysis we used the Kaplan Meier method. All statistical analyses were performed using NCSS 2019 software.

Results: From 2017 to 2022, 43 patients with FLT3+ AML received allo-SCT. 95% (n = 41) were FLT3 ITD mutated and 5% (n = 2) TKD mutation. Median age was 53 (range 19-71). 62% (n = 27), 14% (n = 6) and 2% (n = 1) of patients had NPM1, IDH2 and DNMT3A mutations, respectively. 95% of patients were in CR (CR1 83%, CR2 9%, CR3 2%) and 80% were MRD negative at time of allo-SCT. 2 patients underwent allo-SCT with active disease. Grade 2-4 acute GVHD incidence was 38%. 51% (n = 22) of patients received SOR. The most frequent reasons for not starting SOR were relapse (19%) and GVHD (9%). Considering patients in CR before allo-SCT (n = 41), 8 patients (19%) relapsed before the start of SOR and median day of relapse was 93 days (range 30-153). Median day to start SOR was 120 days (range 59-279). SOR was discontinued because of adverse events in 18% (2 developed heart toxicity, 1 gastrointestinal toxicity and 1 skin toxicity). With a median follow up of 27 months, 3-year overall survival of the whole cohort was 65% and 90% for patients treated with SOR. No patients relapsed during SOR treatment. 10 patients completed the treatment and the median of SOR exposition was 731 days (range 575-752). 5 patients are still on treatment (median time of SOR exposition 422 days (27-638).

Conclusions: Post-transplantation SOR reduces the risk of relapse in FLT3+ AML. In our experience SOR was well tolerated even if 4 patients stopped the treatment because of toxicity. Early relapse, observed in 19% of patients, mostly in the first 3 months after allo-SCT, was the most important factor that impacted treatment feasibility. This underlines that the timing of SOR start should be as early as possible after allo-SCT.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P026

REDUCING THE DOSE OF BUSULFAN IN TBF CONDITIONIG, FOR AML OVER THE AGE OF 60: IS IT ENOUGH TO REDUCE TRANSPLANT RELATED MORTALITY?

Andrea Bacigalupo[1], Federica Sora[2], Carmen di Grazia[3], Anna Maria Raiola[3], Alida Dominietto[3], Francesca Gualandi[3], Sabrina Giammarco[4], Simona Sica[4], Elisabetta Metafuni[4], Eugenio Galli[4], Emanuele Angelucci[3]

[1]Lazio, Roma, Italy, [2]Andrea Bacigalupo, Roma, Italy, [3]IRCCS Policlinico San Martino IST, Genova, Italy, [4]andrea bacigalupo, Roma, Italy

Background: Transplant related mortlity (TRM) remains an important issue in patients with AML above the age of 60 undergoing an allogeneic hemopoietic stem cell transplant (HSCT). Reduced intensity regimens (RIC) have been used, although the problem is an increased incidence of leukemia relapse. One is therefore confronted with the opposing requirement of reduced intensity conditioning to control toxicity, but maintain some degree of myeloablation to control leukemia. We have used the combination of thiotepa, busulfan, fludarabine (TBF) with 3 days of busulfan (total dose 9.6 mg/kg) (TBF3) for patients under the age of 60. Over the age of 60, and for patients considered unfit, we have reduced the dose of busulfan to 3.2 mg/kgx2 (TBF2).

Methods: We are now reporting 107 patients with remission AML receiving TBF2 compared with 175 remission AML receiving TBF3. Donors were matched siblings, matched unrelated, 7/8 unrelated, and haploidentical.

Patients: All patients had acute myeloid leukemia in first (CR1) or second (CR2) remission. The proportion of CR1 was 75% for TBF3 and 69% for TBF2 ($p = 0.5$). The median age of TBF3 was 46 years (range 18-64), and for TBF2 it was 61 years (31-73) ($p < 0.00001$). HAPLO donors comprised 61% in both groups ($p = 0.9$). And post transplant cyclophosphamide GvHD prophylaxis was used in 71% and 72% of patients respectively ($p = 0.7$).

Results: The 8 years disease free survival (DFS) was 78% and for TBF3 and 42% for TBF2 ($p < 0.0001$). The Overal survival was 82% and 41% ($p < 0.0001$)- You will then ask the question: is this due to more relapse or more TRM in older patients receiving TBF2. The cumulative incidence of relapse at 8 years. was 12% for TBF3 and 16% for TBF2 ($p = 0.5$). The cumulative incidence of TRM at 8 years was 9% for TBF3 and 41% for TBF2 ($p = 0.00001$).

Causes of death were respectively for TBF3 and TBF2 as follows: relapse 7% and 10%; GvHD 3% and 7%; infections 3% and 15%; multiorgan failure 1% and 4%.

Conclusions: We conclude that the reduction of TBF3 to TBF2 for older patients is insufficient to control the toxicity of the conditioning regimen, whereas control of leukemia is satisfactory, and not statistically different from TBF3. The regimen needs to be further reduced in AML patients over the age of 60. Alternative options could be one day of busulfan (TBF1) with the addition of total marrow irradiation (Pieri et al, Blood Advance 2021).

Disclosure: The Authors declare no conflict of interest.

19 - Acute Leukaemia

P027

FACTORS ASSOCIATED WITH ACUTE MYELOID LEUKEMIA RELAPSING AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

Juan José Domínguez-García[1], Guillermo Martín Sánchez[1], María de las Mercedes Colorado Araujo[1], Miriam Sánchez Escamilla[1], Juan Manuel Cerezo Martín[1], Carmen Montes Gaisán[1], Enrique María Ocio San Miguel[1], María Aránzazu Bermúdez Rodríguez[1]

[1]Hospital Universitario Marqués de Valdecilla, Santander, Spain

Background: Acute myeloid leukemia (AML) relapsing after first allogeneic hematopoietic stem cell transplantation (ASCT) has a dismal prognosis. The aim of our study is to identify risk factors associated with decreased overall survival (OS) and higher incidence of relapse post-ASCT and how can we manage this group of patients after relapsing.

Methods: We analyzed 135 patients who underwent first ASCT between January 2011 and December 2021. Patient demographic

characteristics, AML and transplant related outcomes were retrospectively collected. We used cox regression for the statistical analysis.

Results: Patients' characteristics and univariable overall survival (OS) and progression free survival (PFS) analysis are shown in Table 1.

With a median follow-up 92.6 months, two-year PFS and OS were 44.7% (95%CI: 36.6-53.6%) and 64.9% (95%CI: 56.0%-72.4%) respectively. Incidence of acute and chronic GVHD were 30.6% (95%CI: 18.9-47.1%) and 60.1% (95%CI: 34.4-86.6%), correspondingly.

Factors significantly associated with a decreased overall survival were age at ASCT, longer time from diagnosis to ASCT, higher disease burden at ASCT, absence of cGVHD ($p < 0.001$), sequential transplant ($p < 0.001$), monosomic or complex karyotype leukemia ($p = 0.008$) and early relapse (< 1 year after ASCT). In the multivariate analysis, only age at transplant, absence of cGVHD development, and sequential ASCT maintained their significance.

Forty-five patients (33.3%) relapsed after ASCT. Four were molecular relapses, 10 were detected by flow cytometry and 31 morphologic relapses. Among them, 27 (60%) were very early-relapses (< 6 months post-ASCT), 6 patients (13.3%) relapsed between 6 to 12 months post-ASCT and 12 (26.7%) beyond one year post-ASCT.

Factors associated with a PFS decreased (Table 1) were AML status at ASCT, peripheral blood as source, lack of acute or chronic GVHD development and monosomic or complex karyotype. Only control of disease and high DRI pre-ASCT, MUD and MMUD SCT, sequential conditioning, and lack of acute and chronic GVHD, maintained the statistical significance in the multivariable analysis

Patients with an overt morphologic relapse and those with an early relapse had significantly worse prognosis. With regards to the management of these relapses, 38% of patients received hypomethylating agents (65% in early-relapse), chemotherapy in 33% (47% in early-relapse), DLI infusion in 44% (50% in early-relapse), and a second transplant in 29% (XX in early relapse). The use of DLI or 2nd transplant was associated with a significantly better prognosis. In fact, in the multivariate analysis, use of 2nd ASCT ($p = 0.001$), early ($p = 0.003$) and morphological relapse ($p < 0.001$) were associated with worse OS.

Table 1.

Variables		*SAMPLE (n = 135)*	*PFS HR (CI95%) p-value*	*OS HR (CI95%) p-value*
Age (y) at dx, mn (SD)		53.8 (13.96)	1.02 (0.99-1.03) 0.083	1.02 (1.01-1.04) **0.026***
Age (y) at ASCT, mn (SD)		54.4 (13.95)	1.02 (0.99-1.03) 0.068	1.02 (1.01-1.04) **0.020***
Time dx-ASCT, mn (SD)		235.5 (349.39)	1.00 (0.99-1.01) 0.052	1.01 (1.01-1.02) **0.002***
Female Sex, n (%)		59 (43.7)	0.69 (0.43-1.10) 0.114	0.60 (0.35-1.02) 0.061
ELN22	Favorable, n (%)	18 (13.4)	1.12 (0.54-2.33) 0.767	1.19 (0.54-2.60) 0.667
	Intermediate, n (%)	74 (55.2)	Reference category	Reference category
	Adverse, n (%)	42 (31.3)	2.09 (1.27-3.45) **0.004***	1.63 (0.93-2.86) 0.091
MRD pre-ASCT	MRD -, n (%)	56 (41.5)	Reference category	Reference category
	MRD +, n (%)	65 (48.2)	2.29 (1.35-3.88) **0.001***	1.90 (1.05-3.45) **0.033***
	PR, n (%)	5 (3.7)	3.73 (1.27-10.93) **0.017***	4.30 (1.44-12.87) **0.009***
	REFRACT, n (%)	9 (6.7)	4.47 (1.89-10.60) **0.001***	5.29 (2.18-12.84) < **0.001***
PB source (vs. BM), n (%)		62 (45.9)	1.70 (1.07-2.71) **0.024***	1.47 (0.88-2.45) 0.143
ASCT	MSD, n (%)	31 (23.0)	Reference category	Reference category
	Haplo, n (%)	40 (30.0)	1.55 (0.85-2.84) 0.154	1.14 (0.60-2.20) 0.685
	MUD, n (%)	48 (35.6)	0.68 (0.36-1.31) 0.250	0.62 (0.31-1.23) 0.169
	MMUD, n (%)	16 (11.9)	0.85 (0.37-1.93) 0.694	0.55 (0.21-1.45) 0.230
Relapse	≤6m Relapse, n (%)	27 (20.00)	NA	6.19 (3.38-11.33) < **0.001***
	6m-1y Relapse, n (%)	6 (4.44)	NA	3.39 (1.29-8.90) **0.013***
	>1y Relapse, n (%)	12 (8.89)	NA	0.64 (0.20-2.12) 0.471

Conclusions: In our 10-year series, it seems that a third of AML relapses after transplant and survival of these patients is highly related to their age, the very early relapse, absent of cGVHD, or high risk cytogenetic/molecular abnormalities. Achieving negative residual disease at transplant seems to improve the results and it must be the primary objective.

AML-relapsed patients, influenced mostly by type and moment of relapse, continues to be a major challenge. Prognosis is poor, and it seems that better results are offered with DLI or 2nd ASCT instead of hypomethylants or chemotherapy.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P028

TREATMENT WITH AZACITIDINE AND VENETOCLAX IS AN EFFECTIVE BRIDGE TO SECOND ALLOGENEIC TRANSPLANTATION IN PATIENTS WITH RELAPSED ACUTE MYELOID LEUKEMIA AFTER FIRST ALLOGENEIC TRANSPLANTATION

Nika Premuž[1], Ljubica Mežnarić[1], Lana Desnica[2], Zinaida Perić[1,2], Ranka Serventi Seiwerth[2], Viktor Blaslov[3], Hrvoje Holik[4], Radovan Vrhovac[1,2], Nadira Duraković[1,2]

[1]University of Zagreb School of Medicine, Zagreb, Croatia, [2]University Hospital Centre Zagreb, Zagreb, Croatia, [3]University Hospital Centre Split, Split, Croatia, [4]General Hospital Dr. Josip Benčević, Slavonski Brod, Croatia

Background: Venetoclax in combination with azacitidine (AZA-VEN) is approved for first line therapy of AML in unfit patients, while initial studies with this combination also showed good results in refractory/relapsed setting. Prognosis of patients in relapse after allogeneic transplantation (allo-HSCT) is dismal, and therapeutic options include DLI, subsequent chemotherapy and second allogeneic transplantation. Here we present outcomes of using AZA-VEN combination therapy in relapse post allo-HSCT in a single-center study.

Methods: We performed a retrospective analysis of 25 AML patients who were treated with AZA-VEN for relapse after allo-HSCT at University Hospital Centre Zagreb in the period between April 2019 and September 2022. Patient data was collected from the medical records and included: demographic data, treatment details, response, and subsequent treatment including second allo-HSCT. Kaplan-Meier method was used for survival analysis, and log-rank test was used for group comparison. All statistical results were obtained using Prism 7 program.

Results: Patient median age was 48 years (22-71), 11 (44%) were female and 14 (56%) male. All patients received prior allo-HSCT, and 23 (92%) were in CR prior to transplant. Nine (36%) patients received prior transplant from an unrelated, 10 (40%) from a related and 6 (24%) from a haploidentical donor. The median number of days from transplantation to relapse was 217 (range

26-1042) while median number of days from transplant to the start of AZA-VEN was 257 (range 57-1151). Median number of AZA-VEN cycles received was 2 (range 1-5). One patient died during first cycle so 24/25 patients were evaluable for response: 19 (79%) responded to treatment, of which 17 (71%) achieved CR/CRi. Best response was noted after a median of 1.67 months (range 1-6.6). Median survival for the entire group was 8.5 months. We compared survival proportions between patients that subsequently received second alloHSCT and those that did not, and significantly better survival was found in the group that was treated with 2nd transplantation, with median survival in that group reaching 14.2 months ($p = 0.0003$). Of 16 patients that did not reach or were not candidates for second transplantation 9 (56%) died due to AML, 1 (6%) of infection and 1 (6%) of other reasons (bleeding). Of 9 patients that reached second allo-HSCT 2 (22%) died of AML, 2 (22%) of infection and 1 (11%) due to transplant toxicity.

Conclusions: In this retrospective analysis we have shown that AZA-VEN is a good treatment option for patients with AML in relapse after allo-HSCT with response rates and time to response comparable to results published for AZA-VEN as the upfront therapy. It can be administered in most cases in the outpatient setting so it relieves some of the strain on inpatient services. However, difference in survival proportions between patients that were able to proceed to second transplantation timely and those that did not suggest that the duration of response is short and unless patients received subsequent transplantation their survival is rather limited.

Disclosure: Nothing to declare

19 - Acute Leukaemia

P029

IMPAIRED ACCESS OF UKRAINIAN PATIENTS TO HEMATOPOIETIC CELL TRANSPLANTATION (HCT) DURING THE RUSSIAN AGGRESSION IN 2022

Kateryna Filonenko[1], Ewa Paszkiewicz-Kozik[2], Maciej Majcherek[3], Olha Kylivnyk[4], Maria Bieniaszewska[5], Anna Czyz[3], Wojciech Legiec[4], Yana Stepanishyna[6], Iryna Korenkova[7], Oleksandr Lysytsia[8], Iryna Kriachok[6], Jan Zaucha[5]

[1]University Clinical Center, Gdansk, Poland, [2]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland, [3]University Clinical Hospital, Wroclaw, Poland, [4]Center of Oncology of the Lublin Region St. Jana z Dukli, Lublin, Poland, [5]Gdansk Medical University, Gdansk, Poland, [6]National Cancer Institute, Kyiv, Ukraine, [7]Kyiv City Center of Bone Marrow Transplantation, Kyiv, Ukraine, [8]National Specialized Children's Hospital "OHMATDYT", Kyiv, Ukraine

Background: Ukraine, with 40 million (mln) citizens in 2021 performed about 250 (including 44 allogeneic) procedures of hematopoietic cell transplantation (HCT) for adult and pediatric patients, which covered 10% of the expected needs of 300 HCT/10 mln. For 11 months of 2022 the number of SCT procedures dropped-off by 30% (at least 204 procedures were performed). Despite that fact the number of allogeneic SCT procedures increased to 55. The full-scale war since February 24th 2022, significantly impaired the transplant activity in Ukraine. About 8,48 mln Ukrainian citizens entered Poland, from which 1,4 mln remained and received equal rights to Polish citizens, including rights to free healthcare. Very robust calculations indicate that at least 45 HCT should be performed to cover the needs of Ukrainian refugees.

Methods: We collected information regarding the HCT procedures performed in Ukrainian refugees in Poland in the period 24.02-31.11.2022 in 24 transplant centers in Poland. The questionary with basic data on patients' demographic, family, clinical characteristics, treatment details, and patients' needs was sent to the centers.

Results: Fifteen patients received HCT in 4 Polish transplant centers over the last nine months. Among them, 3 were male and 12 female, with median age of 32 (19-53) years. At least three patients were from the occupied territories or zones of active military actions, 5 patients were alone (without any family member to support them). Two patients had the diagnosis of AML, 2 - T-ALL, 1 patient had SAA, 7 - HL, 2 - DLBCL, and 1 – PTCL. One patient (with AML) was diagnosed in Poland, other 11 patients continued the treatment, which was started in Ukraine. 6 patients were after at least 2 lines of previous treatment in Ukraine, 8 patients had PD at the moment of the 1st hospitalization to Polish hospitals. Treatment that is unavailable in Ukraine received 3 patients. Auto-HCT was performed in 10 patients, and allo-HCT in 5 patients, including 3 from MUD, 1 from haploidentical donor, 1 from MRD. The biggest issue during the treatment was the language barrier. In 9 patients, the translator's support was needed, including translations of documents. In 3 cases, hospitals helped with the accommodation and caring of dependent family members during the hospitalization. The median time of treatment in Poland was five months (3-9 months). In 9 patients full treatment plan was completed in Poland, six patients returned to Ukraine, and 2 patients died due to complications of allo-HCT.

Conclusions: The Russian aggression against Ukraine significantly impaired the access of the Ukrainian patient to HCT. Our data indicate that the number of HCT performed in Poland, the only European country offering refugee treatment equal to its citizens, does not cover the expected needs. All Ukrainian patients in Poland received treatment either unavailable or limitedly available in their home country. There is a great unmet need to improve the access of Ukrainian patients to HCT in Europe.

Disclosure: No COI

19 - Acute Leukaemia

P030

ADVERSE PROGNOSIS OF LOW AR *FLT3*-ITD IN AML AND CLINICAL BENEFIT OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN AML PATIENTS WITH LOW AR *FLT3*-ITD AND *NPM1*

Hyeoung-Joon Kim[1], TaeHyung Kim[2], Hoon Kook[3], Ga-Young Song[1], Seo-Yeon Ahn[1], Sung-Hoon Jung[1], Mihee Kim[1], Deok-Hwan Yang[1], Je-Jung Lee[1], Seung Hyun Choi[4], Mi Yeon Kim[4], Chul Won Jung[5], Jun-Ho Jang[5], Hee Je Kim[6], Joon Ho Moon[7], Sang Kyun Sohn[7], Jong-Ho Won[8], Seong-Kyu Park[8], Sung-Hyun Kim[9], Zhaolei Zhang[2], Jae-Sook Ahn[1], Dennis Dong Hwan Kim[10]

Chonnam National University Hwasun Hospital, Hwasun, Korea, Republic of, University of Toronto, Toronto, Canada, Chonnam National University Hwasun Hospital, Hwansun, Korea, Republic of, [4]Genomic Research Center for Hematopoietic Diseases, Chonnam National University Hwasun Hospital, Hwasun, Korea, Republic of, [5]Division of Hematology-Oncology, Samsung Medical Center, Seoul, Korea, Republic of, The Catholic University of Korea, Seoul, Korea, Republic of, Kyungpook National University Hospital, Daegu, Korea, Republic of, Soon Chun Hyang University Hospital, Seoul, Korea, Republic of, Dong-A University College of Medicine, Busan, Korea,

Republic of,, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada

Background: There have been questions about whether the acute myeloid leukemia (AML) with *FLT3*-ITD with low AR have a really favorable prognosis. This study analyzed the clinical impact of low AR *FLT3*-ITD and whether the patients with low AR *FLT3*-ITD would benefit from receiving allogeneic hematopoietic stem cell transplantation (HCT).

Methods: Totally, 624 AML patients who received intensive induction therapy from November 1996 to May 2019 were included in the study. Patients who achieved CR received consolidation chemotherapy with or without allogeneic HCT, depending on the availability of a matched donor. Genetic factors were not considered in choosing allogeneic HCT. About the AR of *FLT3*-ITD, low AR (AR^{low}) was defined AR < 0.5 and high AR (AR^{high}) was defined AR ≥ 0.5.

Results: Among the 624 patients, 48 patients (7.7%) were AR^{high} *FLT3*-ITD and 45 patients (7.2%) were AR^{low} *FLT3*-ITD. According to the ELN 2017 risk stratification criteria, 99 patients (15.9%) were adverse risk group, 276 patients (44.2%) were intermediate risk group, and 249 patients (39.9%) were favorable risk group.

In patients who have intermediate cytogenetics risk and did not received allogeneic HCT, overall survival (OS) and relapse-free survival (RFS) were inferior in patients with AR^{low} *FLT3*-ITD than the patients without *FLT3*-ITD (5yr OS 0.0% vs. 25.0%; 5yr RFS 0.0% vs. 22.8%) (OS, HR 2.009, 95% CI 0.939-4.296, p = 0.066; RFS, HR 2.848, 95% CI 1.178-6.883, p = 0.015). Cumulative incidence of relapse (CIR) was higher in patients with AR^{low} *FLT3*-ITD than the patients without *FLT3*-ITD (5yr CIR 100.0% vs. 36.9%) (HR 4.073, 95% CI 1.983-8.368, p = 0.001) There was no difference in cumulative incidence of non-relapse mortality (NRM) between the patients with AR^{low} *FLT3*-ITD and *FLT3*-ITD wild-type (5yr NRM 22.2% vs. 20.5%) (HR 1.122, 95% CI 0.251-5.025, p = 0.880). OS, RFS, CIR and cumulative incidence of NRM were similar between the patients with AR^{low} *FLT3*-ITD and with AR^{high} *FLT3*-ITD (5yr OS 0.0% vs. 7.1%; 5yr RFS 0.0% vs. 7.1%; 5yr CIR 100.0% vs. 58.3%; 5yr NRM 22.2% vs. 7.1%) (OS, HR 1.301, 95% CI 0.510-3.317, p = 0.582; RFS, HR 1.267, 95% CI 0.433-3.704, p = 0.666; CIR, HR 1.444, 95% CI 0.551-3.782, p = 0.517; NRM, HR 3.273, 95% CI 0.344-31.120, p = 0.312).

Then we analyzed the clinical outcome according to allogeneic HCT in the patients with AR^{low} *FLT3*-ITD and *NPM1* in patients with intermediate risk cytogenetics. Twelve patients who received allogeneic HCT showed superior OS, RFS and lower CIR than 6 patients who received only chemotherapy consolidation (5yr OS 75.0% vs. 0.0%; 5yr RFS 75.0% vs. 0.0%; 5yr CIR 8.3% vs. 100.0%) (OS, HR 0.157, 95% CI 0.028-0.888, p = 0.036; RFS, HR 0.126, 95% CI 0.023-0.697, p = 0.018; CIR, HR 0.045, 95% CI 0.005-0.422, p < 0.001). All 6 patients who received chemotherapy consolidation experienced relapse, but only 2 of the 12 patients who received allo HCT relapsed. Cumulative incidence of NRM was not statistically different (5yr NRM 16.7% vs. 0.0%) (p = 0.304).

Conclusions: AML patients with mutated *NPM1* and AR^{low} *FLT3*-ITD have a worse prognosis than mutated *NPM1* and *FLT3*-ITD wild-type, and the adverse prognosis of AR^{low} *FLT3*-ITD could be overcome by allogeneic HCT.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P031

IMPACT OF CYTOGENETIC ABNORMALITIES DEFINING AML MYELODYSPLASIA-RELATED (WHO AND ICC 2022) IN FIRST LINE DECITABINE IN UNFIT AML PATIENTS

Adolfo de la Fuente[1], Paola Beneit[2], Pau Montesinos[3], Ana Muñoz Gama[4], Antonia Sampol Mayol[5], Lucia Castilla Garcia[6], Karla Javier Gonzalez[7,8], Julio Davila Valls[9], Alicia Roldan Perez[10], Angela Figuera[11], Javier Cornago[12], Cristina Barrenetxea Lekue[13], Itziar oiartzabal[14], Sandra Suarez Ordoñez[15], Susana Vivez Polo[16], Carmen Martinez Chamorro[17], Rosa Coll Jordá[18], Montserrat Arnan Sangerman[19], Alfonso Garcia de Coca[20], Maria de los Angeles Foncillas[21], Maria José Otero[22], José María Grassa Ulrich[23], Lara María Gomez Garcia[24], Juan Antonio Vera Goñi[25], Maria Perez Rios[1], Antonio Diaz Lopez[1], Jorge Sierra[26], Mar Tormo[27]

[1]MD Anderson Cancer Center Madrid, Madrid, Spain, [2]H. U. San Juan de Alicante, Alicante, Spain, [3]H. U. Politecnico La Fe, Valencia, Spain, [4]H. U. Virgen de la Salud Toledo, Toledo, Spain, [5]H. U. Son Espases, Palma de Mallorca, Spain, [6]H. U. Principe de Asturias, Alcala de Henares, Spain, [7]H. General Universitario de Valencia, Valencia, Spain, [8]The Hong Kong Politecnic University, Hong Kong, Hong Kong, SAR of China, [9]Complejo Asistencial de Avila, Avila, Spain, [10]H. Infanta Sofia, Madrid, Spain, [11]H. U. La Princesa, Madrid, Spain, [12]H. Fundación jiménez Díaz, Madrid, Spain, [13]H. U. Basurto, Bilbao, Spain, [14]H. U. de Araba Txagorritxu, Vitoria, Spain, [15]H. U. Alvaro Cunqueiro, Vigo, Spain, [16]ICO Hospital Germans Trias i Pujol, Barcelona, Spain, [17]H. Quiron Salud Madrid, Madrid, Spain, [18]ICO Gerona, Gerona, Spain, [19]ICO Duran i Reynals, Barcelona, Spain, [20]H. Clinico U. de Valladolid, Valladolid, Spain, [21]H. Infanta Leonor, Madrid, Spain, [22]H. Central de la defensa, Madrid, Spain, [23]Quiron Salud, Zaragoza, Spain, [24]H. Nuestra Señora de Prado, Talavera de la Reina, Spain, [25]H. U. Virgen de la Macarena, Sevilla, Spain, [26]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [27]H. U. Clínico de Valencia, Valencia, Spain

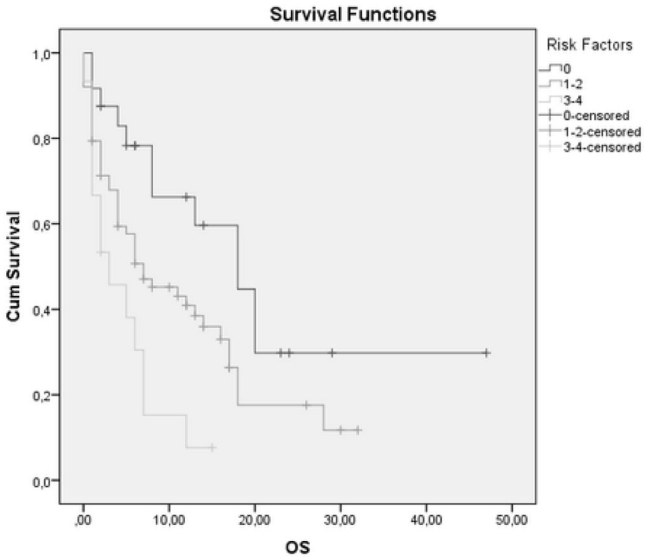
Background: HMAs in monotherapy have been the standard front line for unfit AML patients for a decade (*Kantarjian H et al JCO 2012 and Dombret H et al Blood 2015)*. Risk factors for HMA frontline treatment have been suggested (De la Fuente et al EHA 2014 and EHA 2018). In 2022 the WHO and the ICC classifications for Myeloid Neoplasm have been published updating biological risk factors for AML. The aim of this study is to analyze the impact of the new 2022 Cytogenetic Abnormalities Defining AML Myelodysplasia-related (AML-MRC by WHO and by ICC) in the outcome of unfit AML patients treated with decitabine (Dec) as first line.

Methods: We carried out the analysis on patients with previously untreated AML included in the MDA-AML-2017-05 study from 23 Spanish sites. Inclusion criteria were as follows Age >18, diagnosis of AML under WHO criteria, treated with Dec during the period 01/09/2014 to 31/12/2016. We evaluated impact of the new 2022 Cytogenetic Abnormalities Defining AML Myelodysplasia-related (WHO and ICC). OS by Kaplan-Meier and the mortality within the first 8 weeks (M8wks). The MDA-AML-2017-05 study was approved by the Spanish Medicines Agency AEMPS.

Results: A total of 126p (77M, 49F) were analyzed. Average age 75.7 (48-91), 80 yrs and above 57p, WBC pre-Dec >15.000/µL: 21p, Creatinine>1.3 mg/dL: 23p, ECOG ≥ 2: 38p, adverse cytogenetic: 39p, AML-MRC by WHO 38p, AML-MRC by ICC 48p. A total of 716 cycles were analyzed, median 4 (1-31) per patient. No cases of treatment related mortality. One hundred and three patients were studied for effectiveness ORR 49% (CR 20p, PR 21p, ED 28p). With a mean follow up of 8 mths 77 died. The M8wks was 24.5% and the median OS 8 months.

AML-MRC defined as 2016 WHO classification resulted in non-significant differences for OS (p0.08). The new 2022 AML-MRC definition, both WHO and ICC resulted in significant differences in OS (p 0.005 and p0.03) and both predict M8wks 27% vs 12.3% and 26% vs 10.7% respectively.

The update of the DecLAM scale with the following risk factors: WBC pre-Dec >15.000/μL ($p < 0.01$) creatinine >1.3 mg/dL (p0.02), ECOG ≥ 2 ($p < 0.01$) and AML-MRC WHO 2022 ($p < 0.01$) allows us to identify risk groups with 0 vs 1-2 vs 3-4 risk factors with differences for OS (19 vs 5.5 vs 3.5 m $p < 0.01$). Age >80 revealed no OS differences.



Conclusions: The results of this study confirm AML-MRC 2022 by WHO and by ICC as adverse risk factor in unfit AML patients treated with Dec. The updated DecLAM scale is useful to identify risk groups with differences in OS,

Disclosure: The MDA-AML-2017-05 study was founded by Janssen in 2017. Present post-hoc analysis and abstract is an independent work carried out by co-authors without any financing.

19 - Acute Leukaemia

P032

FOLLOW-UP UPDATE OF THE FLAG-IDA REGIMEN AS BRIDGE THERAPY TO ALLOTRANSPLANTATION IN REFRACTORY/ RELAPSED ACUTE MYELOID LEUKEMIA PATIENTS: 10 YEAR-RESULTS FROM A SINGLE CENTRE EXPERIENCE

Mario Delia[1], Vito Pier Gagliardi[1], Paola Carluccio[1], Corinne Contento[2], Daniela Di Gennaro[2], Wanda Strafella[2], Immacolata Attolico[1], Francesco Albano[2,1], Pellegrino Musto[2,1]

[1]Hematology and Stem Cell Transplantation Unit, Azienda Ospedaliero-Universitaria-Consorziale (AOUC) Policlinico, Bari, Italy, "Aldo Moro" University – School of Medicine, Bari, Italy

Background: The outcome of refractory/relapsed acute myeloid leukemia (AML) is still dismal, and its treatment represents an unmet clinical need. Our group previously reported (Delia M., et al. Clin Lymphoma Myeloma Leuk.2017;17:767-773) the efficacy of the FLAG-Ida regimen in patients with refractory/relapsed AML as a bridge to transplantation demonstrating a median overall survival (OS) of 60 months for patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) in complete remission (CR). In this study we performed a landmark analysis starting observation from the time of allotransplant updating the follow-up on June 30th, 2022, with regard to the post-allotransplant outcomes in terms of OS, disease free survival (DFS), non-relapsed mortality (NRM) and cumulative incidence of relapse (CIR).

Methods: The baseline characteristics of allotransplanted patients are reported in **Table 1**. In addition, time from diagnosis and FLAG-Ida to allotransplant was of 236 (r, 63-1061) and of 133 days (31-365), respectively. Seventeen CR-patients (33%) performed allotransplants in first CR (CR1). Source of stem cells was peripheral blood for 38 allotranplanted patients (73%). All patients received a myeloablative conditioning regimen: busulfan +cyclophosphamide; busulfan+fludarabine; thiothepa+busulfan +fludarabine (TBF) and TBF + post-transplant cyclophosphamide in 15 (29%), 11 (21%),16 (31%) and 10 (19%) allotransplants, respectively. A multivariate analyses of risk factors (disease status at FLAG-Ida (refractory to "3 + 7" or relapsed after CR), disease status at allotransplant, type of donor, recipient age, sex match) associated with OS, DFS, NRM and relapse was also performed.

Table 1. Baseline patients' characteristics at allotransplantation n = 52

		%
Age, median value, years (range)	**47 (16-63)**	
Disease status at allotransplant		
compete response (CR)	**30**	**57**
partial response (PR)	**18**	**35**
active disease	**4**	**8**
Disease status at FLAG-Ida		
refractory to "3 + 7"	**31**	**60**
relapsed after CR	**21**	**40**
Molecular-cytogenetics risk[§]		
poor	**20**	**38**
intermediate	**32**	**62**
ITD		
mutated	**12**	**23**
unmutated	**40**	**77**
Donor type		
Matched Related	**18**	**35**
Matched unrelated	**24**	**46**
Aploidentical	**10**	**19**

Results: The median OS significantly correlated with receipt of allo-HSCT (5 vs 23 months, $p < 0.001$). According to landmark analysis, the 10-year OS and DFS were 33 and 32%, respectively. With a median follow-up of 8 years (r, 0.5-15) for post-allotransplant surviving patients, the median OS and DFS for all series were 37 and 19 months, respectively. According to disease status at allotransplant, the 5-year OS and DFS rates in active disease-, PR- and CR-patients were 23, 12, 51% and 25, 5, 50%, respectively. The 10-year CIR and NRM rate were 57 and 25%, respectively. The 5-year CIR and NRM in active disease-, PR- and CR-patients were 72, 93 and 36% and 25, 29 and 22%, respectively. The 10-year CIR rates of CR-allotransplanted patients in CR1 and CR2 were 35 and 39%, respectively. The 10-year CIR rates of CR-allotransplanted patients belonging to the high and intermediate risk group were 55 and 26% (p=ns), respectively. The CIR of CR-patients was not conditioned by FLT3-ITD mutation status: 33 vs 37% of 10-year CIR in FLT3 unmutated and mutated-patients, respectively. In multivariate analysis, the disease status at allotransplant (CR vs not CR) was confirmed as the factor impacting OS (HR = 0.34, CI95%:0.171-0.685; p = 0.002), DFS (HR = 0.330, CI95%:0.164-0.664; p = 0.002), and relapse rates (HR = 0.262, CI95%:0.113-0.610; p = 0.002).

Conclusions: Our data confirm the value of FLAG-Ida as salvage therapy in relapsed/refractory AML and subsequent allotransplantation if CR is obtained. Furthermore, allotransplant performed in CR seems to counteract the impact of FLT3-ITD mutation in these patients.

Clinical Trial Registry: na

Disclosure: nothing to disclose.

19 - Acute Leukaemia

P033

ACUTE MYELOID LEUKEMIA AND ALLOGENEIC TRANSPLANTATION: SINGLE-CENTER EXPERIENCE

Rafael Colmenares[1], Pilar Martínez-Sánchez[1], José María Sánchez-Pina[1], Magdalena Corona[1], Adolfo J Sáez[1], Daniel Gil-Alós[1], Rodrigo Gil-Manso[1], María Calbacho[1], Joaquín Martínez-López[1]

[1]Hospital 12 de Octubre, Madrid, Spain

Background: Acute myeloid leukemia (AML) was the disease suffered by 39% of allogeneic transplant patients in Europe, according to EBMT data in 2020. In fit patients, allogeneic transplant is the single curative therapy for AML, except classical favorable AML which could be cured only with chemotherapy if negative minimal residual disease (MRD). There is not an established MRD cut-off to receive an allogeneic transplant or more chemotherapy trying to reduce this MRD before transplantation.

Methods: A single-center retrospective analysis was carried out on 40 patients diagnosed with AML who went into an allogeneic transplant between January 2018 and October 2022. We used the 2017 ELN risk stratification and the ELN recommendations for the management of AML. We considered negative MRD if <0.1% (using multiparametric flow cytometry). We determined post-transplant MRD between day 25 and day 40.

Results: 23 (57.5%) patients were women, with a median age of 50 (range 19-67) years. 14 (35%) patients were referred from other centers. There were 5 (12.5%) secondary AML cases, and 9 (22.5%) patients had an HCT-CI/Age score greater than 2.

36 patients (90%) patients had achieved first complete response (CR1), although 5 (12.5%) were favorable-risk AML with positive MRD and 4 (10%) needed 2 chemotherapy-induction cycles; 4 (10%) had achieved second complete response (CR2). Regarding MRD, only 5 (12.5%) had positive pre-transplant MRD.

67.5% of patients received myeloablative conditioning (MAC) and 32.5% received reduced-intensity conditioning (RIC). There were 12 HLA-matched siblings, 18 haploidentical and 10 HLA-matched unrelated donors.

Only 1 patient (2.5%) had positive post-transplant MRD and, after a follow-up of 18 (range 2-57) months from the transplant there were 5 (12.5%) relapses (and all of them had negative pre-transplant and post-transplant MRD; 3 of patients had an adverse cytogenetic risk). 9 (22.5%) patients died; 6 patients with transplant-related mortality (TRM) (5 of them due to respiratory infection and 1 due to sinusoidal obstruction syndrome) and 3 patients with relapse.

Median overall survival (OS) was not reached in the cohort, and OS at 1 year and 2 years was 80%. No statical significative differences were found comparing patients regarding the type of donor or conditioning, but an HCT-CI/Age score of more than 2 had a worse OS (27 months; Log Rank p = 0,012).

Regarding patients with positive pre-transplant MRD, none of them relapsed during the follow-up, but one of patients is receiving azacytidine because of post-transplant positive MRD (Table 1). 4 (10%) patients needed a second allogeneic transplantation (3 because of graft failure and 1 due to relapse).

Patient	Pre-transplant MRD	Donor and conditioning	Post-transplant MRD	Outcome
#1	0.70%	Haploidentical-RIC	0.02%	Dead (respiratory sepsis, day 153)
#2	0.22%	Haploidentical-MAC	Not reached (death)	Dead (respiratory sepsis, day 35)
#3	0.50%	HLA-matched siblings-MAC	0%	Alive without relapse (follow-up, 28 months)
#4	0.90%	Haploidentical-RC	1.50%	Alive, receiving azacytidine, blasts < 5% (follow up, 4 months)
#5	2.00%	HLA-matched siblings-MAC	0%	Alive without relapse (follow-up, 4 months)

Table 1. Patients with positive pre-transplant MRD.

Conclusions: In our small sample, the vast majority of patients have a negative pre-transplant MRD, and none of the patients with a positive MRD relapsed during the transplant, although the results are not significant. The most frequent cause of mortality is TRM, so it may be important to apply comorbidity scales (such as HCT-CI/Age). More studies are needed to clarify the role of pre-transplant MRD in optimizing the timing of the allogeneic transplant.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P034

EARLY ALLOGENEIC STEM CELL TRANSPLANTATION AFTER MELPHALAN-INDUCED APLASIA LEADS TO LONG-TERM SURVIVAL IN PATIENTS WITH PRIMARY REFRACTORY AML

Claudius Söhn[1], Kerstin Schäfer-Eckart[1], Knut Wendelin[1], Wolfgang Hitzl[2], Stefan Knop[1]

[1]Klinikum Nürnberg, Nürnberg, Germany, [2]Paracelsus Medizinische Privatuniversität Salzburg, Salzburg, Austria

Background: Survival rates of younger patients with newly diagnosed acute myeloid leukemia (AML) have improved, but still up to 30% of patients (pts) fail to achieve complete remission after induction therapy. Allogeneic blood stem cell transplantation is the only option for long-term remission in eligible patients. Salvage chemotherapy before allogenic hematopoietic stem cell transplantation (HSCT) is considered as a standard of care by most centers. Yet this approach is associated with considerable treatment-related complications and only

about 50% of patients will achieve CR before transplantation. Here we present our results of an immediate allogeneic transplantation in refractory disease after chemotherapy-induced aplasia.

Methods: All pts from our center with refractory AML after induction chemotherapy who received an allogeneic transplantation in active disease between 2012 and 2021 were retrospectively analyzed. Overall survival was evaluated in regard to time from diagnosis to HSCT using Cox proportional hazard model. The use of one induction cycle vs. two induction cycles after diagnosis was analyzed in regard to overall survival using Kaplan-Meier analysis.

Results: 41 pts were included. Their median age was 56 (range 24-75) years. Melphalan (100-140 mg/m^2) for induction of aplasia was used in 36/41 pts. The conditioning regimen consisted of Treosulfan (30g/m^2) and Fludarabine (150mg/m^2) in most pts (68%). GvHD-prophylaxis was CSA and MTX or CSA and MMF. 34 pts (83%) additionally received ATG-prophylaxis. Mean time from diagnosis to HSCT was 3 (range 0.93-11.03) months (mos). Induction chemotherapy was daunorubicin and cytarabine (DA 3 + 7) in all pts. 17 pts received 1 cycle; 2 induction cycles were given to 24 pts, mostly because of study protocol. 22 of those 24 pts were given high-dose AraC as second induction because of refractory disease after first induction. After a median follow-up of 8.9 (range 0.3-122) mos 14 pts (34.1 %) were alive without relapse. Median observation time for those event free at the last follow up (14/41 patients) was 41 mos (range 7-122 mos). This was considerably longer than the median relapse-free survival of 9.2 mos. The last relapse took place 18 mos after

transplantation. The main cause of death was early treatment-related mortality (59 %) mainly because of septicemia (44 %). Only 7 pts (17 %) relapsed and 2 pts (7 %) had refractory disease. Cox proportional hazard model showed no significant correlation between time from diagnosis to HSCT and overall survival ($p = 0.19$). There was no significant difference of 1 vs. 2 Induction cycles in regard to OS ($p = 0.51$).

Conclusions: In this retrospective analysis, we showed that an immediate allogeneic transplantation after induction of aplasia is feasible in pts with primary refractory AML. With a two-year survival rate of 37%, this approach offers a realistic chance to patients with an otherwise dismal prognosis. The effectivity is compromised by the high rate of early toxicity mainly because of infectious reasons.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P035

OUTCOMES OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN ADULT ACUTE MYELOID LEUKEMIA PATIENTS: A 30-YEAR SINGLE CENTER EXPERIENCE

Tanaz Bahri[1], Maryam Barkhordar[1], Hossein Kamranzadeh[1], Soroush Rad[1], Sahar Tavakoli[1], Ardeshir Ghavamzadeh[2], Mohammad Biglari[1], Mohammad Vaezi[1]

[1]Cell Therapy and Hematopotic Stem Cell Transplantation Research Center, Research Institute for Oncology, Hematology and Cell Therapy, Tehran University of Medical Sciences, Tehran, Iran., Tehran, Iran, Islamic Republic of, [2]Cancer & Cell Therapy Research Center, Tehran University of Medical Sciences, Tehran, Iran, Tehran, Iran, Islamic Republic of

Background: Acute Myeloid Leukemia (AML) is a heterogenous disease with until recently a standard treatment which was unchanged for decades. We began allogeneic transplantation from 1991 in our center with full matched and 1 locus mismatched donors, with the introduction of haplo-donors in 2009-2010 there was a alternative source for patients with no matched donor. We performed this study to verify the efficacy of our treatment and identify further challenges.

Methods: Patients with AML who were transplanted at our center between 1991 and January 2022 were included in the study. Unfortunately due to lack of access to cytogenetic and molecular laboratory services we were unable to complete the risk stratification of the patients. We divided the patients in 2 groups of before and after 2010. The conditioning regimen was myeloablative and consisted of Busulfan 0.8 mg/kg QID for 4 consecutive days (12.8 mg/kg in total) and cyclophosphamide 60 mg/kg per day for two consecutive days. GVHD prophylaxis consisted of cyclosporine in combination with a short course of methotrexate. Patients transplanted from a matched unrelated or mismatch donor received also ATG. Patients with a haplo-HCT received Cyclosporine, ATG and post-CY on days +3 and +4 as GVHD prophylaxis.

Results: We retrospectively analyzed 1337 patients with AML, from 16 to 70 years of age. The median age of patients was 34 years (range 25-44), median follow-up was 61,6 months. The 5-year overall survival (OS) was respectively 61.5% in CR1 and 47.4% and 37.2% in patients transplanted in CR2 and CR^{3}3. In the first complete remission the 5-year overall survival (OS) did not improve in the second timeline (64.1% (D1) vs 60.2% (D2)), but in CR2 the OS did improve from 36.7% (D1) to 54.8% (D2) and in CR ^{3} 3 from 28.3% (D1) to 47.0% (D2). Relapse incidence was less frequent in patients who transplanted in CR1 25.8% compared to CR2 (51.9%) and CR^3 3 (62.4%). Disease free survival did not improve in patients transplanted in the first CR (60.9% (D1) vs 54.6% (D2)) but it did improve in the second 34.4% (D1) vs 50.1% (D2)) and third CR (29.0% (D1) vs 43.0% (D2)). NRM differed significantly by match status: 26.1% in MRD and 42.3% in MUD and 46.7% in haplo-donors.

Conclusions: Allogeneic hematopoietic cell transplantation has evolved considerably since the introduction of haplo-transplantation. Our data suggests that the OS and DFS of patients with AML who received haplo-HSCT were significantly worse from MRD- and MUD-HSCT. NRM is significant higher in haplo-transplants due to more infections post-transplant and more GVHD. The patients transplanted in CR1 have the best outcome and the longest OS. We are aware that a better and more precise risk assessment with cytogenetic and molecular studies and detection of Minimal Residual Disease will help to identify the high risk patients more accurately and provide a better treatment outcome by choosing the right treatment strategy for each patient.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P036

POST ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION MAINTENANCE WITH AZACITIDINE IN COMBINATION WITH VENETOCLAX IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Nour Moukalled[1], Mona Hassan[1], Jean El Cheikh[1], Ali Bazarbachi[1], Iman Abou Dalle[1]

[1]American University of Beirut Medical Center, Beirut, Lebanon

Background: Relapsed/refractory (R/R) T-cell acute lymphoblastic leukemia (T-ALL), is an aggressive disease with few salvage options. Little progress has been seen, where nelarabine is the only approved drug (overall response rate of 50%; associated hematologic/neurological toxicities). Allogeneic-hematopoietic-stem-cell-transplantation(allo-HSCT)continues to be a potentially curative strategy in this setting, however up to half of patients still relapse post-transplant. Post-transplant maintenance treatment has long been debated, and has not been extensively explored in T-ALL, despite previous preclinical/clinical data suggesting a potential role for hypomethylating agents (HMAs) such as 5-azacitidine, in addition to suggested sensitivity to BCL2-inhibition exerted by venetoclax, paving the way for the rationale of using HMAs/venetoclax as post-transplant maintenance in high-risk T-ALL.

Methods: **Case series:** Four adult patients diagnosed with high-risk T-ALL received post allo-HSCT maintenance-5 days of 5-azacitidine (32 mg/m2 daily) with venetoclax 400 mg daily every 28 days, with a median duration of treatment of 18 months with a very good toxicity profile. After a median follow-up of 22 months from transplant, all patients remain in complete remission (CR).

Results: Patient 1: Mature T-ALL, with relapsed disease post hyperCVAD and 2 years maintenance (POMP protocol), received induction (augmented-BFM), achieved CR with negative measurable residual disease (MRD) by T-cell-receptor-(TCR)-rearrangements, underwent a full-matched-related-allo-HSCT (clofarabine/total body irradiation (TBI)-4 Gy conditioning). Maintenance treatment started day 42 post-transplant. Bone marrow 100 days post-transplant showed CR, undetectable MRD. Transplant course complicated by grade-1 skin graft-versus-host-disease (GVHD), managed by topical steroids. Patient is currently 32 months post-transplant, continuing maintenance therapy, remains in CR.

Patient 2: ETP-ALL (mutant *NOTCH1/EZH2)*, received induction with hyperCVAD with persistent MRD (TCR-rearrangements), received re-induction with augmented-BFM/venetoclax, had undetectable TCR-rearrangements, received a haploidentical-HSCT (fludarabine/TBI-8Gy conditioning). Maintenance started day 53 post-transplant; day 100 post-transplant evaluation revealed detectable TCR rearrangements, received donor lymphocyte infusion (DLI), complicated by grade 2 gastro-intestinal and skin GVHD responsive to systemic steroids. Patient is currently 24 months post-transplant with chronic skin GVHD, continuing his maintenance treatment, last disease evaluation showing CR with detectable MRD.

Patient 3: Mature T-ALL (complex cytogenetics/*EZH2/KIT/TET2* mutations), received induction hyperCVAD, achieved CR with detectable MRD, then received Capizzi regimen/venetoclax followed by matched-related allo-HSCT (clofarabine and TBI-8GY conditioning). Post-transplant course was complicated by mild skin-GVHD. Maintenance treatment started at day 115 post-allo-HSCT, continuing for 20 months to date with very good tolerance. Last bone marrow evaluation showed CR but detectable TCR MRD, received two DLI doses complicated with liver GVHD responsive to systemic corticosteroids.

Patient 4: Near-ETP ALL (normal karyotype-*ASXL1/NOTCH1/TET2* mutations), received asparaginase-based treatment (GRAALL regimen), achieved CR with negative MRD, then completed two consolidation cycles, early-intensification followed by a matched-related allo-HSCT (clofarabine/TBI-8Gy conditioning). Maintenance started at day 46 post-transplant without significant toxicity. Patient is currently 18 months post-transplant and still in CR with undetectable MRD.

Two additional patients with T-ALL post-allo-HSCT in CR2, MRD positive, have been recently started on maintenance (1 cycle), remain in CR with detectable TCR.

Conclusions: Encouraging results presenting a foundation for further studies that could assess the efficacy of HMAs combined with BCL2 inhibitors not only in the post-transplant setting but also for high-risk T-ALL patients.

Clinical Trial Registry: NA

Disclosure: No conflict of interest.

19 - Acute Leukaemia

P037

POST-INDUCTION AKT EXPRESSION DOES NOT IMPACT OVERALL SURVIVAL IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

Safa Al-Amrani[1], Fahad Al-Zadjali[1], Yasir Jeelani[1], Zaaima AL-Jabri[1], Mahdiya Al-Bulushi[2], Mohammed AlRawahi[1], Adhari Al Zaabi[1], Jalila AlShekaili[1], Mohammed Al-Huneini[1], Murtadha Al-Khabori[1]

[1]Sultan Qaboos University, Muscat, Oman, [2]Royal Hospital, Muscat, Oman

Background: The activation of the AKT signaling pathway is crucial for cellular survival, proliferation, and regulation of apoptosis in leukemias and other types of cancers. Therefore, this pathway may contribute to the survival of cancer cells. The impact of differences in AKT expression between diagnosis and remission states on patients' survival has not yet been investigated. In the current study, we aim to assess the impact of AKT expression at diagnosis and the difference in expression between diagnosis and remission on overall survival.

Methods: Patients with acute myeloid leukemia (AML) were included in this study. Cell lysates of peripheral blood and bone marrow of these patients were collected at diagnosis and remission. The expression of AKT in these samples was estimated using ELISA assay and normalized to the total protein content. Overall survival was estimated using the Kaplan-Meier curve and groups compared with the COX regression model. All analyses were performed using the R program.

Results: A total of 17 patients (a total of 68 peripheral blood and bone marrow samples) were included with a median age of 47 years (IQR: 23 – 57). At diagnosis, the median hemoglobin, white blood cells, and platelet counts were 8.0 g/dL (IQR: 6.0 – 9.0), $56*10^9$/L (36 – 68), and $33*10^9$/L (8 – 53), respectively. The median blast percentage was 50% (IQR: 26 – 77) in peripheral blood and 64% (IQR: 53 – 83) in bone marrow samples. In the peripheral blood, the median AKT expression was 564 (IQR: 499 – 1347) at diagnosis and 903 (IQR: 117 – 1270) at remission whereas, in bone marrow, it was 520 (IQR: 388 – 698) at diagnosis and 816 (IQR: 489 – 20290) at remission.

During follow-up, nine patients died. The overall survival was not affected by the AKT expression at diagnosis in peripheral blood (HR 0.8, $p = 0.83$) or bone marrow cell lysates ($p = 0.999$). In six out of the 17 patients, the AKT expression decreased in peripheral blood samples at remission. The reduction did not predict the overall survival in these patients (HR 0.5, $p = 0.67$).

Conclusions: Although AKT expression may be high in patients with AML, the level of expression does not predict overall survival. In addition, the reduction of the expression in post-induction samples does not impact overall survival and hence quantification using ELISA assay may not be a useful candidate to test a minimal residual disease. The study is limited in sample size and needs to be confirmed in future studies with larger sample sizes.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P038

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS WITHOUT TOTAL BODY IRRADIATION: A SINGLE-CENTER EXPERIENCE

Fabio Serpenti[1], Giorgia Saporiti[1], Maria Goldaniga[1], Giulia Galassi[1], Filippo Bagnoli[1], Francesca Cavallaro[1], Kordelia Barbullushi[1], Alessandro Bosi[1], Maria Rita Sciumè[1], Nicola Stefano Fracchiolla[1], Wilma Barcellini[1], Francesco Onida[1]

[1]Hematology Unit, Fondazione IRCCS Ca Granda Policlinico di Milano, Milan, Italy

Background: Allogeneic stem cell transplantation (HSCT) is the only curative option for very-high risk or relapsed/refractory acute lymphoblastic leukemia/lymphoma (ALL). Total body irradiation (TBI) is a pivotal component of conditioning regimens for ALL patients <50 yo, especially for its greater disease control and lower relapse risk, but its toxicity and logistic organization can limit its use. We aimed to report outcomes of ALL patients treated with non-TBI conditioned HSCT at our center.

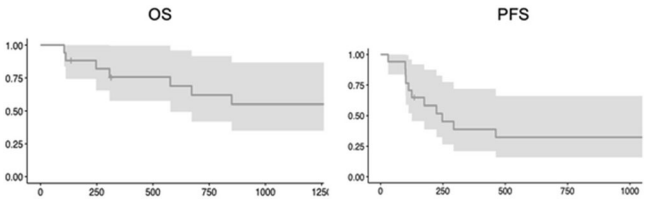
Methods: We retrospectively analyzed all consecutive non-TBI conditioned HSCT performed at our center for ALL patients between 2014 and 2021. Data on disease risk, treatment lines, disease status at transplant and transplant outcomes were recorded. A written consent was given for the use of medical records for research in accordance with the Declaration of Helsinki. Multivariate analysis using Cox regression model was used to detect variables impact on overall survival. Variables included in the model were age, diagnosis (T-ALL vs Ph- B-ALL vs PH+ B-ALL), donor (HLA-id vs MUD vs haplo) and conditioning intensity (MAC vs RIC).

Results: Seventeen patients received non-TBI HSCT for ALL between January 2014 and December 2021 at our center. Patient characteristics are summarized in table 1. Median age was 48 years old (range 31 – 68). Median Comorbidity Index score was 2 (range 0-5). Only one patient had not reached complete remission before transplant. Reasons for avoiding TBI were age >50 yo in 53%, comorbidities in 47% and logistics in 17,6% of cases. Conditioning regimen was myeloablative in 15 cases, with two alkylating agents in 14. GvHD prophylaxis was ATG-based in 11 patients, ptCy-based in 5 and only-Cya based in 1. Median time to neutrophil engraftment was 19 days (12-30). Median time to platelet engraftment was 14 days (11-45), with two patients never achieving it. Febrile neutropenia occurred in all but one patient, viral infection/reactivation in 7 and fungal invasive infection in 3. There was no case of veno-occlusive disease or acute GvHD and there were three cases of moderate chronic GvHD.

After a median follow-up of 28 months (3-79), 2y-overall survival was 61,9% and relapse-free survival was 32,4% (Fig. 1). TRM was observed in one patient and was due to a post-transplant lymphoproliferative disorder. Relapse occurred in 10 patients, six of whom died due to progressive disease. Median time from transplant to relapse was 5 months (1-15). Donor lymphocyte infusions were used in three cases of mixed chimerism, leading to full chimerism reconstitution, and in combination with other agents in five relapsed patients, leading to long-lasting disease control in two.

Multivariate analysis indicated RIC as the only variable highly associated with worse OS (HR = 14, p < 0,1).

Sex (M/F)	9/8
Disease	
• T-ALL	3
• B-ALL Ph- / very high risk B-ALL Ph-	7 / 1
• B-ALL Ph+	7
Disease status at transplant	
• CR1 / CR 2 / > CR2	7 / 5 / 4
• Progressive disease	1
Previous InO / Blina	5 / 7
Donor	
• HLA-id	4
• MUD 10/10 / 9/10	6 / 2
• HAPLO	5
Conditioning regimen	
• TEC	3
• TTCy	3
• TTF	5
• TFM	3
• TreoFlu	1
• FluMel	2



Conclusions: Older high-risk ALL patients can still benefit from HSCT despite TBI avoidance; in our series, around one third of patients was alive and relapse-free at 2 y from transplant and relapsed patients could benefit of salvage treatment coupled with DLI, which led to long-term disease control in 2 cases. Toxicity was low with only one TRM case (5%). RIC was the only variable associated to poor outcome.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P039

MYELOID SARCOMA OF THE BREAST IN POST-ALLOGENEIC STEM CELL TRANSPLANT RELAPSE: RETROSPECTIVE ANALYSIS FROM A REFERENCE TRANSPLANT CENTER

Evelyn Zapata[1], Pablo Garcia[1], Carlos Puerta[1], Ana Garcia[1], Monica Cabrero[1], Monica Baile[1], Alejandro Avendaño[1], Cristina De Ramon[1], Almudena Cabero[1], Ana Martin[1], Fermin Sanchez[1], Estefania Perez[1], Lucía Corral[1], Lourdes Vazquez[1]

[1]Hospital Universitario de Salamanca, Salamanca, Spain

Background: Allogeneic stem cell transplantation (AlloSCT) is a recognized curative therapy for higher risk acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). Unfortunately, post-transplant relapse is still a challenge. Relapse as myeloid sarcoma is a rare condition which most common locations are skin, lymph nodes or gastrointestinal. Breast involvement is a rare location for a post-AlloSCT relapse, presenting sometimes as an isolated location that could be misdiagnosed as a breast carcinoma. Further understanding of these extramedullary relapses and its mechanism of escape from donor immune system is mandatory to a better management.

Methods: Here we present a series of 5 patients with AML relapsing post-AlloSCT with breast involvement, selected from a total of 603 patients receiving and AlloSCT in our center from 2015, resulting in an incidence of 0.83%.

Results: All breast relapses occurred in women, with a median age of 38 (24-57) years. Diagnosis was AML in 2 and MDS in 3 patients. None of them had previous diagnosed breast pathology or extramedullary myeloid disease. All patients were in complete remission (CR) at AlloSCT and received myeloablative conditioning regimen. Donor was related in 4 and GVHD prophylaxis was based on methotrexate plus tacrolimus. All patients were in CR at day +100 and 3 of them maintained CR 1 year after AlloSCT. Only 1 patient developed chronic GVHD after AlloSCT and she achieved CR with first line steroids treatment.

Relapse occurred after a median of 40 months (7-99) after AlloSCT. Breast infiltration occurred in 1st relapse in 3 patients, and 2nd and 3rd relapse in 1 each. Two patients were diagnosed after initial suspicion of breast carcinoma with no other extramedullary locations affected, whereas 3 patients had blast infiltration in pericardium, muscle and bone. Two patients had bone marrow infiltration with 0.89 and 15% blasts respectively.

Treatment at relapse was chemotherapy based on schema Flag-Ida (n = 2), 5-azacitidine (n = 1) or Vyxeos® (n = 1) combined with radiotherapy in 2 of them. One patient received palliative care. All 4 treated patients achieved CR; 3 of them underwent a 2nd AlloSCT 3, 5 and 13 months after relapse, and it is planned for the 4th one at the moment of the analysis. One patient relapse 7 months after 2nd transplant and died from progression disease, whereas 3 patients are alive after 7, 64 and 75 months.

We retrospectively collected stored samples from patients at diagnosis and at relapse to evaluated clonal evolution. By now, one sample have been analyzed showing that clonal infiltration of the breast is related with the one at diagnosis in bone marrow with acquisition of NRAS y PTPN11 that could be responsible for extramedullary relapse (this patient had an isolated breast relapse).

Conclusions: Myeloid sarcoma of the breast in a rare condition after AlloSCT and differential diagnosis with breast carcinoma is mandatory since it can be the only relapse location.

Treatment based on chemotherapy combined or not with radiotherapy followed by a 2nd AlloSCT can lead to long-term survival in selected patients.

Disclosure: Nothing to declare

19 - Acute Leukaemia

P040

SEQUENTIAL REGIMEN AND REDUCED-INTENSITY CONDITIONED TRANSPLANTATION FOR ACUTE MYELOBLASTIC LEUKEMIA AND MYELODYSPLASTIC SYNDROMES. UNICENTRIC EXPERIENCE

Alejandro Avendaño Pita[1], Monica Cabrero Calvo[1], María Cortés Rodríguez[1], Pablo García Jaen[1], Evelyn Zapata Tapia[1], Carlos Puerta Vázquez[1], Ana Garcia Bacelar[1], Marta Fonseca Santos[1], Cabero Martínez Almudena[1], Mónica Baile González[1], Ana África Martín López[1], Estefania Pérez López[1], Fermín Sánchez Guijo[1], Lourdes Vázquez López[1], Belén Vidriales Vicente[1], María Diéz Campelo[1], Lucía López Corral[1]

[1]University Hospital of Salamanca, Salamanca, Spain

Background: Acute myeloblastic leukemia (AML) and myelodysplastic neoplasms (MDS) are the two main indications of allogeneic stem cell transplantation (ASCT) in the present time. Refractory disease is a poor scenario and even with new drugs, in some patients, we don't reach any response so sequential conditioning is an option to proceed to transplant.

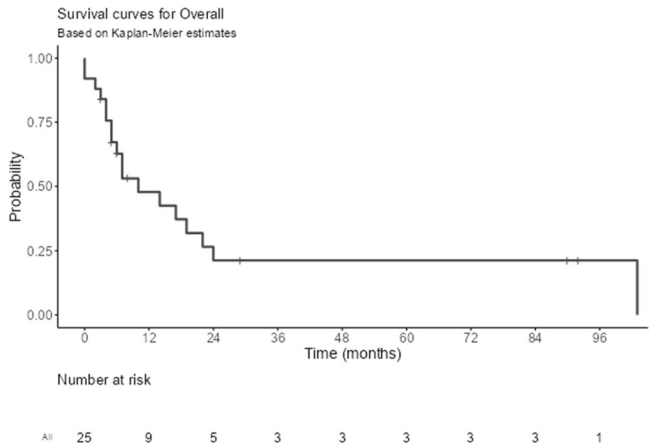
Methods: We retrospectively analysed 25 consecutive patients collected during the last 15 years in our institution. Statistics analysis were performed with IBM SPSS statistics v.26.

Results: Clinical and ASCT characteristics are shown in table 1 and table 2. Three patients (12%) were allocated as therapy related and another 3 patients (12%) evolved from a previous MDS or MPN as diagnostic qualifiers according European Leukemia Net (ELN 2022).

	n (%) / median (range)
Median age	53 (25-61)
Diagnosis	
· AML	22 (88%)
· MDS	3 (12%)
AML ELN 2022 (n = 22)	
· Favorable risk	1 (4%)
· Intermediate risk	10 (40%)
· Adverse risk	11 (44%)
Treatment	
· HMA	5 (20%)
· HMA + venetoclax	1 (4%)
· AML induction regimen	16 (64%)
· ASCT as first line	3 (12%)
Bone marrow blast pre ASCT	31.3 (7-83)
Status at ASCT	
· Primary refractory	11 (44%)
· 1st relapse	9 (36%)
· 2nd relapse	2 (8%)
· ASCT as first line	3 (12%)
ECOG < 2	19 (76%)
Cytoreductive treatment	
· Fludarabine based	8 (32%)
· Clofarabine based	16 (64%)
· Others	1 (4%)
Conditioning platform	
· Fludarabine + Busulfan	23 (92%)
· Others	2 (8%)
Post-transplant Cyclofosfamide	10 (40%)
Stem cell source	
· Peripheral blood	24 (96%)
· Bone marrow	1 (4%)
Type of donor	
· MSD	15 (60%)
· MUD	5 (20%)
· Haploidentical	5 (20%)
GVHD prophylaxis	
· CNI + MMF	9 (36%)
· Tacro + PT-Cy	4 (16%)
· Tacro + Sirolimus	12 (48%)
Acute GVHD (n = 13)	
· Grade I-II	9 (36%)
· Grade III-IV	4 (16%)
Chronic GVHD	
· Limited	1 (4%)
· Extensive	3 (12%)

We have *Next Generation Sequencing (NGS)* data of 10 patients (40%). Median number mutation per patient were 3 (0-9). Most recurrent mutations were DNMT3 and FLT3 in 30% and KRAS, PTPN11, RUNX1and SF3B1 in 20% of patients with available data.

With a median follow up of 19.5 months (1-103) the median, the estimated 1-year and 5-year OS was 48% [31%-74%, 95% CI] and 21% [9%-50%, 95% CI] respectively (graph 1)



In univariate analysis, those patients with ³ 2 treatment had worse survival ($p = 0.039$) and on the contrary, to reach complete remission at day +100 improves outcomes ($p = 0.0012$). Sixteen patients (64%) reached profound response consistent with CR MRD^{neg} and full donor chimerism at some point but on the formal evaluation at day +100, 9 patients (36%) experienced relapse and we lost 4 patients (16%) due to early mortality. The main causes of dead were progression in 10 cases (40%), infection in 5 cases (20%), bleeding in 2 cases (8%) and other reasons in 1 case (4%).

Conclusions: Our data shows the dismal prognosis of those patients with refractory disease but at the same time reveals that there are a small subset of long term survivors. Identification of who are the patients who benefits the most, the correct timing to transplant and optimization of cytoreductive and conditioning platforms require further studies.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P041

LONG-TERM OUTCOMES OF ALLOGENEIC STEM CELL TRANSPLANTATION IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Anna Płotka[1], Anna Wache[1], Anna Łojko-Dankowska[1], Magdalena Matuszak[1], Dominik Dytfeld[1], Jolanta Kiernicka-Parulska[1], Anna Mierzwa[1], Ewa Bembnista[1], Krzysztof Lewandowski[1], Lidia Gil[1]

[1]Poznan University of Medical Sciences, Poznan, Poland

Background: Allogeneic hematopoietic cell transplantation (alloHCT) is a standard treatment of patients (pts) with Philadelphia positive (Ph+) acute lymphoblastic leukemia (ALL), especially with detectable minimal residual disease (MRD+) or with relapsed disease. Long term survival after alloHCT is influenced by relapse and non-relapse mortality (NRM). Herein, we present a retrospective analysis of the long-term outcomes of alloHCT in pts with ALL in one institution with respect on MRD status and HCT-CI index prior to the procedure.

Methods: The study group consisted of 92 de novo ALL pts, median age 33 (range, 18-65) years, transplanted at our institution between 2007-2021. 35% pts underwent alloHCT form HLA-identical sibling donor, while 65% from 9-10/10 matched unrelated donor. The stem cells were collected from peripheral blood (71%) or bone marrow (29%). Graft versus host disease (GvHD) prophylaxis consisted of calcineurin inhibitor combined with methotrexate, plus ATG in 68% of pts. Only first transplantations were analyzed.

Results: In the whole cohort 82% of pts were transplanted in the first complete remission (CR1), while 18% beyond CR1. 84% of pts were conditioned with myeloablative therapy, including 77% based on total body irradiation (TBI). 70 pts (76%), 19 pts (21%) and 3 pts (3,2%) had low, median and high HCT-CI index, respectively. 60% of pts were MRD+ prior to the procedure. 8% of pts were older than 60 years.

The median follow-up time was 34 month. The median time of neutrophil recovery was 20 (range, 11-36) days. Acute GvHD was diagnosed in 23% of pts, while chronic in 15% of pts. Relapse of disease occurred in 23 pts (25%), mostly within first year after alloHCT (79%).

During follow-up the median overall survival (OS) was 36 months, and 35 (38%) pts died. The main reason for death was the relapse of the disease (18 pts), followed by infectious complications (12 pts). The 2-year estimated OS was 68% and the relapse free survival (RFS) was 20%. In the analysed cohort, MRD status prior to alloHCT, HCT-CI index and older age of pts did not influenced OS, RFS or NRM significantly.

Conclusions: In long-term observations of pts with ALL after alloHCT, relapse of the disease remains the main cause of death. Most relapses occur within first 1 year after alloHCT. Infectious complications contributes to substantial number of deaths.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P042

POST-INDUCTION IDH2 EXPRESSION DOES NOT IMPACT OVERALL SURVIVAL IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

Safa Al-Amrani[1], Fahad Al-Zadjali[1], Yasir Jeelani[1], Zaaima AL-Jabri[1], Mahdiya Al-Bulushi[2], Mohammed AlRawahi[1], Adhari Al Zaabi[1], Jalila AlShekaili[1], Mohammed Al-Huneini[1], Murtadha Al-Khabori[1]

[1]Sultan Qaboos University, Muscat, Oman, [2]Royal Hospital, Muscat, Oman

Background: Isocitrate dehydrogenases (IDHs) are enzymes that play important roles in numerous cellular metabolic and epigenetic processes. About 20% of patients with acute myeloid leukemia (AML) have mutations in either IDH1 or IDH2. To our knowledge, the impact of differences in IDH2 expression between diagnosis and remission states on patients' survival has not been investigated. In this study, we aim to assess the impact of IDH2 expression at diagnosis and compare the difference in the expression between diagnosis and remission on overall survival.

Methods: Patients with acute myeloid leukemia (AML) were included in this study. Cell lysates of peripheral blood and bone marrow of these patients were collected at diagnosis and at remission. The expression of IDH2 in these samples was estimated using ELISA assay and normalized to the total protein content.

Overall survival was estimated using the Kaplan-Meier curve and groups were compared with the COX regression model. All analyses were performed using the R program.

Results: A total of 19 patients (a total of 76 peripheral blood and bone marrow samples) were included with a median age of 47 years (IQR: 27 – 59). At diagnosis, the median hemoglobin, white blood cells, and platelet counts were 8.3 g/dL (IQR: 6.3 – 9.4), $24*10^9$/L (8 – 49), and $53*10^9$/L (33 – 63), respectively. The median blast percentage was 50% (IQR: 27 – 68) in peripheral blood and 70% (IQR: 53 – 83) in bone marrow samples. In peripheral blood, the median IDH2 expression was 4.4 (IQR: 2.0 – 17.5) at diagnosis and 19.0 (IQR: 6.6 – 42.1) at remission whereas, in bone marrow, it was 5.3 (IQR: 3.3 – 5.6) at diagnosis and 6.7 (IQR: 4.6 – 12.5) at remission.

During follow-up, nine patients died. The overall survival was not affected by the IDH2 expression at diagnosis in peripheral blood (HR 1.3, $p = 0.755$) or bone marrow cell lysates (HR = 0.7, $p = 0.68$). In one out of the 19 patients, the IDH2 expression decreased in remission peripheral blood samples.

Conclusions: The level of IDH2 expression does not predict overall survival in peripheral blood and bone marrow samples. In addition, the reduction of the expression occurs in a small minority in post-induction samples and hence quantification using ELISA assay may not be a useful candidate as a minimal residual disease test. The study is limited in sample size and needs to be confirmed in future studies with larger sample sizes.

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P043

CD33+ TARGETING, CONSOLIDATIVE HSCT AND INTEGRATION OF MIDOSTAURIN IN FLT3 POSITIVE AML PEDIATRIC PATIENTS: A SINGLE CENTER EXPERIENCE

Manuela Tumino[1], Maria Gabelli[1], Chiara Mainardi[1], Marta Pillon[1], Antonio Marzollo[1], Elilsabetta Calore[1], Giulia Reggiani[1], Maria Caterina Putti[1], Martina Pigazzi[2], Anna Leszl[1], Barbara Buldini[1], Alessandra Biffi[1]

[1]Pediatric Onco-Hematology and Hematopoietic Stem Cell Transplantation Division, Azienda Ospedale-Università Padova, Padova, Italy, [2]Pediatric Onco-Hematology and Hematopoietic Stem Cell Transplantation Unit, Padova University, Padova, Italy

Background: FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) characterizes a high-risk form of acute myeloid leukemia (AML). FLT3-ITD mutations are associated to an increased expression of CD33. In 2017, Midostaurin was approved by the FDA as first FLT3 inhibitor and as first targeted therapy in adult AML. Gemtuzumab ozogamicin (GO) is an anti-CD33 monoclonal antibody approved by EMA in 2018 for the treatment of patients aged 15 years and above with previously untreated de novo CD33-positive AML, in combination with daunorubicin and cytarabine.

Methods: We report two pediatric patients affected by relapsed/refractory AML FLT3-ITD. Case 1 is a 9-years-old male with diagnosis of M1 AML positive for FLT3-ITD and t(3;5)(NPM1-MLF1); blasts expressed CD45, CD7, CD33 and CD38, detected by flow cytometry. Cytogenetic analysis confirmed t(3;5) translocation. The patient received four cycles of chemotherapy according to the AIEOP-AML2013 Protocol, high-risk group (ICE, FLA-My, AVE, HAM). Morphological and cytofluorimetric complete remission (CR) occurred at the end of the first cycle of induction, with persistency of FLT3-ITD and t(3;5) signal at high level. Disease relapse occurred after the 4th cycle, immediately before allogeneic hematopoietic stem cell transplantation (alloHSCT). Two additional cycles (Clofarabin-daunorubicin-Cytarabin and high dose Etoposide) were administered, without response. The patient then received additional treatment based on the association of GO, Doxorubicin, Aracytin and Midostaurin. Haploidentical HSCT with peripheral TCRalpha/beta-CD19 depleted cells from father was then performed in aplasia, preceded by a myeloablative conditioning regimen based on TBI-Melphalan. Case 2 is a 12-year-old female with diagnosis of AML positive for FLT3-ITD and t(5;11), with positive expression of CD33, CD45, CD99, CD38, CLL1, CD11a, CD44 detected by flow cytometry. Cytogenetic analysis confirmed t(5;11) translocation. The patient received the first two treatment cycles according to the AIEOP-AML2013 Protocol, high-risk group (ICE, ICE), without disease remission. Additional treatment with Fludarabin-Aracytin-Myocet-G CSF could not prevent disease progression. The patient then received one cycle based on the association of GO, Clofarabin, Aracytin and Midostaurin. Thereafter, alloHSCT from a HLA-matched sibling donor was performed in aplasia, preceded by a myeloablative conditioning regimen based on TBI-Melphalan.

Results: Post-HSCT course of both patients was complicated by pneumonia (atypical mycobacteria in the case 1, fungal in case 2) that required prolonged hospitalization. No GvHD occurred. Bone marrow evaluation at neutrophil engraftment showed morphological, cytofluorimetric and molecular CR, with full donor chimerism in both patients. Midostaurin was restarted in patient 1, at day +40 days post HSCT and continued up to 2 years post HSCT. Both patients are still alive and in persistent complete remission at + 3 years and +1 year after HSCT respectively.

Conclusions: GO integration into the FLT3-AML therapy before HSCT resulted in improved outcomes for pediatric patients with refractory AML. Combination of targeted inhibition of FLT3 and CD33 followed by allogeneic HSCT could be a promising therapeutic opportunity for refractory/relapsed pediatric AML.

Disclosure: nothing to declare.

19 - Acute Leukaemia

P044

THE OUTCOME OF SECONDARY AML PATIENTS WITH PRIOR BREAST CANCER UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION IS AS GOOD AS DE NOVO AML

Merve Aydoğan[1], Bülent Karakaya[1], Gül Yavuz Ermiş[1], Güldane Cengiz Seval[1], Sinem Civriz Bozdağ[1], Selami Koçak Toprak[1], Pervin Topçuoğlu[1], Meltem Kurt Yüksel[1]

[1]Ankara University, Ankara, Turkey

Background: Treatment-related acute myeloid leukemia (t-AML) may develop in patients exposed to DNA-damaging agents, including alkylating agents, topoisomerase-II-inhibitors and antimetabolites and ionizing radiation. 71% patients with t-AML had a previous solid cancer and breast cancer was the most common neoplasm. Compared to de novo AML, patients with t-AML tend to exhibit worse clinical outcomes, including significantly inferior complete remission rates, relapse-free survival, and overall survival. Based on this, 5 cases of t-AML followed in our center will be presented.

Methods: The data of 5 female who undergoing allogeneic stem cell transplantation (ASCT) at Ankara University, Stem Cell Transplantation Unit, with a history of breast cancer, were analyzed retrospectively.

Results: **Case Series**

Case-1: A 48-year-old female patient. 5 years ago, she had breast cancer. The patient received 6 courses of chemotherapy (CT) and radiotherapy (RT) after mastectomy. While she was in remission with tomoxifen treatment, she was diagnosed with AML(FLT3-ITD+, WT1+). After receiving 7 + 3+midostaurin and 3 courses of azasitidine+ venetoclax, ASCT was performed from his fully matched brother. She is in second month and has poor graft function, now.

Case-2: A 63-years-old female patient. She was diagnosed with breast cancer 35 years ago. The patient who received bilateral mastectomy and then CT + RT, was cured. She had AML-M5 (FLT-ITD+, NPM1A+) one year ago. After 7 + 3+midostaurin and 2 courses of IDAC+midostaurin, relapsed 4 months later. ASCT was performed from a female donor. After 4 months, she had gastrointestinal(GI) graft-versus-host disease(GvHD).

Case-3: A 57-year-old female patient. When she was 47 years old, she had breast cancer and mastectomy, CT and RT was applied. After 9 years, she had AML-M5 (NPM1A+). She received 3 courses of HiDAC after 7 + 3 induction therapy. She had haploidendic ASCT from his brother. She had hemorrhagic cystitis in the 2nd month after transplantation

Case-4: 35-year-old female patient.7 years ago, she was diagnosed with, breast cancer. After mastectomy, she received 8 courses of CT and RT. 4 years ago, she had AML-M5 (11q23, MLL +). After 7 + 3 induction therapy ve 2 courses of HiDAC, she was relapsed 2 months later. She had ASCT from a female donor. Afterwards, she had acute skin and GI-GvHD and thrombotic microangiopathy(TMA). The disease relapsed 2 years after the transplant and the patient died at the age of 35.

Case-5: A-58-year-old female patient. At age 45, 13 years ago, she was diagnosed breast cancer. After receiving 6 courses of CT and RT, she received tamoxifen. At age 50, she had AML M4/5. After 7 + 3 induction therapy, 4 courses of FLAG therapy were given, as she did not has remission. Finally, ASCT was performed from an unrelated donor. At the first month of transplantation, she had skin-GvHD. The patient continues to be followed in the 7th year of transplantation.

Conclusions: In our center, 5 cases diagnosed with t-AML after breast cancer, followed by ACST are presented. The outcomes of ASCT of the patients are as good as de novo AML. Overall survival is 80%

Disclosure: Nothing to declare.

19 - Acute Leukaemia

P045

OUTCOMES IN SURVIVAL IN PATIENTS WITH ACUTE LEUKEMIA IN PEDIATRIC AND YOUNG ADULTS WITH ALLOGENIC HSCT AND HAPLOIDENTICAL HSCT IN A MEXICAN PUBLIC HEALTH HOSPITAL

Guillermo Sotomayor Duque[1], Severiano Baltazar Arellano[1], Guadalupe Gonzalez Villarreal[1], Juan Daniel Garza Escobar[1], Rosa Elva De León Cantu[1], Roberto Hernández Valdez[1]

[1]IMSS UMAE 25 Monterrey, Monterrey, Mexico

Background: Hematopoetic Stem Cell Transplantation (HSCT) in acute leukemias is an indication in those with high-risk disease in first remission or those who achieve a second response after relapse. The first option is to find a match related donor; in our country due to the limited access of a match unrelated donor, Haplo HSCT has become a feasible option in our center.

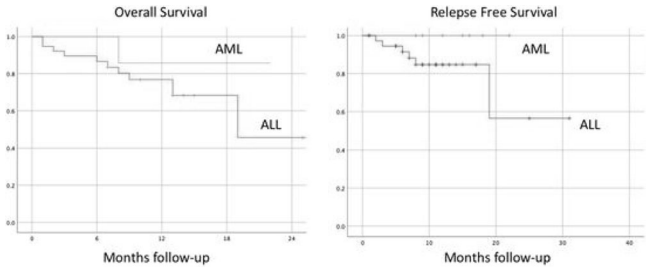
Methods: Objective: Describe the results of patients undergoing allogeneic HSCT and HaploHSCT with acute leukemia.

Retrospective analysis of patients diagnosed with acute leukemia who underwent transplantation from 2017 to 2022 at the Hospital IMSS UMAE 25 Monterrey Mexico. Descriptive analysis with measures of central tendency, analysis of overall survival (OS) and relapse-free survival (RFS) with the Kaplan Mier method.

Results: A total of 45 patients were included, 29 men (65%) and 16 women (35%) with a median age of 17 years (1-44). AML were 7 (15.6%) ALL 38 (84.4%). Seven patients had detectable minimal residual disease prior to transplantation. The type of transplant was allogenic HSCT in 21 and Haplo HSCT in 24 patients. The conditioning regimen was myeloablative in 97.8% of patients (Flu/Bu protocol). By type of donor, the most common was father 35.6%(16), mother 2.2%(1), brother 42.2%(19), sister 20%(20). Disparity in the AB0 group was presented in 11.1%. The median CD 34 was 10.6/kg (3.0-60.3) obtained from peripheral blood replete with T lymphocytes. The median engraftment of the myeloid series was 14 days (10-32) and platelets 14 days (9-33).

The median post-transplant follow-up was 11 months (1-31 months). OS for ALL was 45% and for AML 85% at 20-month follow-up. For allogeneic transplant, ALL had an OS of 25% and for AML an OS of 100% at 20 months; for Haplo HSCT in ALL the OS was 80% and AML 75% at 18 months of follow-up.

The RFS was 100% for AML and 57% for ALL at 20 months. For allogeneic transplant in ALL the RFS was 42%, LMA was 100%. In the Haploc HSCT in ALL the RFS was 82% and in LMA 100% at 20 months.



Conclusions: Our retrospective analysis has limitations such as the lack of characterization of genetic risk of leukemia and the number of patients.

In our analysis, the HSCT Haplo compared to the match allogeneic HSCT shows a trend of better results in high-risk ALL and refractory behavior with a greater OS in the 20-month follow-up of this analysis; while the LMA found similar OS rates. The use of myeloablative conditioning with the Bu/Flu protocol demonstrates a tendency to reduce relapse in our center in both transplant modalities.

Our results show that both Haplo HSCT and allogeneic HSCT have comparable results in relapse-free survival in acute leukemias as reported in recent studies by CIMBTR.

Disclosure: Nothing to declare.

20 - Aplastic Anaemia

P046

COMPARISON OF THE OUTCOMES OF IMMUNOSUPPRESSIVE THERAPY WITH RABBIT - VS. HORSE-ANTI-THYMOCYTE GLOBULIN FOR THE TREATMENT OF SEVERE APLASTIC ANEMIA IN CHILDREN

Ayami Yoshimi[1], Peter Noellke[1], Jan Starý[2], Krisztián Kállay[3], Owen Smith[4], Franco Locatelli[5], Jochen Buechner[6], Ivana Bodova[7], Julian Sevilla[8], Markus Schmugge[9], Marc Bierings[10], Tania Masmas[11], Michael Dworzak[12], Veerle Labarque[13], Katarzyna Pawelec[14], Kirsi Jahnukainen[15], Sophia

Polychronopoulou[16], Paula Kjollerstrom[17], Marko Kavcic[18], Miriam Erlacher[1], Charlotte M Niemeyer[1], Brigitte Strahm[1]

[1]University of Freiburg, Freiburg, Germany, [2]Charles University and University Hospital Motol, Prague, Czech Republic, [3]Central Hospital of Southern Pest - National Institute of Hematology and Infectious Diseases, Budapest, Hungary, [4]Our Lady's Children's Hospital, Dublin, Ireland, [5]IRCCS Ospedale Pediatrico Bambino Gesù; Catholic University of the Sacred Hearth, Rom, Italy, [6]Oslo University Hospital, Oslo, Norway, [7]Detská Fakultná Nemocnica s Poliklinikou v Bratislave, Bratislava, Slovakia, [8]Hospital Infantil Universitario Niño Jesús, Madrid, Spain, [9]University Children's Hospital, Zurich, Switzerland, [10]Princess Máxima Center for Pediatric Oncology and Wilhelmina Children's Hospital, Utrecht, Netherlands, [11]Center for Hemoglobinopathies, Herlev University Hospital, Herlev, Denmark, [12]St. Anna Children's Hospital, Medical University of Vienna, and St. Anna Children's Cancer Research Institute (CCRI), Vienna, Austria, [13]University Hospital Leuven Gasthuisberg, Leuven, Belgium, [14]Warsaw Medical University, Warsaw, Poland, [15]Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [16]Aghia Sophia Children's Hospital, Athens, Greece, [17]Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal, [18]University Children's Hospital, Ljubljana University Medical Centre, Ljubljana, Slovenia

Background: Immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and cyclosporine A (CSA) is an effective treatment for many patients with severe aplastic anaemia (SAA). Most previous studies including a randomized control trial comparing horse (h-ATG: Lymphoglobulin® or Atgam®) and rabbit ATG (r-ATG: Thymoblobulin®) indicated superiority of h-ATG. However, there is limited data comparing the outcomes of Atgam® and Thymoblobulin® outside US. Here, we report on the outcomes of IST with ATG and CSA in 150 children with SAA registered in the European Working Group of Severe Aplastic Anemia (EWOG-SAA) and consecutively treated with Atgam® or Thymoblobulin®.

Methods: Among the 150 children (M/F = 92/58, median age 10.2 years [1.1-18]), 110 patients received h-ATG (ATGAM®, 40 mg/kg x 4 days), while 40 patients received r-ATG (Thymoglobulin®, 3.5 mg/kg x 5 days). Granulocyte-colony stimulating factor was administered to patients with an absolute neutrophil count (ANC) < 0.5.10*9/L. None of the patients received eltrombopag at start of IST, but it was added in 5 non-responders at a median time of 192 days (122-671) after IST start. Remarkably, 85% of patients had very SAA with <0.2.10*9/LANC and 41% had zero neutrophils in peripheral blood prior to IST. There were no significant differences in patient characteristics between two ATG groups. The median time from diagnosis to IST was 36 (7–305) days and the median follow-up time 3.1 (0.1-8.9) years.

Results: The overall (complete + partial) response rate at 6 months was significantly higher in the h-ATG compared to the r-ATG group (42% vs. 22%, p = 0.03). In univariate and multivariate analyses, lower ANC prior to IST and use of r-ATG were associated with an inferior response to IST at 6 months. Due to late responses > day 180 (28% vs. 20%) and fewer relapses (0/9 vs. 9/46 of responders at day 180) in the r-ATG group compared to the h-ATG cohort, there was no difference in the response rates between two groups at time of last follow-up (39% vs. 35%). To note, 55% and 53% of patients in the h-ATG and r-ATG groups received allogeneic hematopoietic stem cell transplantation during their treatment course, and 20% and 28% before day 180, respectively. Only two patients had clonal evolution (1 in each group). There were no differences in the overall survival (OS: 93% vs. 88%) and failure-free-survival (33% vs. 38%) between h-ATG and r-ATG groups. Causes of deaths were transplant-related complications (n = 9), lymphoma after HSCT (n = 1), and infection prior to HSCT (n = 1). Responders at 6 months (n = 55) showed 100% OS. Importantly, non-responders with <0.2 x10*9/L ANC at day 90 had inferior OS compared to those with > 0.2 x10*9/L ANC (74% vs. 95%, p < 0.01).

Conclusions: In conclusion, there was no difference in response rate and survival at time of last follow-up between the patients receiving h-ATG or r-ATG. However, earlier response in patients treated with h-ATG may be a great benefit, because prolonged severe neutropenia is associated with increased mortality in patients with SAA.

Disclosure: Nothing to declare.

20 - Aplastic Anaemia

P047

OUTCOMES AFTER CORD BLOOD TRANSPLANTATION FOR INHERITED BONE MARROW FAILURE SYNDROMES: A REPORT FROM THE JSTCT INHERITED DISEASE WORKING GROUP

NAO YOSHIDA[1], Miharu Yabe[2], Hiromasa Yabe[2], Katsutsugu Umeda[3], Shinya Osone[4], Takashi Koike[2], Shoji Saito[5], Katsuyoshi Koh[6], Hiroyuki Ishida[7], Maho Sato[8], Koji Kato[9], Atsushi Sato[10], Yoshiko Hashii[11], Yoshiko Atsuta[12]

[1]Children's Medical Center, Japanese Red Cross Aichi Medical Center Nagoya First Hospital, Nagoya, Japan, [2]Tokai University School of Medicine, Isehara, Japan, [3]Graduate School of Medicine, Kyoto University, Kyoto, Japan, [4]Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [5]Shinshu University School of Medicine, Matsumoto, Japan, [6]Saitama Children's Medical Center, Saitama, Japan, [7]Kyoto City Hospital, Kyoto, Japan, [8]Osaka Women's and Children's Hospital, Izumi, Japan, [9]Central Japan Cord Blood Bank, Seto, Japan, [10]Miyagi Children's Hospital, Sendai, Japan, [11]Osaka University Graduate School of Medicine, Suita, Japan, [12]Japanese Data Center for Hematopoietic Cell Transplantation, Nagakute, Japan

Background: Recent advances in cord blood transplantation (CBT) have increased options available in hematopoietic cell transplantation. However, studies describing the outcomes of CBT for inherited bone marrow failure syndromes (IBMFS) are limited.

Methods: Using data from the Japanese Society for Transplantation and Cellular Therapy registry, we assessed the outcomes of 52 children (< 16 years old) with IBMFS (14 Fanconi anemia [FA], 5 dyskeratosis congenita [DC], 14 severe congenital neutropenia, 11 Diamond-Blackfan anemia and 8 others) who underwent CBT (5 related and 47 unrelated) between 1995 and 2018. Eight of the patients with FA were transplanted after malignant transformation (2 myelodysplastic syndrome [MDS] and 6 acute leukemia). Cord blood units were HLA-A, -B, -C, and -DR serologically matched (n = 12) or had 1 (n = 23) or 2-3 (n = 17) disparities with the recipient, and the median total number of nucleated cells (TNC) infused was 7.4 x 10^7/kg. Fludarabine-based reduced intensity conditioning was used in 39 patients (75%).

Results: The probability of neutrophil engraftment at day 60 was 83%; limited HLA disparity was the only favorable factor for engraftment (91% in the matched or 1 mismatched vs. 65% in the 2 or more mismatched; $P = 0.034$). The 5-year overall survival (OS) and event-free survival (EFS) were 77% and 58%, respectively, which varied depending on the underlying disease. Patients with FA or DC had inferior OS (56% vs. 90%; $P = 0.002$) and EFS at 5 years (41% vs. 68%; $P = 0.034$) than other patients. The main cause of treatment failure was graft failure (n = 11; 6 primary and 5 secondary), 9 of which were salvaged by retransplantation; limited to FA, leukemia relapse or development of a second

malignancy was most common (n = 5), all of which occurred in patients who had progressed to MDS/acute leukemia before CBT. The cumulative incidence of grade II-IV acute GVHD at day 100 and of chronic GVHD at 5 years was 34% and 14%, respectively. Other than HLA disparity and underlying disease, no other factors were associated with transplant outcomes, including the TNC infused.

Conclusions: The current study reveals that a significant proportion of children with IBMFS, especially other than FA and DC, can be cured with CBT. Given that graft failure was a major cause of treatment failure and was more associated with the use of CB units with greater disparities in HLA, better HLA matching may further improve the outcomes. For patients with FA, transplantation before progression to MDS/acute leukemia may be a good option.

Disclosure: Nothing to declare.

20 - Aplastic Anaemia

P048

PREGNANCY OUTCOMES AND MANAGEMENT IN ACQUIRED BONE MARROW FAILURE SYNDROME AND PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA: A SINGLE CENTRE EXPERIENCE

Marta Bortolotti[1,2], Roochi Trikha[1], Sarah Salter[1], Joanna Large[1], Shreyans Gandhi[1], Austin Kulasekararaj[1]

[1]King's College Hospital NHS Foundation Trust, London, United Kingdom, [2]University of Milan, Milan, Italy

Background: Onset and relapse of acquired aplastic anaemia (AA), hypoplastic myelodysplastic syndrome (hypo-MDS) and paroxysmal nocturnal haemoglobinuria (PNH) during pregnancy are rare events and little is known about foeto-maternal outcomes and management of cytopenias during pregnancy.

Methods: We conducted a single-centre retrospective study evaluating impact of AA, hypo-MDS and PNH on pregnancy, focusing on disease severity, treatment need and foeto-maternal outcomes.

Results: Seventy pregnancies occurring in 52 women were registered between 1989 and 2022 (*Table 1*). Thirty-three women had a previous diagnosis (21 AA; 4 AA/PNH; 5 PNH; 3 hypo-MDS) while 19 had an onset during pregnancy (14 AA; 2 PNH; 3 hypo-MDS). Mean age at diagnosis of disease and of pregnancy was 24(3-38) and 30 (20-40) years, respectively. Among the 21 with previous AA diagnosis, 8 were non-severe, 8 severe and 5 very-severe; median time between diagnosis and pregnancy was 10 years (0.5-26). Twenty-one women had received at least 1 therapy line (12 ATG; 3 cyclosporin (CSA); 1 tacrolimus; 5 eculizumab), ≥2 lines in 3 and 3 patients were CSA-dependent. Twenty-two were on treatment at pregnancy onset (3 CSA; 1 eltrombopag; 18 eculizumab). PNH-clone was present in 32 patients with median granulocyte clone of 16.3% (0.08-99). Considering only pregnancies with previous AA/hypoMDS diagnosis (N = 38), relapse occurred in 9 (24%), with 1 severe case. Overall, onset/relapse occurred in 11, 7 and 4 pregnancies during the 1st, 2nd and 3rd trimester respectively (not known for 6). At the time of onset/relapse, median haemoglobin was 80 g/l (49-113), reticulocytes 59 $x10^9$/l (32-66), neutrophils 2.27 $x10^9$/l (0.1-6.61) and platelets 32 $x10^9$/l (2-87). Transfusions were necessary in 61% of cases and 45 women required treatment during pregnancy. CSA was used in 12 cases; 8 patients started CSA during pregnancy, with response in 5 and of the 4 patients, who were on CSA before pregnancy (1 switched from Eltrombopag at pregnancy onset), 2 relapsed. Eculizumab was administered during 33 pregnancies, pre-emptively (granulocyte clone >20% and minimal haemolysis LDH < 2 x ULN) in 13 and for haemolysis in 20. Eculizumab dose was increased in 17/33 (52%) and thromboprophylaxis was performed in 31/33 (94%). Spontaneous improvement in blood counts after delivery/miscarriage occurred in 29 pregnancies (55%). Post-partum therapy was required in 14 (6 ATG, 6 CSA, 1 transplant and 1 androgens) with 75% response rate. Five (7%) spontaneous miscarriages were reported (4/5 in the 1sttrimester), all in PNH women. Maternal adverse events occurred in 24% of pregnancies, including a Budd-Chiari syndrome after delivery, 6 infections, 4 peripartum bleedings, 5 placental complications (2 pre-eclampsia, 2 retained placenta, 1 premature rupture of the membrane) and 6 urgent caesarean sections/preterm vaginal delivery. Seven women needed peripartum transfusions. Foetal complications occurred in 10% of pregnancies, including 5 premature births, 1 foetal growth restriction and a baby with a talipes foot.

Table 1

N° of women, n	52
N° of pregnancies, n	70*
Age at AA/hypo-MDS/PNH diagnosis, mean (range)	24 (3-38)
Age at pregnancy, mean (range)	30 (20-40)
Diagnosis before pregnancy, n	33
• AA (NSAA; SAA/VSAA; na), n	21 (8; 5; 8)
• AA/PNH, n	4
• Hypo-MDS, n	3
• PNH, n	5
Treatment before pregnancy, n	21
• ATG-based regimen, n	12
• CSA, n	3
• Tacrolimus, n	1
• Eculizumab, n	5
Treatment ongoing at pregnancy onset, n	22
• CSA, n	3
• Eltrombopag, n	1**
• Eculizumab, n	18
AA/hypo-MDS relapse during pregnancy, n (%)	9 (24)§
Onset during pregnancy, n	19
• AA (NSAA; SAA/VSAA; na), n	14 (5; 4; 5)
• Hypo-MDS, n	3
• PNH, n	2
Transfusion needs during pregnancy, n (%)	40 (61%)
• for onset/relapse;	24
• without frank relapse or for PNH-related haemolysis	16
Treatment needs during pregnancy, n	45
• CSA, n	12
• Eculizumab, n	33
• Steroids, n	3
Spontaneous improvement after delivery, n (%)	29 (55)
Treatment needs after pregnancy, n (%)	39 (58)
• ATG-based, n	6
• CSA ± Eltrombopag, n	6
• Androgens, n	1
• Eculizumab, n	25
• HSCT, n	

	1 (3 further patients were transplanted afterwards)
Maternal complications, n (%)	16 (24)*
• Thrombotic complications	1
• Infective complications	6
• Bleeding complications	4
• Placental complications (pre-eclampsia; retained placenta; PROM)	5 (2; 2; 1)
• Needs of urgent caesarean section or delivery before full term (for any causes)	6
• Needs of transfusion support during and after delivery	7
Foetal complications, n (%)	7 (10)*
• Prematurity	5
1. Extremely preterm (less than 28 weeks)	2
2. Very preterm (28-32 weeks)	1
3. Moderate-late preterm (32-37 weeks)	2
• Foetal growth restriction	1
• Other (talipes foot)	1
Miscarriage, n (%)	5 (7)*
• - I trimester	4
• - II trimester	1

*Two pregnancies are still ongoing.
**Switched to CSA after positive pregnancy test.
§Percentage calculated considering only pregnancies with a previous diagnosis of AA/hypo-MDS (N = 38).
AA, aplastic anaemia; ATG, anti-thymocyte globulin; CSA, cyclosporin; hypo-MDS, hypoplastic myelodysplastic syndrome; NSAA, non-severe aplastic anaemia; PNH, paroxysmal nocturnal haemoglobinuria; PROM, premature rupture of membrane; SAA, severe aplastic anaemia; VSAA, very-severe aplastic anaemia.

Conclusions: At our best knowledge, this is one of the largest cohorts reported so far and suggest that, even though pregnancy should not be discouraged in these women, it surely requires a high level of awareness and multidisciplinary approach.

Disclosure: Nothing to declare.

20 - Aplastic Anaemia

P049

SHORT TELOMERES BEFORE TRANSPLANT ARE ASSOCIATED WITH GRAFT FAILURE FOLLOWING HEMATOPOIETIC CELL TRANSPLANT FOR CHILDREN WITH APLASTIC ANEMIA

Atsushi Narita[1], Hideki Muramatsu[1], Masayuki Imaya[1], Daiki Yamashita[1], Daichi Sajiki[1], Ryo Maemura[1], Yusuke Tsumura[1], Ayako Yamamori[1], Manabu Wakamatsu[1], Kotaro Narita[1], Shinsuke Kataoka[1], Rieko Taniguchi[1], Nobuhiro Nishio[1], Yoshiyuki Takahashi[1]

[1]Nagoya University Graduate School of Medicine, Nagoya, Japan

Background: Short telomeres are associated with aplastic anemia (AA) as well as telomere biologic disorders. Hematopoietic stem cell transplantation (HSCT) in patients with telomere biologic disorders is associated with a high risk of transplant-related mortality. In children with AA, however, the correlation between pre-transplant telomere length (TL) and outcomes following HSCT is still not clear.

Methods: Of the patients enrolled in the Central Review of Bone Marrow Morphology for children in Japan, 101 children with AA who underwent HSCT were retrospectively studied. We measured TL by flow-fluorescence in situ hybridization using the Telomere PNA Kit (DakoCytomation, Glostrup, Denmark) from peripheral blood (PB) lymphocytes for all patients. Data of patients with AA were expressed as "delta relative TL" to compare with TL of patients with age-matched healthy controls. To distinguish between engraftment and graft failure, receiver operating characteristic (ROC) curves were generated.

Results: The median age at HSCT was 11.0 (1.3–27.2) years. The etiology was idiopathic in 94 and hepatitis associated in 7 cases. The severity was moderate in 19, severe in 42, and very severe in 40 cases. The median TL at diagnosis was -1.12 SD (-4.60 to $+2.06$ SD). The median time from the diagnosis to HSCT was 10 months (1–261 months), and 51 patients received immunosuppressive therapy including anti-thymocyte globulin before undergoing HSCT. Graft sources included 88 bone marrows (BM), 10 cord blood, 2 BM plus PB, and 1 PB. Fifty-nine patients were completely matched at HLA-A, HLA-B, HLA-C, and HLA-DR allele; 25 were mismatched at 1 HLA allele; 10 were mismatched at 2 HLA alleles, and 7 were mismatched at ≥ 3 alleles. Primary graft failure was observed in one patient. Since 8 patients experienced secondary graft failure, sustained engraftment was seen in 92 patients. Acute graft-versus-host-disease (GVHD) of grade II–IV was observed in 29 patients, while chronic GVHD was in 15 patients. The three-year overall survival (OS) rate was 96.0% (95% CI, 89.8%–98.5%). The median TL was significantly shorter in the patients who had graft failure than in those who sustained engraftment. According to the ROC curve, 29 patients were assigned to the group with shorter TL (< -1.73 SD) and the others to the group with longer TL. The incidence of graft failure was significantly higher in the group with shorter TL than in the group with longer TL (27.6% vs. 1.4%, $p < 0.001$). Meanwhile, there was no significant correlation found between TL and acute/chronic GVHD or OS. In multivariate analysis, TL shortening was an independent prognostic predictor of graft failure (OR, 37.1; 95% CI, 3.9–358.0; $p = 0.002$).

Conclusions: This study indicates that short TL is a prognostic predictor of graft failure after allogeneic HSCT in children with AA. Patients with shorter TL before undergoing transplantation may clinically behave like patients with telomere biologic disorders rather than idiopathic AA and may need to be managed accordingly. Our results suggest a potential role for telomere length in the risk stratification of children with AA in regard to their HSCT outcomes.

Disclosure: Nothing to declare.

20 - Aplastic Anaemia

P050

PEDIATRIC PATIENTS WITH VERY SEVERE APLASTIC ANEMIA AND HIGH-RISK TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY CAN BE SUCCESSFULLY TREATED WITH ECULIZUMAB

Maria Isabel Benitez Carabante[1], David Bueno Sanchez[2], Jose Maria Fernandez Navarro[3], Maria Luz Uria Oficialdegui[1], Laura Alonso García[1], Melissa Panesso[1], Luisa Sisinni[2], Antonio Pérez Martínez[2], Cristina Díaz de Heredia Rubio[1]

[1]Hospital Universitario Vall d'Hebron, Barcelona, Spain, [2]Hospital Infantil Universitario La Paz, Madrid, Spain, [3]Hospital Universitari i Politècnic la Fe, Valencia, Spain

Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is a fatal complication of hematopoietic stem cell transplantation (HSCT) associated with high morbidity and mortality.

Patients with severe aplastic anemia (SAA), especially those who received pre transplant immunosuppression, are known to be under special risk to develop this complication. Eculizumab, a complement C5 inhibitor, has significantly increased the survival of high-risk TA-TMA (hrTA-TMA). Its use in this subgroup of patients has been reported in few case reports.

Methods: We conducted a national multicenter retrospective study. Children (from birth to 18 years of age) diagnosed of SAA and treated with Eculizumab for hrTA-TMA until December 31, 2021, were included.

All patients included presented hrTA-TMA features.

Results: Seven patients with SAA were diagnosed of hrTA-TMA after a first allogeneic HSCT. Four patients were male and 3 female. Median age at transplantation was 11 years (9 - 15).

All but 1 patient (n = 6;85.7%) had received immunosuppression prior to transplantation because a suitable donor was not available at diagnosis; however, none of them achieved sustained complete remission and subsequently underwent HSCT (n = 1 bone marrow (BM) matched unrelated donor (MUD); n = 1 BM 9/10 MMUD; n = 2 9/10 MMUD with CD34+/CD3 add-back; n = 2 CD3+CD45RA+ haploidentical HSCT). One patient received an upfront HSCT from a matched family donor. Most patients (n = 6;85%) received peripheral blood as stem cell source.

Four patients presented grade II-IV acute graft versus host disease (3 were grade IV) and four patients presented either CMV, adenovirus, EBV or BK virus reactivation.

Median time from HSCT to TA-TMA was 154 days (130-387). All patients fulfil the characteristic triad (hypertension, proteinuria and elevated LDH). sC5b-9 was increased in 4/5 where measured. Three patients presented extrarenal involvement (1 pulmonary hypertension; 1 posterior reversible encephalopathy and gastrointestinal bleeding; 1 serositis). Renal (n = 3) and pulmonary (n = 1) biopsy confirmed the diagnosis in 2/4 (50%) patients. Three patients required intensive care unit admission.

Median time from hrTA-TMA diagnosis to the initiation of eculizumab treatment was 18 days (1-56). CH50 was monitored to ensure complement blockade. Five patients initiated eculizumab weekly with a standard body weight adjustment and 2 required intensified treatment for the first two doses. Overall, 6(85%) patients responded to eculizumab of whom 5 (83%) are alive and off treatment. The median duration of eculizumab in patients with resolution of hrTA-TMA was 145 days (80-198).

With a median follow up of 35 months, 5(71%) patients were alive at 12 months after initiation of eculizumab. Two of the three patients with extrarenal involvement died (one due to severe pulmonary hypertension and right cardiac failure and one of idiopathic pneumonia syndrome).

Conclusions: To our knowledge, this is the largest cohort of hrTA-TMA patients with very SAA treated with eculizumab. Despite the high-risk profile, the response rate and overall survival were high.

To conclude, special attention should be taken to very SAA who received pre-transplant immunosuppression, as they are at particular risk of developing hrTA-TMA: early detection strategies, aggressive treatment of concomitant complications, intensifying the initial induction dose and eculizumab pharmacokinetic monitoring could be of utmost importance to achieve the best outcomes.

Disclosure: Nothing to declare.

20 - Aplastic Anaemia

P051

COMPARABLE OUTCOMES OF PTCY AND BUCY REGIMENS FOR FIRST-LINE HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM UNRELATED AND MATCHED SIBLING DONORS IN PATIENTS WITH SEVERE APLASTIC ANEMIA

Xiaowei Chen[1], Cunte Chen[1], Ming Zhou[1], Yuping Zhang[1], Wenjian Mo[1], Shunqing Wang[1]

[1]Guangzhou First People's Hospital, South China University of Technology, Guangzhou, China

Background: To explore the feasibility of a posttransplant cyclophosphamide (PTCy) regimen for the unrelated donor (URD) allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the treatment of patients with severe aplastic anemia (SAA), we conducted a retrospective single-center study to compare it with the busulfan and cyclophosphamide (BuCy) regimen for matched sibling donor (MSD) allo-HSCT.

Methods: The clinical outcomes were collected from 28 SAA patients treated with PTCy regimen for URD allo-HSCT and 43 patients treated with BuCy regimen for MSD allo-HSCT between May 2020 and June 2022.

Results: The overall survival (OS) and restricted mean survival time (RMST) were not significantly different between SAA patients treated with PTCy regimen for URD allo-HSCT and patients treated with BuCy regimen for MSD allo-HSCT ($P = 0.174$, 2-year OS: 100% vs. 93%). PTCy regimen for URD allo-HSCT had an increased cumulative incidence of cytomegalovirus (CMV) viremia (82.1% vs. 48.8%, $P = 0.010$), but similar rates of grade II acute graft-versus-host disease (aGVHD) ($P = 1.000$), chronic GVHD (cGVHD) ($P = 0.704$), CMV disease ($P = 0.422$), cystitis ($P = 0.501$), Epstein-Barr virus (EBV) viremia ($P = 1.000$) and EBV positive post-transplant lymphoproliferative disease (EBV-PTLD) ($P = 1.000$) compared with patients treated with BuCy regimen for MSD allo-HSCT during the same period. After using propensity score matching to reduce the influence of potential confounders before transplantation, the OS and 2-year RMST was similar ($P = 0.352$, 2-year OS: 100% vs. 93.3%), and no significant differences in the aforementioned outcomes were observed between the two groups.

Conclusions: PTCy may be an effective conditioning regimen for URD allo-HSCT in SAA patients.

Disclosure: Nothing to declare.

20 - Aplastic Anaemia

P052

LIVER AND KIDNEY IRON OVERLOAD IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Vitalii Latyshev[1], Kira Lukina[1], Alexandra Kitsenko[1], Elena Lukina[1]

[1]National Medical Research Center for Hematology, Moscow, Russian Federation

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic disease characterized by intravascular hemolysis, prothrombotic state, and bone marrow insufficiency. Bone marrow aplasia often precedes or accompanies PNH. Iron metabolism in patients with PNH differs from other hemolytic anemias due to intensive iron losses with urine in non-treated patients. On the other hand, patients receiving anti-complement therapy may develop liver iron overload, which can be detected by MRI in T2* (T2-star) sequence. This study investigates liver and kidney iron content in patients with PNH.

Methods: Between August 2016 and October 2022, overall 70 MRI-R2* investigations of liver and 62 of kidneys were performed. Liver iron concentration (LIC, mg/g) was measured by MRI-R2* and converted according to formulas as described elsewhere. For kidneys values were given in relaxation time (ms). Median age of

patients was 39 years (20-75). Patients were divided into a treatment-naïve cohort and receiving therapy (either eculizumab or ravulizumab). Thirty-two patients (32/70) had a history of bone marrow aplasia (BMA+ group). Statistic analysis was performed using an unpaired t-test.

Results: Overall, 62 MRI-T2* investigations of kidney were available for analysis. All treatment-naïve patients (n = 45) had iron overload of renal cortex with median T2*-time of 4,0 ms versus 42,0 ms in the group receiving anti-complement therapy (p < 0,01). There was no significant difference in kidney iron overload between BMA+ and BMA- groups (p = 0,62).

Total 70 MRI-T2* investigations of liver were available for analysis. LIC values were significantly lower in treatment-naïve group with a median of 2,68 mg/g versus 6,3 mg/g in group receiving anti-complement therapy (p < 0,01). In treatment-naïve group only 13/57 (25%) had an iron overload of liver (LIC>2mg/g). There was no significant difference in liver iron overload between BMA+ and BMA- groups (p = 0,8).

Conclusions: Iron overload of renal cortex is common in treatment-naïve patients with PNH. After treatment initiation PNH-patients may develop liver iron overload. Performing liver and kidneys MRI in R2* sequence may be useful for tissue iron overload detection and subsequent decision if chelation therapy is indicated. History of bone marrow aplasia does not significantly affect values of tissue iron content measured by MRI-R2*.

Disclosure: Nothing to declare.

20 - Aplastic Anaemia

P053

SUCCESSFUL OUTCOMES OF UPFRONT HAPLOIDENTICAL TRANSPLANT USING 4GY TBI AND POST TRANSPLANT CYCLOPHOSPHAMIDE IN PEDIATRIC SEVERE APLASTIC ANEMIA

Esha Kaul[1], Rohit Kapoor[1], Gagan Saini[1], Nivedita Dhingra[2], Akriti Khare[1], Nitin Dayal[3], Ritika Pahwa[1], Titus Philip[1]

[1]Max SuperSpeciality Hospital, Vaishali, Vaishali, India, [2]Max Super-Speciality Hospital, Patparganj, India, [3]Max SuperSpeciality Hospital, Saket, India

Background: Immuno-suppressive Therapy (IST) is considered standard treatment for management of severe aplastic anemia(-SAA) in children in the absence of a full match. There have been concerns of high rates of primary and secondary graft failure with upfront haploidentical stem cell transplant (hapSCT). Increasing the dose of total body irradiation (TBI) can decrease this risk. We present our outcomes of upfront hapSCT in SAA in using 4Gy TBI instead of 2Gy TBI with post-transplant cyclophosphamide (PTCy).

Methods: We retrospectively analysed data of 4 consecutive children who underwent haplo SCT with PTCy and 4Gy at our center.

Results: Four patients were transplanted using increased radiation dose using 4Gy TBI with PTCy. The median age was 5.5 years (4 –14years). The Female : male ratio was 3:1. Diagnosis was very severe aplastic anemia -1,very severe aplastic anemia with celiac disease-1, congenital amegakaryocytic thrombocytopenia with severe aplastic anemia-1,severe aplastic anemia with LIG4 deficiency-1. Stem cell source was peripheral blood stem cells(PBSC) in 3 patients and bone marrow in one. The conditioning regimen was Flu(150mg/m2, Cy,29mg per kg, ATG and TBI 4Gy. In two patients cumulative dose of rabbit ATG was 4.5mg per kg and in other 2 patients cumulative dose of horse ATG was 45mg per kg (used due to non-availability of rabbit ATG). The donor specific antibody (DSA) was weakly positive with a MFI of 1500 in 1 and negative in the other 3. Three -fourth transplants were ABO mismatched. GVHD prophylaxis was PTCy, MMF, Tac in all. All of the patients received a single dose of Rituximab pre-transplant to decrease the risk of antibody mediated rejection. The mean cell dose was 8.1 million CD34 positive cells/kg of the recipient (Range- 6.4-10 Million/kg). All patients engrafted. The median day of neutrophil engraftment was 14 days. The median day of platelet engraftment was 17 days. Chimerism was fully donor in all. One patient developed grade II mucositis. Incidence of acute GVHD was 25%(1/4) and was Grade I acute GVHD of skin. Two patients had asymptomatic CMV viremia which responded to oral valganciclovir. One patient with LIG4 deficiency developed post-transplant immune cytopenias which resolved with a short course of steroids. There was no chronic GvHD. All patients are alive until the last follow-up with a median follow-up of 358 days (Range 307-1004 days) and all of them are off immunosuppression with full donor chimerism and normal blood counts.

Conclusions: Upfront haploSCT using 4Gy TBI and PTCy in pediatric severe aplastic anemia is feasible and practical without risk of primary or secondary graft failure. Given the dismal response rates with IST in this population, upfront haploSCT should be considered over immunosuppressive therapy especially in resource limited settings where patients often have just one shot at definitive treatment.

Acknowledgement: Our sincere thanks to Mr Vinay Kumar and Ms Diksha to organizing and retrieving data for analysis.

Disclosure: We do not have any conflicts of interest.

20 - Aplastic Anaemia

P054

THERAPEUTIC MODALITIES AND EVOLUTION PATTERNS IN 597 PATIENTS WITH INHERITED AND ACQUIRED BONE MARROW FAILURE DISORDERS: A LARGE AND COMPREHENSIVE SINGLE CENTRE EXPERIENCE

Marta Bortolotti[1,2], Roochi Trikha[1], Sarah Salter[1], Joanna Large[1], Shreyans Gandhi[1], Austin Kulasekararaj[1]

[1]King's College Hospital NHS Foundation Trust, London, United Kingdom, [2]University of Milan, Milan, Italy

Background: Inherited (IBMF) and acquired bone marrow failure syndromes are a group of rare disorders characterised by pancytopenia and hypoplastic bone marrow, with risk of transformation to myeloid neoplasms. Data about the natural history of IBMF, aplastic anaemia (AA) and hypoplastic myelodysplastic syndromes (hypo-MDS) are increasing and provide help in their better management.

Methods: We conducted a single-centre retrospective study, including patients with IBMF, acquired AA and hypo-MDS referred to our institute in the last 15 years. Data about clinical features, management, evolution and outcomes were compared among the three groups with the aims of describe their natural history, management and disease evolution.

Results: Overall, 597 patients (459 AA; 82 hypo-MDS; 56 IBMF) were included (*Table 1*). Among IBMF, 11 were Fanconi Anaemia, 3 Diamond-Blackfan Anaemia, 2 Shwachman-Diamond syndrome, 18 telomeropathies and 22 had other mutation related to IBMF or, even without the pathogenic gene identified, presenting with classical clinical features and strong family history. Among AA, according to Camitta's Criteria, 22% were very severe, 34% severe, 28% non severe while 16% had no severity specification. Mean

age at diagnosis was 43 years (0.1-86) and with older patients in hypo-MDS group. A correct diagnosis before the first visit at our institute was performed more often in AA and IBMF patients but it could take up to 8 years for IBMF diagnosis. A concomitant autoimmune disease was present in 16% in AA versus 5% in IBMF. Overall, 81% of patients required medical treatment (86% AA, 79% hypo-MDS, 45% IBMF) and 26% were transplanted. With a median follow-up of 4.5 years (0-24), an abnormal karyotype at first visit was found in 13% of patients with an increase to 28% at last visit. Myeloid gene mutations were detected in 21% overall and in 30% of hypo-MDS patients. Paroxysmal nocturnal haemoglobinuria (PNH) clone was present in 52% of AA patients versus 11% of IBMF, with a higher PNH clone (2.4% vs 0.65%) and an increasing trend in AA. Increase in disease severity overtime was observed in 1.8% while clonal evolution was reported in 24% overall. In particular, IBMF patients showed progression to MDS in 21% and to AML in 3.5%, comparing to 10% and 1.5%, respectively, in AA. Evolution to overt PNH occurred in 11% of AA patients versus a 3.6% in hypo-MDS. Time to evolution was shorter in hypo-MDS patients comparing with AA (1.7 years vs 5.4) and, in 5 IBMF patients, a MDS or AML diagnosis was concomitant with that of IBMF. Overall, 24% patients dead during the observation period, reaching 39% in hypo-MDS patients.

Table 1

	Overall	AA	Hypo-MDS	IBMF
N° patients	597	459	82	56
M/F	309/287	230/229	44/38	35/21
Age at diagnosis (years), mean (range)	43 (0.1-86)	41.5 (2.4 - 85)	57 (13 - 86)	30 (0.1-71)
Time diagnosis-first visit at KCH (years), mean (range)	3.5 (-8 - 47.7)	3.9 (-6.7 - 47.7)	1.3 (-1.1 - 16.6)	3.7 (-8 - 36.5)
Associated autoimmune disease, n (%)	87 (15)	72 (16)	10 (12)	5 (9)
Treated, n (%)	483 (81)	393 (86)	65 (79)	25 (45)
Transplanted, n (%)	158 (26)	125 (27)	20 (24)	14 (25)
Abnormal karyotype at first visit, n (%)"n" evaluable = 449	60 (13)	35 (11)	15 (20)	11 (25)
Abnormal karyotype at last FU, n (%)"n" evaluable = 262	73 (28)	54 (28)	12 (28)	7 (27)
Abnormal myeloid panel NGS, n (%)"n" evaluable = 238	51 (21)*	32 (19)	10 (30)	9 (25)
PNH clone at first visit, n (%)	284 (48)	241 (52)	37 (45)	6 (11)
Granulocyte PNH clone, median (range)	2.2 (0.02 - 99.9)	2.4 (0.02 - 99.9)	1.6 (0.03 - 97)	0.65 (0.02 - 3.8)
PNH clone at last FU, n (%)	284 (48)	237 (52)	42 (51)	5 (9)
Granulocyte PNH clone, median (range)	3.8 (0.01 - 100)	4.3 (0.02 - 100)	2.9 (0.02 - 98)	0.2 (0.01 - 3.8)
Increase in severity overtime, n (%)	10 (1.8)	8 (1.7)	3 (3.6)	-
Evolution, n (%)				
• overall	144 (24)	114 (25)	16 (19)	14 (25)
• MDS	70 (12)	47 (10)	11 (13)	12 (21)
• AML	10 (1.7)	7 (1.5)	1 (1.2)	2 (3.5)
• overt PNH	54 (10)	51 (11)	3 (3.6)	-
• other	10 (1.7)	9 (1.9)	1 (1.2)	-
Time to evolution (years), median (range)	4.7 (-1 - 38.2)	5.4 (0.2 – 32.5)	1.7 (0.2 – 38)	1.9 (-1 - 14)§ 31.7 (23 - 71)*
Outcome, n (%)				
• alive	331 (55)	265 (58)	33 (40)	33 (59)
• death	142 (24)	99 (21)	32 (39)	11 (20)
• lost at FU	124 (21)	95 (21)	17 (21)	12 (21)

§ Median time to evolution calculated from date of diagnosis
* Median time to evolution calculated from date of birth
AA, aplastic anaemia; hypo-MDS, hypoplastic myelodysplastic syndrome; IBMF, inherited bone marrow failure; KCH, King's College Hospital; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal haemoglobinuria.

Conclusions: We report the largest single institute series of cases with various BMF syndromes, including hypo-MDS and IBMFs in adult patients. Bone marrow failure syndromes are a heterogeneous group of disorders with a majority requiring treatment, including transplantation in 26% of patients, and increased risk of clonal evolution.

Disclosure: Nothing to declare.

20 - Aplastic Anaemia

P055

SINGLE CENTRE STUDY OF ROMIPLOSTIM ADDED TO IMMUNOSUPPRESSIVE THERAPY AS A FIRST-LINE TREATMENT IN SEVERE APLASTIC ANAEMIA: A CASE SERIES

Ashok Kumar Rajoreya[1,1], Gaurav Dingra[2]

[1]RJN Apollo Spectra Hospital, Gwalior, India, [2]All India Institute of Medical Sciences, Rishikesh, India

Background: Romiplostim, a thrombopoietin (TPO) mimetic protein, has been shown to promote trilineage haematopoiesis in patients with acquired aplastic anaemia (AA) that are refractory to immunosuppressive therapy (IST). However, its efficacy in the combination therapy with IST, i.e. anti-thymocyte globulin (ATG) plus cyclosporine (CSA) as a first-line treatment remains unexplored.

Aim: To evaluate the efficacy and safety of Romiplostim in combination with ATG and CSA as first-line treatment in patients with aplastic anaemia.

Methods: A Single centre, retrospective study of aplastic anaemia patients, every patient was given ATG + CSA + Romiplostim as a first-line treatment. Romiplostim 5µg/kg weekly for 1 month, post that dose was increased to 10µg/kg weekly for next 5 months. Data was evaluated at baseline, after 3rd and 6th month.

Results: Data of 12 patients with Median age of 18 years was evaluated. At a median follow-up of six months, the hematological response rate was 66.6% (25% achieved complete response, 41.6% achieved partial response) and 16.7% had no response. Two mortalities within 3 months of treatment were due to sepsis with pneumonia and cerebral haematoma with infection. Patients Haemoglobin level, total leukocyte count (TLC), Absolute Neutrophil count and Platelet count showed statistical significant improvement.

Conclusions: Although a larger number of patients and a longer follow-up period are needed to confirm our findings, our results show the efficacy of Romiplostim with ATG plus CSA as first-line treatment in patients with aplastic anaemia.

Disclosure: no conflict of interest.

20 - Aplastic Anaemia

P056

QUALITY OF LIFE AFTER IMMUNE SUPPRESSIVE TREATMENT FOR APLASTIC ANEMIA

Table 1: Mean values of Hb, TLC, ANC and platelet count at baseline, 3 months and 6 months

	Baseline values (mean ± SD)	Values at 3 months (mean ± SD)	p-value	Values at 6 months (mean ± SD)	p-value
Haemoglobin	5.6 ± 1.9	7.3 ± 1.9	0.169*	9.3 ± 2	0.010*
Total Leukocyte count (TLC)	2662.2 ± 999.5	3544.4 ± 1497.6	0.216	4662.5 ± 1611.5	0.048*
Absolute Leucocyte count (ANC)	501 ± 251.7	1443.8 ± 603.2	0.007*	2435.7 ± 916.8	0.001*
Platelet count	8300 ± 3497.6	37800 ± 25507.3	0.006*	87444.4 ± 60145.5	0.005*

(* $p < 0.05$; statistical significant)

Iris Nicola Lommerse[1], Constantijn Jozef Marie Halkes[1], Chris Hinnen[1], Jennifer May-Ling Tjon[1]

[1]Leids Universitair Medisch Centrum, Leiden, Netherlands

Background: Acquired aplastic anemia (AA) leads to progressive bone marrow failure and is treated with either immune suppressive therapy (IST) or allogeneic stemcell transplantation (alloSCT). Quality of live (QoL) after alloSCT can be diminished due to chronic complications like Graft Versus Host Disease (GVHD) but little is known about QoL after IST. We investigated the QoL in AA patients after successful IST.

Methods: For our research we used an AA/PNH specific QoL questionnaire developed by a German research group (Niedeggen et al. 2019; *Annals of Hematology*). Fifty-four multiple choice questions were translated in Dutch and send to 48 AA patients who were treated with IST (anti-thymocyte globulin (ATG), Ciclosporin and/or Eltrombopag). Four answer options could be chosen: 'not at all', 'a little', 'a lot' or 'very often'. The questions represent possible issues within 12 different domains. Four domains were physically oriented (fatigue (FA), infections (IN), physical functioning (PF) and other symptoms (OS)), eight were more psychologically oriented (body image (BI), cognitive functioning (CF), emotional functioning (EF), illness intrusiveness (II), fear of progression (PAF), role functioning (RF), social support (SS) and stigmatization (ST)). Results were analyzed for all patients who responded to IST and grouped based on type of response (complete response (CR, normalization of blood counts) or partial response (PR, transfusion independent, but no normalization).

Results: Thirty-nine patients returned the questionnaire of whom 36 were successfully treated with IST (15 CR and 21 PR). Median age of these 36 patients was 54 years (range 21-71) Median time between last IST and the survey was 5 years, with a maximum of 41 years. Fatigue was experienced by 83% of patients and was scored 'very often' by 8%. Other physical-related domains such as PF, IN and OS were scored 'not at all' or 'a little' in the majority of patients. In contrast, most patients experienced psychological effects of their (past) illness. Specific items within PAF and BI were a major concern ('a lot' or 'very often') for up to respectively 31% and 36% of patients. When stratified based on hematological response, patients with PR scored worse than patients with CR in almost all domains. The difference was most clear in PAF: 'very often' was scored by up to 24% of patients with PR versus 7% of patients with CR.

QoL Domain	Mean % of patients with 'a lot' or 'very often' problems within this domain		
	Patients after successful IST (n = 36)	PR (n = 21)	CR (n = 15)
FA	24	26	21
IN	7	8	7
PF	20	16	25
OS	15	15	15
BI	27	34	17
CF	11	5	20
EF	23	28	16
II	19	23	15
PAF	24	29	15
RF	29	34	21
SS	10	10	11
ST	20	25	12

Conclusions: Patients with AA after successful IST still experience psychological and physical effects. Physical complaints appear to be less prominent, though fatigue is experienced by a large majority of patients. Partial responders to IST seem to experience more impact on their quality of life than complete responders. We have shown that QoL is affected also after successful IST and that the level of blood count normalization further influences QoL, especially in psychological domains.

In conclusion, evaluating QoL in AA patients might identify specific domains requiring extra attention and can be used to improve personalized supportive measures. In the future, it could be insightful to include QoL as a parameter in studies evaluating AA treatment effects, too.

Disclosure: Nothing to declare.

21 - Autoimmune Diseases

P057

EXPERIENCE IN THE USE OF ABATACEPT FOR THE MANAGEMENT OF REFRACTORY AUTOIMMUNE HEMOLYTIC ANEMIA IN PEDIATRIC PATIENTS AFTER ALLOGENIC STEM CELL TRANSPLANTATION

Carlos Echecopar Parente[1], Maria Dolores Corral Sánchez[1], David Bueno Sánchez[1], Luisa Sisinni[1], Yasmina Mozo Del Castillo[1], Gema Casado Abad[2], Antonio Pérez Martínez[1,3,4]

[1]Pediatric Hemato-Oncology, University Hospital La Paz, Madrid, Spain, Hospital La Paz, Madrid, Spain, [3]University Hospital La Paz Research Institute (IdiPAZ), Madrid, Spain, Universidad Autónoma de Madrid, Madrid, Spain

Background: Autoimmune hemolytic anemia (AIHA) is a rare complication after hematopoietic stem cell transplantation (HSCT) with significant morbidity and mortality. Response to standard therapy in this patients is worse than in cases not associated with HSCT, so it's necessary to seek for alternative therapies.

Methods: We describe our experience using abatacept for the treatment of refractory or corticodependant AIHA after HSCT since July 2019 to April 2020.

Table 1. Patients characteristics and treatment of AIHA

Patient	Age	Primary disease	Donor	Exvivo lymphocyte deplection	In vivo lymphocyte deplection	Time from HSCT at AIHA diagnosis (months)	Standard treatment	Duration of standard treatment (days)	Clinical response to standard treatment	Number of doses of abatacept	Days until complete response	Relapse
1	5 months	Primary HLH	MMUD	None	Alemtuzumab	11	MP; MMF	498	No	13	14	Yes
2	7 years	CDG	MMUD	None	ATG	4	MP; MMF; RX	49	No	10 (ongoing)	268	No
3	2 years	CDG	Haplo	TCR alpha/ beta	ATG	6	MP; MMF; CsA; IGIV	14	No	13	14	No
4	4 years	LLA B	Haplo	CD45RA	None	2	MP; MMF; RX; IGIV	88	No	9	20	No
5	6 years	LLA T	Haplo	CD45RA	None	7	MP; MMF	115	Yes	10	174	No

HLH Hemophagocytic lymphohistiocytosis; *CGD* Chronic granulomatous disease; *MMURD* mismatch unrelated donor; *Haplo* haploidentical donor; *TCR* T-cell receptor; *ATG* Anti-thymocyte globulin; *MP* Methylprednisolone; *MMF* Mycophenolate; *RX* Ruxolitinib; *CsA* Cyclosporine; *IGIV* Intravenous immunoglobulin.

Results: We used abatacept in five patients with AIHA after HSCT, four cases with refractory AIHA after standard therapy and one case with corticodependant AIHA. All patients had clinical response associated to the therapy and a complete withdrawal of steroids was possible in all cases. To date, 4 patients completed treatment with abatacept, one of them had a relapse after withdrawal of treatment. We did not see any side effects associated with the use of this therapy.

Conclusions: Abatacept can be an alternative therapy for refractory or corticodependent AIHA after HSCT.

Disclosure: Nothing to declare.

21 - Autoimmune Diseases

P058

SARS-COV-2 VACCINATION IN SYSTEMIC SCLEROSIS PATIENTS TREATED BY AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION, ON BEHALF OF MATHEC-SFGM-TC GROUP

Lucie Biard[1], Grégory Pugnet[2], Carlotta Cacciatore[1], Ingrid Munia[1], Pauline Lansiaux[1], Christine Le Maignan[1], Benjamin Crichi[1], Fanny Urbain[3], Zora Marjanovic[4], Sabine Berthier[5], Doron Rimar[6], Dominique Farge[1]

[1]AP-HP Saint-Louis Hospital, Paris, France, [2]CHU Rangueil, Toulouse, France, [3]AP-HP Bicetre Hospital, Paris, France, [4]AP-HP Saint-Antoine Hospital, Paris, France, [5]CHU Dijon, Dijon, France, [6]Bnai Zion Medical Centre, Haifa, Israel

Background: On December 27th 2020, the implementation of SARS-CoV-2 vaccination in France first became available amongst all immunosuppressed patients, specifically Hematopoietic Stem Cell Transplant (HSCT) recipents or other fragile immunosupressed patients. In July 2021, the ADWP-EBMT guidelines recommended vaccination against SARS-CoV2 as early as 3 months after HSCT, but only one Israeli study so far analyzed the efficacy of SARS-CoV-2 vaccination after autologous HSCT (AHSCT) for Systemic Sclerosis (SSc). We designed this study to assess the acceptance and effectiveness of such vaccination program in SSc patients treated by AHSCT as compared to other fragile SSc individuals.

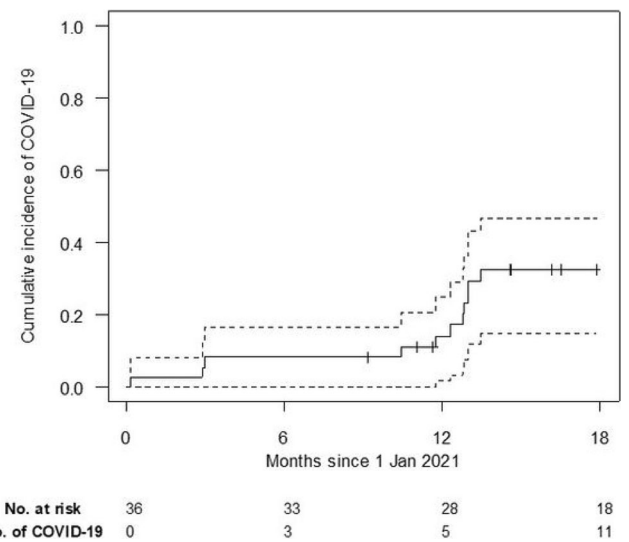
Methods: This retrospective case-control cohort analysis included SSc patients above 18 years old, diagnosed according to the 1980 ARA or the 2013 ACR/EULAR criteria, followed in two French expert centers and who were offered SARS-CoV-2 vaccination according to the French Good Clinical Practices (with at least either a two-dose mRNA vaccine or single-dose adenoviral vector) between January 1st 2021 to June 30th 2022. AHSCT SSc patients (cases) were matched 1:1 with non-AHSCT SSc patients (controls) according to the following criteria on January 1st 2021: sex, age (+/- 5 years), disease duration since first non-Raynaud phenomenon (+/-5 years). Nearest-neighbor Mahalanobis distance matching was performed.

Primary endpoint: cumulative incidence of asymptomatic (positive PCR on routine testing) or symptomatic (positive PCR plus COVID-19 clinical symptoms) infection.

Secondary endpoints: proportion of patients refusing vaccination, cumulative incidence of symptomatic COVID-19 infection, time of onset of first COVID-19 infection (symptomatic or asymptomatic) during the study after completing at least 2 vaccines injections, COVID-19 severity, proportion of patients with at least 1 grade≥3 adverse event (CTC-AE v5.0) and humoral response after vaccination.

Results: 36 SSc patients treated by AHSCT and 36 controls (22 females in each group, overall cohort median age 53 (46;63) years, prior median SSc duration 11 (7;15) years) were retrospectively studied from January 1st 2021 until June 30th 2022. Five (14%) of the AHSCT patients refused vaccination while the others received either 1 (n = 1, 3%), 2 (n = 4, 11%) or 3 (n = 26, 72%) vaccine injections, essentially BNT162b2-Pfizer (94% for 1st injection, 93% for 2nd injection and 88% for 3rd injection). Among the 36 AHSCT patients, 11 experienced one COVID-19 infection during the study period, of whom 1 had refused vaccination. All were symptomatic: 9 (82%) with mild symptoms and 2 (18%) with moderate symptoms which required hospitalization outside ICU. Among AHSCT patients, the cumulative incidence of symptomatic COVID-19 starting from 1st January 2021 was 8% (95%CI 2-20), 14% (95%CI 5-28) and 33% (95%CI 18-49) at 6, 12 and 18 months respectively (figure 1). There was no death from COVID-19 infection in the controls.

Figure 1



Conclusions: Out of 11 COVID-19 infections occurring in SSc patients treated by AHSCT once the vaccination campaign had started, only 2 required hospitalization that occurred in the first quarter of 2021, amongst patients who had not received a complete vaccination. In this unique cohort, most COVID-19 infections occurred by the end of 2021– early 2022, during the 5th epidemic wave in France.

Disclosure: Nothing to declare.

21 - Autoimmune Diseases

P059

THE FIRST AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT FOR A MULTIPLE SCLEROSIS PATIENT IN THE UNITED ARAB EMIRATES

Inas El-Najjar[1], Ruqqia Mir[1], Yendry Ventura-Carmenate[1], Fatema Al-Kaabi[1], Maysoon AlKaram[1], Yandy Castillo-Aleman[1], Hiba Abdelrahman[1], May Martinez[1], Dina El-Mouzain[1], Antonio Bencomo-Hernandez[1], Alzahraa Abouhelal[1], Tarek Diab[1], Pierre Krystkowiak[1], Nameer Al-Saadawi[1]

[1]Abu Dhabi Stem Cell Centre, Abu-Dhabi, United Arab Emirates

Background: Autologous hematopoietic stem cell transplant (AHSCT) is recommended for patients with certain types of multiple sclerosis (MS). We endeavored to make AHSCT locally accessible to patients living in the UAE, to avoid the need to travel for treatment. We report clinical lessons learnt with the first AHSCT in a MS patient done in the Gulf region, Abu Dhabi, UAE.

Methods: The patient is a 24 year old female diagnosed with aggressive, highly active MS in November 2021 with Expanded Disability Status Scale (EDSS) 8.5. She had treatment with Ocrelizumab on 02/02/2022, despite this treatment, a MRI in three months revealed new active MRI lesions, in keeping with disease progression. She was assessed in the Hematology clinic in August 2022 and deemed fit for AHSCT.

She was mobilized on 24/09/2022, utilizing Cyclophosphamide priming 2.0g/m^2, followed five days later by granulocyte colony stimulating factor (G-CSF) 5 mcg/kg/day for five days. A single leukapheresis procedure achieved a dose of 17.7 x 10^6 CD34+ cells/Kg. She was admitted on 01/11/2022 to start conditioning. A non-myeloablative protocol was utilized includes cyclophosphamide 50 mg/kg/iv over 2 hours daily for four days(D-5 to D-2) along with MESNA 50 mg/kg/day continuous infusion. Rabbit antithymocyte globulin (ATG) in increasing doses was infused over five days (D-5 to D-1). We infused 8.6 x 10^6 CD34+ cells/Kg on D0 (07/11/2022). She was on our standard anti-infective prophylaxis.

Results: **Engraftment:** Patient engrafted on D + 9, with neutrophil count > 0.5 x 10^9/L.

Transfusions: No platelet transfusion required, platelets did not drop below 45 x 10^9/L, she had two Packed Red Blood Cells (PRBC) transfusions during admission on D + 9 and D + 10, that were irradiated and leukodepleted.

Fever and Infections: ATG associated fever on D0, this abated on restarting methylprednisolone(MP) 500 mg once daily(OD) for two days. She had further fever D + 2 treated with 2 further days of MP 250 mg OD for two days. During this time she had had a full septic work up, including blood cultures, urine culture, and a chest X-ray She developed fever again on D + 10 but was clinically well. In addition to another septic screen, CMV and EBV PCR were sent. She was on broad spectrum antibiotics and her central line was removed. A CT chest/abdomen/pelvis revealed only splenomegaly on D + 17. CMV PCR report positive 3050 IU/ml (CMV log 3.48, she was CMV PCR negative on admission). She was started on valganciclovir on D + 17. Patient's fever settled within 48 hours. She was discharged on D + 20.

Neurology: She had mild neurological improvement whilst still an inpatient D + 15 improving in functional scores in the cerebellar and pyramidal systems.

Conclusions: Unlike AHSCT in adult malignant diseases, MS patients may not require platelet transfusions at all. In addition, monitoring and suspicion of CMV infection is essential as it may cause fever at D + 10, which we didn't expect. Early neurological improvement is feasible post AHSCT, the patient will be followed up to assess for further sustained improvement. We believe this is the first step in making AHSCT accessible for MS patients in the UAE.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P060

TREATMENT OF SYSTEMIC SCLEROSIS AND ANTI-SYNTHETASE SYNDROME WITH CD19-CAR T CELLS

Fabian Müller[1], Sebastian Böltz[1], Christina Bergmann[1], Johannes Knitza[1], Simon Völkl[1], Michael Aigner[1], Soraya Kharboutli[1], Arnd Kleyer[1], Hannah Reimann[1], Sascha Kretschmann[1], Jochen Wacker[1], Wolf Rösler[1], Bernd Spriewald[1], Gerhard Krönke[1], Gerhard Schett[1], Andreas Mackensen[1]

[1]University Hospital of Erlangen, Erlangen, Germany

Background: Using CD19 CAR T cells, we recently achieved lasting remission in 5 of 5 patients with severe and treatment refractory systemic lupus erythematosus (SLE, Mackensen et al. NatMed; 2022). Similar to lupus, other autoimmune diseases may depend on pathologic B cell clones including anti-synthetase syndrome (SAA), a form of inflammatory myositis or systemic sclerosis (SSc). In line, B cell directed treatment often induces remission in SAA or SSc even though refractory or rapidly relapsing cases show insufficient B cell depletion. Thus, we hypothesized that patients with severe, refractory forms of SAA or SSc may achieve durable responses following CD19 CAR T cells.

Methods: In this pilot study we used autologous CD19 CAR T cells produced in house with the Miltenyi prodigy. Patients received lymphodepletion with 3x25 mg/m^2 Fludarabin, days-5 to -3 and Cyclophosphomaid 1g/m^2 d-3 followed by 1 mio/kgBW CAR T cells on day 0. CAR T cells were analyzed using flow cytometry. SAA was assessed by MRI and by serum creatinine kinase (CK) and severity of SSc by fibroblast activation protein inhibitor (FAPI)-PET CT scan. Both diseases were also staged by clinical scores.

Results: A heavily pretreated patient with SAA (prednisolone (250 mg/day), rituximab, IVIG, tacrolimus, and cyclophosphamide) proved refractory with progressive, severe muscle weakness, pulmonary involvement with increasing oxygen supplementation and progressive alveolitis by CT. At CAR-infusion, CK was 9305 U/l (normal <190 U/l). CK increased further following lymphodepletion and before Car expansion to a maximum of 13,600 U/l. CAR T cells expanded by more than 600-fold. Apart from fever (CRS grade 1) treated with tocilizumab, the patient did not show relevant side effects. Then, CK started to slowly decline over weeks to finally normal values. Manual muscle test score of 115/150 at baseline improved to full muscle strength at day +180 (149/150). Myositis by MRI was abrogated and maximum walking distance increased from 10 m to more than 5 km. Alveolitis mostly disappeared.

A second patient with SSc showed anti-RNAP antibodies and progressive systemic sclerosis by skin biopsies. Furthermore, the patient presented with joint pain, diffuse lung fibrosis, and heart-involvement as demonstrated by MRI. Despite several treatment lines (steroids, MTX, and mycofenolat mofetil), disease progressed with increasing skin lesions and worsening of lung and heart function. Before CAR T, the patient received 50% lymphodepletion due to reduced kidney function. CAR T cells expanded well and peaked at day 9 with >1200 CAR T cells/nl. Except for mild fever which was treated symptomatically, the patient had no side effects. More than 3 months after CAR T therapy, the patient was treatment-free, skin sclerosis remained stable, FAPI-PET showed minimal enhancement, joint pain was greatly reduced, and clinical tests gradually improved.

Conclusions: As in SLE, CAR T cell therapy is safe in two cases of SAA and SSc. While in established SSc disease progression was arrested, disease activity and clinical symptoms in SAA were abrogated with a single shot of car T. These promising early response signals prompt further clinical evaluation.

Disclosure: FM and AM have received travel support and honoraria from Miltenyi.

All other authors do not declare relevant conflicts of interest.

4 - CAR-based Cellular Therapy – Clinical

P061

THIRD-GENERATION CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS IN ADULT ALL PATIENTS

Maria-Luisa Schubert[1], Anita Schmitt[1], Angela Hückelhoven-Krauss[1], Brigitte Neuber[1], Philip Waldhoff[1], Dominik Vonficht[2,3], Schayan Yousefian[4,5,6], Lea Jopp-Saile[2,3], Felix Korell[1], Simon Haas[3,2,5,4,6,7], Anthony D. Ho[1,7], Carsten Müller-Tidow[1,7], Peter Dreger[1,7], Michael Schmitt[1,7]

[1]Heidelberg University Hospital, Heidelberg, Germany, [2]Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany, [3]Institute for Stem Cell Technology and Experimental Medicine, Heidelberg, Germany, [4]Max Delbrück Center, Berlin, Germany, [5]Berlin Institute of Health, Berlin, Germany, [6]Charité University Medicine, Berlin, Germany, [7]German Cancer Consortium, Heidelberg, Germany

Background: Third-generation chimeric antigen receptor (CAR)-engineered T-cells (CARTs) might improve clinical outcome of patients with B-cell malignancies. Here we report a phase-1/2 investigator-initiated trial (HD-CAR-1) on a third-generation CART dose-escalating, investigator-initiated trial treating adult patients with acute lymphoblastic leukemia (ALL).

Methods: Refractory and/or relapsed (r/r) adult ALL patients received escalating doses of CD19-directed third-generation CARTs comprising the costimulatory domains CD28 and CD137 (4-1BB) after lymphodepletion with fludarabine and cyclophosphamide. Leukapheresis, manufacturing and administration of CARTs were performed in-house.

Results: 15 patients with r/r ALL were enrolled. Median age of patients was 41 (range 21 to 67) years. Median time from initial diagnosis to CART administration was 22 (range 5 to 117) months and patients had received a median of 4 (range 2 to 9) prior treatment lines, including allogeneic stem cell transplantation (alloSCT) in 12 patients (80%). For all patients, CART manufacturing was feasible. Median duration of CART manufacturing was 10 (range 10 to 14) days. Median transduction efficiency was 52.7% (range 39.3% to 66.9%) with a viability of CARTs of > 85%. Six patients received bridging therapy between leukapheresis and lymphodepleting therapy. Thirteen patients were treated with HD-CAR-1 CARTs (1×10^6 CARTs/m^2 (n = 3), 5×10^6 CARTs/m^2 (n = 3), 2×10^7 CARTs/m^2 (n = 4), 5×10^7 CARTs/m^2 (n = 3)). Two patients did not receive CARTs due to progressive disease during CART manufacturing. None of the thirteen treated patients developed any grade of immune effector cell-associated neurotoxic syndrome (ICANS) or a higher-grade (≥ grade III) cytokine release syndrome (CRS).

CART expansion and long-term CART persistence were evident in the peripheral blood of evaluable patients. At end-of-study (EOS) on day 90 after CART administration, ten patients were evaluable for disease response: eight patients (80%) achieved a complete remission (CR), including five patients (50%) with MRD-negative CR. Response and outcome were associated with the administered CART dose. Persistent, high-grade (≥ III) neutropenia beyond day 90 was observed in two patients. At EOS, all evaluable patients had ongoing B-cell aplasia, even though recovered levels of immunoglobulins were detectable in six patients. At 1-year-follow-up, median overall survival (OS) was not reached and progression-free survival (PFS) was 38%. Median PFS was reached on day 120. Responders displayed higher frequencies of a specific memory-like T cell subset within the CART-product. Also, a physiological pattern of immune cells and lower monocyte counts in the PB were associated with response.

Conclusions: Third-generation HD-CAR-1 CARTs were remarkably safe and of promising efficacy. A specific subset of memory T cells within the CART product could predict response to treatment. Overall, HD-CAR-1 appears to be a promising step towards safe and effective ALL eradication.

Clinical Trial Registry: NCT03676504 (www.clinicaltrials.gov)

Disclosure: AS: Travel grants from Hexal and Jazz Pharmaceuticals. Research grant from Therakos/Mallinckrodt. Consultancy BMS, Janssen-Cilag. Co-founder and part-time employee of TolerogenixX LtD. of TolerogenixX Ltd.

CMT: research support from Bayer AG. Advisory board member Pfizer, Janssen-Cilag GmbH. Grants and/or provision of investigational medicinal products from Pfizer, Daiichi Sankyo, BiolineRx.

MS: research grants from Apogenix, Hexal and Novartis. Travel grants from Hexal and Kite. Financial support for educational activities and conferences from bluebird bio, Kite and Novartis. Advisory board member of MSD. (Co-)PI of clinical trials of MSD, GSK, Kite and BMS. Co-Founder and shareholder of TolerogenixX Ltd.

PD: consultancy AbbVie, AstraZeneca, Gilead, Janssen, Novartis, Riemser, Roche; speakers bureau AbbVie, Gilead, Novartis, Riemser, Roche; research support from Neovii and Riemser.

ADH, AHK, BN, DV, LJS, MLS, PW, SH, SY: none.

4 - CAR-based Cellular Therapy – Clinical

P062

TORQUE TENO VIRUS PLASMA DNA LOAD: A NOVEL PROGNOSTIC BIOMARKER IN CAR-T THERAPY

Rafael Hernani[1], Estela Giménez[2], Gloria Iacoboni[3,4], Manuel Guerreiro[5], Ana Benzaquén[1], Eliseo Albert[2], Cecilia Carpio[3], Aitana Balaguer[5], Ariadna Perez[1], Mario Sánchez-Salinas[3], Pedro Chorão[5], José Luis Piñana[1], Francisco Beas[3], Juan Montoro[5], Juan Carlos Hernández-Boluda[1,6], Ana Facal[5], Blanca Ferrer[1], Marta Villalba[5], Paula Amat[1], María José Terol[1,6], Jaime Sanz[5,6], Pere Barba[3,4], David Navarro[2,7], Carlos Solano[1,6]

Hospital Clínico Universitario, INCLIVA Research Institute, Valencia, Spain, Hospital Clínico Universitario, INCLIVA Research Institute, Valencia, Spain, Hospital Universitari Vall d'Hebron, Barcelona, Spain, [4]Universitat Autònoma de Barcelona, Bellaterra, Spain, Hospital

Universitari i Politècnic La Fe, Valencia, Spain, University of Valencia, Valencia, Spain, University of Valencia, Valencia, Spain

Background: Disease-refractory and immunological toxicities are associated with significant morbidity and failure in chimeric antigen receptor T-cell (CAR-T) therapy. Novel biomarkers could be of value to predict these complications. Torque teno virus (TTV) has been identified as a surrogate marker of immunocompetence both in solid organ (SOT) and hematopoietic stem cell transplantation (HSCT).

Methods: Adult patients who received commercial CAR-T (tisacel or axi-cel) for B-cell non-Hodgkin lymphoma (B-NHL) in three Spanish centers between January 2020 and June 2022 were included. TTV DNA plasma loads were quantified by real-time PCR at different timepoints before (prelymphodepletion [TTVpreLD], preinfusion [TTVd0]) and after CAR-T infusion (days +1, +3, +5, +7, +14, +21, +28, +60 and +90). Cytokine-release syndrome (CRS) and immune-effector cells associated neurotoxicity (ICANS) were graded following ASCTC criteria. The association between baseline factors and overall response (ORR), CRS and ICANS was estimated by univariate logistic regression model. Overall survival (OS) was calculated using the Kaplan–Meier method and the log-rank test was used for statistical comparison. Cumulative incidences were analyzed by Gray test. Preliminary data of preinfusion plasma samples is provided here.

Results: Seventy-nine patients were included. CRS and ICANS were developed in 63 (79.7%) and 24 (30%) patients, being severe in 7 (9%) and 18 (22.7%) patients, respectively. Seven (9%) patients died of toxicity (infection, n = 5; ICANS, n = 1; undetermined, n = 1) at a median time of 46 days (7 – 772). The 1-year cumulative incidence of therapy-related mortality (TRM) was 6% (1 – 12). ORR was achieved in 54 (68%) patients (complete response, n = 39; partial response, n = 15) at a median time of 38 days (25 – 351). ORR was maintained in 32 patients at last follow-up with a median duration of response (DOR) of 14 months. Forty-five (57%) patients remained alive at a median follow-up of 371 days (91 – 882). OS at 3 months and 1 year was 85% (77 – 93) and 56% (44 – 68), respectively. In multivariate analysis, lower TTVd0 was associated with OS (HR 1.15, 95% CI, 1.006 – 1.322, P = 0.041). OS at 1 year was 75% (61 – 94) and 40% (25 – 66) for patients with TTVd0 under 5 log10 copies/mL or equal/above 5 log10 copies/mL (P = 0.041). TTVpreLD and TTVd0 were also related to ORR (P = 0.068 and 0.013, respectively), but no association was found in multivariate analysis. Neither CRS, ICANS, DOR nor TRM were related to TTV plasma load.

Conclusions: In this study, preliminary analyses show that preinfusion TTV plasma load may be associated with OS in adult patients receiving CAR-T therapy for B-NHL. Lower TTV could be linked to a better immunocompetence, which may translate into an improved CAR-T effect. These results suggest that TTV monitoring could be useful in predicting CAR-T therapy efficacy and may have a potential for the development of personalized strategies for CAR-T patients, as previously suggested in SOT and HSCT receptors. To our knowledge, this is the first time TTV is used as a biomarker in CAR-T therapy. More data is warranted to confirm these preliminary findings.

Clinical Trial Registry: The Institut Paoli-Calmettes (Marseille, France) was also included as a collaborator center. The study was considered as a clinical trial in France (NCT04822974). Unfortunately, covid pandemic avoid the implementation of the study in France. All the authors would like to express our thanks to our colleagues from Marseille, especially to Pr Didier Blaise and Dr Raynier Devillier.

Disclosure: A Gilead grant (Beca FEHH-GILEAD para Formación en Investigación en Terapia Celular en un centro internacional Convocatoria 2019) was conceded to Ana Benzaquén. Rafael Hernani was the principal investigator of the grant-associated study. The rest of authors declare no conflict of interest related to this study.

4 - CAR-based Cellular Therapy – Clinical

P063

IMMUNE RECONSTITUTION AND INFECTIONS AFTER TREATMENT WITH COMMERCIAL CAR-T CELL THERAPY

Eva Catalá[1,2], Diego Carbonell[1,2], Gillen Oarbeascoa[1,2], Mariana Bastos[1,2], Rebeca Bailén[1,2], Ana Pérez Corral[1], Paula Fernández-Caldas[1,2], Ana Alarcón[1,2], Ignacio Gómez-Centurión[1,2], Diego Conde[1,2], Jose Luis Díez[1,2,3], Jorge Gayoso[1,2], Javier Anguita[1,2], Mi Kwon[1,2]

Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain, School of Medicine, Complutense University of Madrid, Madrid, Spain

Background: Commercial anti-CD19 CAR-T cell therapy with tisacel and axi-cel has improved outcomes in refractory/relapsed DLBCL patients, but infection rates are significant after receiving this therapy. Our aim was to analyze differences in terms of immune reconstitution dynamics and infection rates between both commercial products.

Methods: We performed a single center retrospective study in 50 patients receiving commercial CAR-T cell products from August-2019 to July-2022. Immune reconstitution dynamics were monitored at +3, +7, +14, +30, +90, +180 and +360 days after infusion. Peripheral blood lymphocyte subsets were analyzed by flow cytometry. Infections were classified as early (<30 days) and late (> 30 days) and by microbial etiology. Mann Whitney U test was used to analyze differences in cell population levels and immunoglobulins between tisa-cel and axi-cel. ROC curves were used to obtain the best cut-off point of cell number to subsequently perform cumulative incidence (CI) analysis. Fine-Gray test was used to calculate the CI of infection from the day of obtaining the variable analyzed in each case, considering death as competitive event.

Results: Characteristics of patients and complications associated to CAR-T cell therapy are shown in Table 1. 50 patients received commercial CAR-T cell therapy, with a minimum follow-up of 3 months. A total of 48 infections were detected during de follow-up, 22 were early infections: 12 (54%) were bacterial, 9 (41%) viral and 1 (5%) fungal. Four (18%) patients required hospitalization and none of them required intensive care. 26 were late infections: 10 (38%) bacterial, 15 (58%) viral and 1 (4%) fungal, with a median of appearance at day 102 (range 32-489) after infusion. 13 (50%) required hospitalization and 1 (4%) required intensive care. No differences were found in the rate of infections between tisa-cel or axi-cel, either total incidence, early and late infections, or bacterial or viral infection.

Total T cell count depleted after LD chemotherapy, showing a better expansion of total T cells (specifically CD4) after infusion in tisa-cel compared to axi-cel from +3 to +180 days after infusion (p < 0,001). CD8 T cells were significantly higher in tisa-cel from day +3 to +14. 14 (28%) patients presented serum IgG levels <400 mg/dL after LD chemotherapy, 9 (18%) of them received endovenous immunoglobulins. By day +90, 11 (22%) patients did not reach >400 mg/dL IgG, with no differences between both products. Finally, values of 643 T cells/uL and 424 CD8 T cells/uL were identified as cut-off points that stratify patients into low and high-risk of infection after day +90 (p < 0.01).

Table 1. Patient characteristics

	Tisa-cel N = 18	Axi-cel N = 32
Sex, male, n (%)	11 (61)	14 (44)
Age, median (range)	63 (41-73)	63 (33-79)
Bridging therapy, n (%)	12 (67)	31 (97)
ECOG, n (%)		
0-1	18 (100)	32 (100)
2-3	0 (0)	0 (0)
Histology, n (%)		
DLBC	16 (89)	26 (81)
Transformed FL	2 (11)	2 (6)
Primary mediastinal lymphoma	0 (0)	4 (13)
Disease status at apheresis, n (%)		
Progressive disease	8 (44)	19 (60)
Stable disease	6 (33)	4 (13)
Partial response	2 (11)	6 (19)
Complete response	2 (11)	3 (10)
Primary refractory, n (%)	8 (44)	20 (63)
Previous lines, median (range)	2 (2-4)	2 (2-5)
Prior ASCT, n (%)	9 (50)	11 (34)
Prior Allo-SCT, n (%)	1 (6)	0 (0)
CRS 2, n (%)	2 (11)	12 (38)
Tocilizumab	2 (11)	12 (38)
Corticosteroids	0 (0)	10 (31)
ICANS, n (%)	1 (6)	6 (19)
Corticosteroids	1 (6)	6 (19)
Siltuximab	0 (0)	4 (13)
Anakinra	0 (0)	4 (13)

Conclusions: Infections after CAR-T cell therapy are frequent and may be severe. Low rates of total T cell counts and CD8 T cells are associated to an increase risk of infections after day +90 after commercial CAR-T cell therapy. Tisa-cel shows a better CD4 T cell reconstitution although this does not seem to influence in presenting significant higher infection rates compared to axi-cel. Microbial etiology is similar in both products, with bacterial infections predominant in the first 30 days and later viral infections.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P064

OUTCOMES AFTER ANTI-BCMA CAR T-CELLS FOR MULTIPLE MYELOMA, A RETROSPECTIVE ANALYSIS ON BEHALF OF THE CTIWP OF THE EBMT

Florent Malard[1], Edouard F. Bonneville[2], Francesca Bonifazi[3], Johan Maertens[4], Tobias Gedde-Dahl[5], Michael Daskalakis[6], Goda Choi[7], Hermann Einsele[8], Alessandro Busca[9], Christof Scheid[10], Jacques-Olivier Bay[11], Paolo Corradini[12], Lucía López Corral[13], Anne Sirvent[14], Ibrahim Yakoub-Agha[15], Nico Gagelmann[16], Patrick Hayden[17], Laurent Garderet[18], Jorinde D. Hoogenboom[19], Jurgen Kuball[20], McLornan Donal P.[21], Annalisa Ruggeri[22]

[1]Sorbonne Université, Paris, France, [2]Leiden University Medical Center, Leiden, Netherlands, [3]IRCCS Azianda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [4]University Hospital Gasthuisberg, Leuven, Belgium, [5]Oslo University Hospital, Oslo, Norway, [6]University Hospital Bern, Bern, Switzerland, [7]University Medical Center Groningen (UMCG), Groningen, Netherlands, [8]Universitaetsklinikum Wuerzburg, Wuerzburg, Germany, [9]S.S.C.V.D Trapianto di Cellule Staminali, Torino, Italy, [10]University of Cologne, Cologne, Germany, [11]CHU ESTAING, Clermont-Ferrand, France, [12]University of Milano, Milano, Italy, [13]Hospital Clínico, Salamanca, Spain, [14]CHU Lapeyronie, Montpellier, France, [15]CHU de Lille, Univ Lille, INSERM U 1286, Infinite, Lille, France, [16]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [17]St. James's Hospital, Dublin, Ireland, [18]Hôpital Pitié-Salpêtrière, Paris, France, [19]EBMT Leiden Study Unit, Leiden, Netherlands, [20]University Medical Centre, Utrecht, Netherlands, University College London Hospital, London, United Kingdom, [22]San Raffaele Scientific Institute, Hematology and Bone Marrow Transplantation Unit, Milan, Italy

Background: Idecabtagene vicleucel (ide-cel) and Ciltacabtagene Autoleucel (cilta-cel) are autologous B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T-cell therapies, approved for relapsed/refractory multiple myeloma (RRMM). We aimed to evaluate outcomes of patients treated with standard of care (SOC) ide-cel and cilta-cel and reported to the cellular therapy registry of the EBMT.

Methods: The EBMT Cellular Therapy and Immunobiology Working Party (CTIWP) conducted a retrospective analysis amongst EBMT registered centers to evaluate outcomes of patients with MM receiving anti-BCMA CAR T-cells. Patient-, disease- and treatment characteristics were collected. Patient outcomes with a focus on disease response rates and rates/grades of cytokine release syndrome (CRS) were also evaluated. Descriptive statistics were utilized to report patient, disease and treatment characteristics as well as patient outcomes for both cohorts (ide-cel and cilta-cel).

Results: Overall, 53 patients with MM were reported with available data (33 patients infused with ide-cel and 20 with cilta-cel by time of data cut-off). Median age was 63 years for patients treated with ide-cel and 59 years for cilta-cel. A total of 25% of the patients had light chain multiple myeloma. The majority of patients had a history of autologous HCT (ide-cel, 73%; cilta-cel 85%) and had received an immunomodulatory drug (ide-cel, 84%; cilta-cel 87%), a proteasome inhibitor (ide-cel, 84%; cilta-cel 80%) and anti-CD38 monoclonal antibody (ide-cel, 74%; cilta-cel 53%).

Median time between leukapheresis and CAR T-cells infusion was 1.76 months for ide-cel and 2.53 months for cilta-cel. The majority of patients were treated within a clinical trial setting (ide-cel, 84%; cilta-cel 100%).

Regarding CRS, data was available from 15 patients treated with cilta-cel and 9 patients treated with ide-cel, that all developed CRS. For patients treated with cilta-cel, 53% developed grade 1 CRS, 40% grade 2 and 7 % grade 3, none developed grade 4 CRS. For patients treated with ide-cel, 44% developed grade 1 CRS, 56 % grade 2 and none developed grade 3-4 CRS. Best overall response rate (≥ partial response) and ≥ complete response (CR) at day 100 post infusion were 88% and 38% respectively for ide-cel and 94% and 67% for cilta-cel, respectively. With a median follow-up of 9.2 months, 10 patients had died (ide-cel, n = 8, cilta-cel, n = 2).

Conclusions: Therapy with the anti-BCMA CAR T-cell products ide-cel and cilta-cel translate into high response rates in patients with highly pretreated MM, including previous lines of treatment including autologous HCT, immunomodulatory drugs, proteasome inhibitors and anti-CD38 monoclonal antibodies. Furthermore, in patients that developed CRS, the majority developed grade 1-2 CRS and severe CRS appeared very uncommon. Overall, analysis of real-life data is important, regarding response, but also toxicities, in order to guide treatment choice; not only between available anti-BCMA CAR T-cells but also with regard to bispecific

monoclonal antibodies that are increasingly available for patients with MM.

Disclosure: Florent Malard received honoraria from BMS, Ibrahim Yakoub-Agha received honoraria from BMS and Janssen. Others authors did not disclose conflict of interest.

4 - CAR-based Cellular Therapy – Clinical

P065

REAL-WORLD EXPERIENCE OF TISAGENLECLEUCEL FOR CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH ALL IN JAPAN

Itaru Kato[1], Shinsuke Hirabayashi[2], Daisuke Tomizawa[3], Atsushi Manabe[2], Masahiro Irie[4], Yoji Sasahara[4], Yuki Arakawa[5], Katsuyoshi Koh[5], Hirotoshi Sakaguchi[3], Masanaka Sugiyama[6], Chitose Ogawa[6], Takahiro Kamiya[7], Motohiro Kato[8], Shoji Saito[9], Yozo Nakazawa[9], Nobuhiro Nishio[10], Yoshiyuki Takahashi[10], Takako Miyamura[11], Naoko Iwai[1], Souichi Adachi[1], Junko Takita[1], Satomi Yokoyama[12], Wakako Kato[12], Hiroaki Ono[12], Yuhki Koga[12], Hidefumi Hiramatsu[1]

[1]Kyoto University, Kyoto, Japan, [2]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [3]National Center for Child Health and Development, Tokyo, Japan, [4]Tohoku University Graduate School of Medicine, Sendai, Japan, [5]Saitama Children's Medical Center, Saitama, Japan, [6]National Cancer Center Hospital, Tokyo, Japan, [7]Tokyo Medical and Dental University Hospital, Tokyo, Japan, [8]The University of Tokyo, Tokyo, Japan, [9]Shinshu University School of Medicine, Matsumoto, Japan, [10]Nagoya University Graduate School of Medicine, Nagoya, Japan, [11]Osaka University Graduate School of Medicine, Osaka, Japan, [12]Kyushu University, Fukuoka, Japan

Background: Although the majority of pediatric B-cell acute lymphoblastic leukemia (ALL) patients have great outcomes, about 15% of individuals will experience a relapse. In the case of relapse, one major new treatment option is chimeric antigen receptor (CAR) T cells that target CD19. The pivotal phase 2, multicenter, global trial of a CAR T-cell therapy (ELIANA; NCT02435849) included 9 patients (median, 11 years old [5-24 years old]) in Japan (*Int J Hematol*. 2020;111:303–310). Tisagenlecleucel was approved in 2019 in Japan, and more than 3 years have passed since then.

Methods: The Japan CAR-T Consortium developed a database for children, adolescents, and young adults with relapsed and/or refractory B-ALL who received tisagenlecleucel to investigate the real-world (RW) experience. Eleven centers in Japan contributed to the retrospective RW registry analysis after May 22, 2019, and a total of 42 infused patients (median, 10 years old [1-23 years old]) were analyzed as of Feb 1, 2022. The best overall response of complete remission (CR), event-free survival (EFS), and overall survival (OS) were evaluated as efficacy, and cytokine release syndrome (CRS) was graded using the American Society for Transplantation and Cellular Therapy criteria as a safety profile.

Results: In RW registry, the median follow-up period of the survivors was 312 days (63-813 days). The best overall response rate (CR/CRi) was 92.9%. MRD after infusion was evaluated in 36 patients and 35 (97.2%) were negative. The 1-year OS and EFS rates after infusion were 81.6% and 56.3%, respectively. Twenty-seven patients (64%) had low-disease burden (LB, defined as <5% bone marrow (BM) lymphoblasts) pre-tisagenlecleucel infusion, and LB was associated with superior outcomes, with 1-year EFS rate of 80% compared with that of 24% in cases with a high-disease burden (≧5% BM lymphoblasts) ($p < 0.0001$), that is the same observation as previously reported (*J Clin Oncol*. 2022;40(9):945-955). Notably, multivariate analyses revealed an association of prior hematopoietic stem cell transplantation (HSCT) (n = 23, 55%) with superior outcomes (HR 0.084, 95%CI 0.02 to 0.3, $p < 0.001$), with a 1-year EFS rate of 75% compared with that of 24% in patients without prior HSCT.

Compared with ELIANA trial data, the blast percentage in BM before infusion were significant lower in RW registry (median, 1.3% [0-100%]) than ELIANA cohort (93%, [2.3-98%]). Although similar efficacy was observed (the 1-year OS and EFS rates after infusion were 67%, and 44% in the ELIANA cohort), CRS grades were significantly lower in RW registry (median; grade 1), compared with the ELIANA cohort (median; grade 4) and the death within 100 days after infusion were lower in RW registry (0% vs 22%).

Conclusions: This first analysis of patients with ALL undergoing commercial tisagenlecleucel in Japan confirmed LB and prior HSCT to be associated with superior EFS and showed more favorable safety profile compared with pivotal trials. Under RW setting, tisagenlecleucel tended to be administered at LB status, which contributed to the decrease of severe CRS. Long-term follow-up data will provide further insights into the use of tisagenlecleucel in RW setting.

Disclosure: Itaru Kato, Speakers Bureau(Novartis);
Daisuke Tomizawa, Membership on an entity's Board ofDirectors or advisory committees and Speakers Bureau (Novartis);
Takahiro Kamiya,Speakers Bureau(Novartis);
Motohiro Kato,Speakers Bureau (Novartis);
Shoji Saito, Research Funding (Toshiba Corporation);
Hidefumi Hiramatsu, Speakers Bureau (Novartis).

4 - CAR-based Cellular Therapy – Clinical

P066

MODIFIED EASIX PREDICTS DISSEMINATED INTRAVASCULAR COAGULOPATHY, CRS AND PROGNOSIS IN PATIENTS TREATED WITH ANTI-CD19 CAR-T CELLS

Eugenio Galli[1,2], Federica Sorà[1,2], Ilaria Pansini[1], Francesco Autore[2], Elisabetta Metafuni[2], Alberto Fresa[1,2], Maria Assunta Limongiello[2], Idanna Innocenti[2], Sabrina Giammarco[2], Luca Laurenti[1,2], Andrea Bacigalupo[1,2], Patrizia Chiusolo[1,2], Stefan Hohaus[1,2], Valerio De Stefano[1,2], Simona Sica[1,2]

[1]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Rome, Italy, [2]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Background: Cytokine release syndrome (CRS) and consumptive coagulopathy can complicate the treatment with chimeric antigen receptors T (CAR-T) cells. The modified version of Endothelial Activation and Stress Index EASIX (mEASIX), a score derived from hematopoietic stem cell transplantation, combines platelets, CRP, and LDH and has been correlated with CRS and endothelial biomarkers.

Methods: In 38 consecutive patients with aggressive lymphoproliferative disease we measured a coagulative laboratory panel at baseline and early after infusion of anti-CD19 CAR-T. The panel was investigated also in the presence of CRS graded ≥2, or immune effector cell-associated neurotoxicity syndrome (ICANS).

ISTH score (platelets, PT, FDP, fibrinogen) for diffuse intravascular coagulopathy was applied.

Results: **CRS and ICANS**

All patients experienced CRS during the first 10 days after CAR-T cells reinfusion (max CRS of grade 2 or more in 79%). ICANS occurred in 31% patients (Grade 3-4 in 10% patients).

Coagulopathy and CRS/ICANS

No patient experienced a major bleeding; one patient had a symptomatic catheter-related deep vein thrombosis (DVT) with pulmonary embolism (PE).

Patients with CRS grade ≥ 2 had prolonged PT and aPTT values, a lower platelet count, and decreased antithrombin levels in comparison with those with CRS mild or absent. In moderate-to-severe CRS we have observed fibrinogen, D-dimer, FVIII, vWF antigen levels higher than in mild or absent CRS. Similar results were found for ICANS.

At baseline, immediately before CAR-T cells reinfusion, all but one patient had an ISTH score lower than 5. Conversely, if assessed while experiencing CRS grade 2 or more, 30% of the evaluable patients presented an ISTH score of 5 or more, consistent with DIC. Overall, 13/38 (34%) patients fulfilled ISTH criteria for DIC during the first two weeks after CAR-T cells infusion.

Endothelial activation and Coagulopathy

Overt DIC was strongly associated with simultaneous mEASIX scoring. Moreover, baseline mEASIX higher than 6.89 predicted DIC during the two weeks after infusion. Coagulopathy defined as per ISTH criteria occurred in 29%, 33% and 40% of patients treated with axi-cel, brexu-cel and tisa-cel, respectively ($p = 0.8$).

Higher mEASIX was associated with laboratory findings suggesting an active coagulative process and endothelial involvement (Higher aPTT, fibrinogen, D-dimer, factor VIII, and vWF, and lower antithrombin).

We have also found a positive correlation with sST2 (Soluble Suppression of tumorigenicity 2, secreted in response to stress or injury by a plethora of cell types, including immune-cells, fibroblasts, and endothelial cells) and suPAR (Soluble urokinase-type plasminogen activator receptor, widely associated with markers of endothelial damage and activation).

mEASIX and prognosis

PFS at day 180 after CAR-T cells infusion was 60% vs 33% for patients with a baseline mEASIX lower or higher than 6.89, respectively ($p = 0.031$). OS at day 180 was 90% vs 50% for patients with a baseline mEASIX lower or higher than 6.89, respectively ($p = 0.024$).

Conclusions: Overall, the role of endothelium is emerging as pivotal in the pathophysiology of CRS and ICANS. Further studies are needed to explore the role of endothelial activation and coagulopathy in order to improve the safety and efficacy of CAR-T cell therapies.

Disclosure: Authors disclose no competing conflict of interests.

4 - CAR-based Cellular Therapy – Clinical

P067

ADOPTION OF BENDAMUSTINE LYMPHODEPLETION AS STANDARD OF CARE IN SETTING OF DRUG SHORTAGES

Richard Maziarz[1], Andy Chen[1], Levanto Schachter[1], Peter Ferreira-Gandolfo[1], Brandon Hayes-Lattin[1], Jessica Leonard[1], Staci Williamson[1], Amber Diaz[1]

[1]Oregon Health & Science University, Portland, United States

Background: Cyclophosphamide and fludarabine (Cy/Flu) lymphodepleting chemotherapy (LDC) has been adopted universally prior to administration of CAR T-cell therapy. A prior comparative analysis suggested that acceptable outcomes can be achieved, substituting bendamustine (Benda) for Cy/Flu prior to administration of Tisagenlecleucel (Tisa-cel) (Ghidelli, Ann Onc, 2022). Due to an unanticipated absence of availability of Flu, Benda was adopted as a standard of care for all CAR-T administrations of commercially available product (Maziarz, JTCT, 2022) including CAR T-cell products using the CD28 activation domain.

Methods: For calendar year 2022, all subjects receiving CAR T-cell therapy for standard indications (ALL, lymphoma, myeloma) were reviewed and separated into 2 cohorts, those receiving Cy/Flu vs Benda as LDC. The retrospective analysis was limited to the current year to provide a contemporary comparative cohort. Data were collected from institutional data bases and were assessed for disease response, adverse events, and depth of lymphodepletion. Ongoing data analysis for quality assurance of safety has been performed consistent with institutional regulatory guidelines.

Results: Thirty-five subjects (19 NHL; 11 ALL; 5 MM) received CAR T-cell therapy after Cy/Flu LDC during 2022; 23 subjects (20 NHL; 3 MM) were treated with CAR T-cell after Benda LDC since Aug 2022. For those receiving Cy/Flu LDC, best observed response included 19 CR, 8 PR, 1 Stable, 4 Prog, 3 NE due to early death). Restricted assessments to the MM and NHL cohort, 19/26 had gained CR/PR status as best response. Sixteen of 35 developed CRS, with 9/16 with Gr II-IV CRS observed. Fourteen of 35 developed ICANS with 12/14 with Gr II-IV observed. Absolute lymphocyte count (ALC) nadir was assessed with a median ALC of 20 (range 0-240).

Subjects receiving Benda LDC had shorter follow-up, given the timing of LDC transition. For those receiving Benda LDC, best observed response included 5 CR, 7 PR, 2 Stable, 7 Prog, 2 NE due to not yet reach first evaluable date). Thirteen of 23 developed CRS, with 2/13 with Gr II-IV CRS observed. Five of 23 developed ICANS with 2/5 with Gr II-IV observed. Absolute lymphocyte count (ALC) nadir was assessed with a median ALC of 100 (range 0-1460). No subjects with ALL received Benda LDC.

Conclusions: Bendamustine has been shown in a comparative institutional analysis to be an acceptable agent to be utilized for LDC prior to CAR T-cell therapy. Due to an unforeseen drug shortage with limited availability, strict institutional guidelines for use were developed impacting leukemia, transplant and immune effector cell programs. Ongoing assessment of impact occurs via oversight of a newly established Oncology Stewardship Committee. Current review suggests adequate clinical outcomes are achieved with Benda LDC. CRS and ICANS rates are observed to be lower than with Cy/Flu. Continued evaluation will be required to assure long term goals are achieved.

Clinical Trial Registry: Not applicable

Disclosure: No conflicts of interest are reported re: the contents of this abstract.

Thus, nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P068

EFFICACY AND TOXICITY FOR CD7 CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN PATIENTS WITH RELAPSED/ REFRACTORY T-CELL LYMPHOMA

Guoai Su[1], Fan Yang[1], Hui Shi[1], Rui Liu[1], Ruiting Li[1], Teng Xu[1], Shaoma Feng[1], Peihao Zheng[1], Yuelu Guo[1], Lixia Ma[1], Biping Deng[2], Xiaoyan Ke[1], Kai Hu[1]

Beijing Gobroad Boren Hospital, Beijing, China, [2]Cytology Laboratory, Beijing Gobroad Boren Hospital, Beijing, China

Background: The prognosis of refractory/relapsed T-cell lymphoma is extremely poor, especially for the patients who failed to allogeneic hematopoietic stem cell transplantation (alloHSCT).

Methods: From August 2017 to December 2022, 20 patients were enrolled. The median age was35 (18-72) years old. The diagnosis included T cell lymphoblastic leukemia/lymphoma (T-LBL) (n = 17), hepatosplenic T-cell lymphoma (HSTL, n = 1), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL, n = 1) and cutaneous T-cell lymphoma (CTCL, n = 1). The disease status was progressive disease (PD) in all patients who failed to multi-line therapies, including autologous HSCT (n = 5), and alloHSCT (n = 9). Six patients (6/20, 30%) had central nervous system involvement. In order to further reduce the tumor burden, 8/20 (40%) patients were treated with bridging therapy before CAR-T cell infusion. Before the trial, the expression of CD7 antigen in tumor tissue was positive confirmed by pathology. Infusion of donor-derived CD7 CAR-T cells in patients who have relapsed after alloHSCT, whereas infusion of autologous CAR-T cells in other patients. Patients received fludarabine and cyclophosphamide regimens before CAR-T cell infusion. The kinetics and function of CAR-T cells was monitored by quantitative PCR and flow cytometry. The efficacy was evaluated by PET-CT as well as bone marrow puncture after CAR-T infusion.

Results: The median CAR-T cells infused were 1×10^5/kg (range,0.06-34$\times10^5$/kg). For CAR T cell expansion,the peak time in vivo was on median 14 (range, 11-29) days after CAR-T cell infusion. The median peak kinetics of CAR-T cells in peripheral blood of individual patients measured by flow cytometry was 23.65 (range,1.61-49)$\times10^6$/L, which was no correlation with the number of CAR-T infused (P = 0.0818). Peak CAR-T amplification is also independent of whether CART cells are sufficiently donor-derived(P = 0.4692). Levels of CAR-T cells were very low after the first 1 months postinfusion. The incidence of grade 3 cytokine release syndrome (CRS) was 15% (3/20), and the incidence of grade 1-2 neurotoxicity was 10% (2/20). Although CD7-positive normal T cells were depleted, CD7-negative T cells expanded in all patients. Seventeen patients had occurred cytopenias. Nine patients (9/20,45%) had prolonged cytopenias (1 month). Viremia occurred in 12/20 (60%) patients. 2/20 (10%) patient developed post transplant lymphoproliferative disorders (PTLD) associated with EBV infection.1/9 (11%) patients after allogeneic HSCT were found to have grade IV aGVHD (intestinal).

With a median follow-up of 5.96 months (95% CI: 0.56-18.6), one-year overall survival (OS) and progression-free survival (PFS) were 65.5% and 56.6%, respectively. The overall response (ORR) was 60% (CR 55% and PR 5%). However, patients treated with donor-derived CAR-T had significantly worse PFS (33.3% versus 100%) than other patients, which may be due to the very high incidence of infections. Data from scRNA-seq of PBMCs from patients treated with donor-derived CAR-T indicated a fulfilled T lymphocytes immune function by CD7-negative T cells. The major challenge on prevent post-treatment infection may be the protection from loss of monocytes.

Conclusions: Our study showed promising efficacy of CD7 CAR-T cell therapy in r/r T-cell lymphoma. CRS is manageable. For patients who have relapsed after allogeneic transplantation, bridge second transplantation is recommended if CD7 CAR-T therapy is effective.

Clinical Trial Registry: ChiCTR2200058969 and http://www.chictr.org.cn/index.aspx

Disclosure: The authors confirm that there are no conflicts of interest.

4 - CAR-based Cellular Therapy – Clinical

P069

EARLY POST-CAR-T MARKERS OF PROGRESSION, DESPITE CONCOMITANT PET REMISSION: A MONOCENTRIC EXPERIENCE IN THE SETTING OF AGGRESSIVE B-CELL LYMPHOMA

Massimiliano Gambella[1], Anna Maria Raiola[1], Chiara Ghiggi[1], Livia Giannoni[1], Riccardo Varaldo[1], Anna Ghiso[1], Silvia Luchetti[1], Alberto Serio[1], Monica Centanaro[1], Alessandra Bo[1], Angelo Gratarola[1], Emanuele Angelucci[1]

[1]IRCCS Ospedale Policlinico San Martino, Genova, Italy

Background: Metabolic remission of lymphoma 1 month after CAR-T therapy (PET-1) is challenging: some patients will remain lymphoma-free; a proportion will progress over time. Clinical factors associated with the risk of early progression, as depicted concomitantly with PET-1, lack and could help the decisional process (observation vs pre-emptive strategies). We sought to identify these factors.

Methods: Twenty-five consecutive patients affected by aggressive B cell lymphoma, treated at our center from October 2020 to July 2022 with anti-CD19 CAR-T (tisagenlecleucel or axicabtagene ciloleucel) were analyzed. Patients with PET-1 metabolic remission (i.e., complete or partial remission, as per Cheson criteria) were considered; primary mediastinal lymphomas were excluded. Clinical/laboratory variables considered relevant for progression were collected 1 month after CAR-T infusion; their association with subsequent progression was evaluated through the two-tailed Fisher's exact test. Variables with a $p < 0.25$ for association with progression entered a dichotomic score (two groups: 0-1 vs ≥2 points). Progression-free survival (PFS) was calculated for the two groups from PET-1 through the Kaplan-Meier estimator. Log-rank test was employed for comparisons.

Results:

Tab.1a

Variables	No Progression within 6 months (N = 8)	Progression within 6 months (N = 6)	p-value
CRP, n (%)			
> ULN	1 (12.5)	0 (-)	1.0
< UNL	7 (87.5)	6 (100)	
PLT, n (%)			
< 25x10^9/L	0 (-)	3 (50)	**0.05**
> 25x10^9/L	8 (100)	3 (50)	
LDH, n (%)			
> 1.5 ULN	2 (25)	4 (66.7)	**0.24**
< 1.5 ULN	6 (75)	2 (33.3)	
fibrinogen, n (%)			
< LLN	2 (25)	5 (83.3)	**0.1**
> LLN	6 (75)	1 (16.7)	
dexamethasone, n (%)			
> 40mg	0 (0)	3 (50)	**0.05**
< 40mg	8 (100)	3 (50)	
Tab.2a			
Risk-Group, n (%)			
High-Risk (≥ 2 points)	0 (-)	4 (66.7)	**0.015**
Low-Risk (0-1 points)	8 (100)	2 (33.3)	

CRP C-Reactive Protein; *UNL* Upper Limit of Normal; *PLT* platelets; *LDH* lactate dehydrogenase; *LLN* Lower Limit of Normal.

Fourteen patients fulfilled the pre-specified criteria at PET-1 evaluation, 10 CR and 4 PR; 6/14 (42%) progressed within 6 months from infusion, 4 from PET-1 PR and 2 from CR. Among variables evaluated one month post-infusion, four (i.e., fibrinogen < lower limit of normal, lactate dehydrogenase > 1.5 upper limit of normal, platelets count < 25x10^9/L, total dexamethasone dose > 40mg, administered for inflammatory complications) were considered relevant for subsequent progression ($p < 0.25$; table 1a) and gathered together in a dichotomic score, each variable accounting for 1 point: low-risk (0-1 points); high-risk (≥ 2 points). Ten patients were classified as low-risk and 4 patients as high-risk; among the high-risk patients, 2/4 had a concomitant PET-1 CR. The high-risk score resulted significantly associated with progression ($p = 0.015$). With a median follow-up of 17 months from PET-1 (95% CI: 14.6 – 19.4), 4 patients (100%) in the high-risk group progressed, as compared to 3/10 (30%) in the low-risk group ($p = 0.003$).

Conclusions: Simple clinical factors evaluated following infusion, likely representing a "hostile" environment for CAR-T cells, emerge as risk factors for progression. Their use, gathered together in a risk score, might be of particular interest in PET-1 responding patients, allowing prophylactic/pre-emptive strategies before progression, such as allogeneic transplant. We recognize that the index probably identifies patients inherently with a major risk of relapse due to a high tumor burden at CAR-T. However, it is still difficult to foresee whether and when to treat patients who achieve an early, major response.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P070

BREXUCABTAGENE AUTOLEUCEL FOR ADULT PATIENTS WITH REFRACTORY/RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA: COST-EFFECTIVENESS IN THE CLINICAL SUBSETS

***Monia Marchetti*[1]**

[1]Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

Background: Acute Lymphoblastic Leukemia (ALL) is a rare aggressive neoplasm incurring in about 2/100,000 adults per year, but less than half of them are projected to survive 5 years after diagnosis. Expected overall survival (OS) is particularly poor (i.e. less than 12 months) in patients relapsing or not responding after/to frontline therapy (R/R) despite being offered standard of care (SOC) with targeted agents (Blinatumomab (BLIN), Inotuzumab Ozogamicin (INO)) or chemotherapy (CIT), +/- tyrosin-kinase inhibitors (TKI), possibly followed by allogeneic stem cell-transplantation (aSCT). Brexucabtagene autoleucel is a chimeric antigen receptor (CAR) T-cell therapy that allowed 56% of R/R LLA patients to achieve a durable complete response and a median OS of 25.4 months. The present study aimed at comparing the clinical and economic outcomes of R/R LLA patients treated with Brexucabtagene autoleucel versus the standard of care (SOC) in the Italian Healthcare System.

Methods: We developed a partitioned-survival model to extrapolate event-free, overall survival and healthcare costs of R/R LLA patients and intended to receive KTE-X19 or SOC. The source of safety and survival data for Brexucabtagene autoleucel was the mITT cohort of ZUMA-3 trial (16.4 month median follow-up data; 77% received CAR-T infusion), while historical trial data (e.g. INO-VATE, PACE and TOWER) were used for for SOC. Long-term OS and EFS were estimated using mixture cure modelling methods: log-logistic and log-normal parametrization of OS and EFS curves was usually employed, respectively. Moreover, consolidation aSCT was modelled in 23.48% of patients achieving a response to SOC and in 18% of the patients treated with Brexucabtagene autoleucel, based on trial data. Patients whose disease had not progressed after 2 years were assumed to experience long-term remission.

Patients' quality of life (i.e. utilities) were driven from ZUMA-3 trial and the published literature. Resource consumption was based on trial data and published literature. Unit costs were estimated from an Italian National Healthcare System perspective and based on national charges, ex-factory drug costs and published economic analyses. Costs and health outcomes were discounted at 3% per year. Sensitivity analyses were performed to test model robustness.

Results: Median estimated survival was 9.68 life years for Brexucabtagene autoleucel, while it was 2.78-4.98 LYs for SOC. Discounted and quality-adjusted life expectancy was 4.96-5.51 quality-adjusted years (QALY) for Brexucabtagene autoleucel versus 1.34-3.04 for SOC. Cumulative discounted costs in the 50-year time horizon were €387,904-405,023 for patients intended-to-receive Brexucabtagene autoleucel, versus €111,976-271,651 for SOC, which corresponds to a cost of €46,415-76,384 per QALY gained. At a willingness-to-pay threshold of 100,000/QALY probabilistic sensitivity analysis demonstrated that Brexucabtagene autoleucel has a probability higher than 85% of being cost-effective versus SOC. The most influential model parameters were patients' quality of life, Brexucabtagene autoleucel acquisition cost, and the proportion of patients receiving HSCT. The results were also sensitive to the time horizon of the analysis.

Conclusions: Brexucabtagene autoleucel is a cost-effective alternative to SOC for adult patients with R/R LLA, both Ph+ and Ph-.

Disclosure: MM (Gilead consultancy fees).

4 - CAR-based Cellular Therapy – Clinical

P071

OPTIMIZING MULTITARGET APPROACH IN THE PEDIATRIC PATIENT: NEW PERSPECTIVES OF DUAL CD19/CD22 CAR-T

***Víctor Galán-Gómez*[1], *Berta González Martínez*[1], *Isabel Mirones Aguilar*[2], *Carlos Echecopar Parente*[1], *Adela Escudero*[3], *Cristina Ferreras*[4], *Alfonso Navarro-Zapata*[4], *Carmen Mestre-Durán*[4], *Marta Cobo*[2], *Alicia Pernas*[2], *Susana Vallejo*[2], *Raquel de Paz Arias*[5], *Jordi Minguillón*[4], *Isabel Martínez-Romera*[1], *Pilar Guerra-García*[1], *Sonsoles San Román*[1], *Antonio Pérez-Martínez*[1]**

Hospital La Paz, Madrid, Spain, [2]Advanced-Production Therapy Unit; University Hospital La Paz, Madrid, Spain, University Hospital La Paz, Madrid, Spain, [4]La Paz Research Institute; University Hospital La Paz, Madrid, Spain, La Paz University Hospital, Madrid, Spain

Background: CD19 CAR-T *tisagenlecleucel* has been proved to be effective in B-cell precursor acute lymphoblastic leukemia (B-ALL). However, 30-50% of patients will suffer a relapse after CD19 CAR-T infusion, sometimes CD19 negative. New CAR-T targets have been supposed to be considered, such as CD22 or multitarget approach as dual CD19/CD22.

Methods: To evaluate the safety and efficacy of the use of an *in-house* manufactured dual CD19/22 CAR-T through a compassionate use program in patients diagnosed with a relapsed or refractory ALL-B.

Five batches of the drug under investigation for advanced therapy CD19/22 CAR-T cells have been manufactured under Good Manufacturing Practices (GMP), authorized by the Spanish Agency for Medicines and Health Products (AEMPS) under a

compassionate use program. The starting material in all cases was immobilized apheresis. After immunoselection of the populations of CD3+ T lymphocytes (CD4/CD8) and activation with CD3/CD28, they were transduced with a CD19/CD22 lentiviral vector provided by Miltenyi Biotec. Cell expansion was performed in the CliniMACS Prodigy® device with TexMACs culture medium supplemented with IL-7 and IL-15. During manufacturing, process and quality controls were carried out and the finished product was fresh-available or cryopreserved in vapor phase liquid nitrogen until it was administered to the patient.

Results: A total of 6 dual CD19/22 CAR-T infusions have been performed in a total of 5 patients. Three patients (60%) were diagnosed with a relapsed B-ALL after *tisagenlecleucel* infusion. Of them, 2 patients (67%) had also previously received hematopoietic stem cell transplantation (HSCT). These two patients did not present CD19 expression at relapse. One of them also expressed low CD22. One patient (20%) was diagnosed with a refractory B-ALL, and the last patient (20%) with a relapsed B-ALL. Both were no eligible for *tisagenlecleucel* treatment.

The age range of the patients was 6-17 years. The time range between the start of manufacturing and the availability of the CAR-T for infusion was 9-11 days. The pre-infusion minimal residual disease range was 0.01-87%. Bridging therapy was individualised in each patient, and lymphodepletion regimen consisted on fludarabine and cyclophosphamide. The infused dose range was 7.5x1e5-3x1e6 cells/kg.

Regarding toxicity, a total of 4 patients (80%) presented cytokine release syndrome (CRS): 2 patients (50%) grade 3 (ASBMT guidelines). Two patients (20%) presented grade 3 immune effector cell-associated neurotoxicity syndrome (ICANS).

On day +28, 3 (60%) of the patients were in complete remission (CR). Two (40%) suffered disease progression and received palliative treatment.

Conclusions: The manufacturing of dual CD19/22 CAR-T therapy is feasible and reproducible under GMP conditions. The infusion of the product seems to be well tolerated without severe toxicities in the majority of patients, with an adequate safety profile. Data from our experience suggest the efficacy of its use. A larger number of patients is needed, so the use of the CAR-T in the context of a clinical trial should be necessary.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P072

RETROSPECTIVE MULTICENTRIC COMPARISON OF OUT-OF-SPECIFICATION AND STANDARD-OF-CARE TISAGENLECLEUCEL INFUSION FOR DIFFUSE LARGE B-CELL LYMPHOMA

Daniele Mannina[1], Chiara De Philippis[1], Cristina Zucchinetti[1], Flavio Pistolese[1], Mauro Krampera[2], Francesca Bonifazi[3], Annalisa Chiappella[4], Alice Di Rocco[5], Enrico Orciuolo[6], Maria Chiara Tisi[7], Laura Giordano[1], Armando Santoro[1,8], Stefania Bramanti[1]

[1]IRCCS Humanitas Research Hospital- Humanitas Cancer Center, Rozzano (Milano), Italy, [2]University of Verona, Verona, Italy, [3]Istituto di Ematologia L. e A. Seràgnoli, Bologna, Italy, [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, [5]Sapienza University of Rome, Rome, Italy, [6]University of Pisa, Pisa, Italy, [7]Ospedale San Bortolo, Vicenza, Italy, [8]Humanitas University, Pieve Emanuele (Milano), Italy

Background: CAR-T treatment requires a complex manufacturing process that includes multiple functional tests, to guarantee strict quality criteria and ensure the safety and the efficacy of the product[1,2]. A final product that complies with all the quality criteria is acknowledged as "standard-of-care" (SOC), while the ones presenting at least one feature not fitting the benchmark are considered "out-of-specification" (OOS)[2]. CAR-T infusion is often urgent because of disease aggressiveness, and infusion of OOS product could be the only chance to cure some patients[3,4]. Recently published literature suggests that OOS occurrence is not negligible and it may occur more frequently in highly pre-treated patients (≥ 4 prior therapies or bendamustine exposure).[5] It is still unclear whether the outcome of OOS tisa-cel is significantly different from SOC.

Methods: This retrospective multicentric study aims at evaluating the outcomes of the administration of OOS tisa-cel in comparison with SOC product, both in term of toxicity and efficacy. We enrolled 40 DLBCL patients from 6 italian centers, 11 treated with OOS tisa-cel, 29 with SOC tisa-cel in a real life-setting, according to Italian Medicines Agency criteria. Patients treated within an experimental trial were excluded.

Results: Table 1 summarizes patient characteristics, homogeneously distributed across the cohorts. Reason for defining OOS was viability below range in 1 case, inadequate transgene copies in 2 case, insufficient CAR expression by cytofluorimetry in 2 cases, high IFN-gamma secretion in 4 cases, T-cell expansion below range in 1 case, inadequate reporting of microbiological contamination (mycoplasma) in 1 case. After a median follow-up of 11 months, one-year PFS was 54.5% and 39.5% for OOS and SOC patients, respectively ($p = 0.99$). One-year OS was 55.5% and 64.5% for OOS and SOC patients, respectively ($p = 0.31$) Complete remission was achieved in 6/11 OOS patients (54.5%), and in 18/29 SOC patients (62.1%), without any statistically significant difference ($p = 0.664$). CRS, ICANS and infections occurred in similar proportions across the groups, with no statistically significant difference. Prolonged cytopenia, defined as persistence of at least one grade 3-4 cytopenia at 45 days after infusion, was absent in the OOS group, while it was found in 11/29 (39.3%) patients in the SOC group ($p = 0.017$).

Table 1. Patients characteristics

		OOS (n = 11)	SOC (N = 29)	Total (n = 40)	p. value
Sex	Male	6 (54.5%)	13 (44.8%)	19	0.727
	Female	5 (45.5%)	16 (55.2%)	21	
Age	Median (range)	56 (25-69)	59 (28-72)	58 (25-72)	
Diagnosis	de novo DLBCL	10 (90.9%)	27 (93.1%)	37	1.000
	transformed DLBCL (t-FL)	1 (9.1%)	2 (6.9%)	3	
MYC/BCL2/ BCL6 status	Double-hit	1 (9%)	3 (10.3%)	4	0.328
	Double/ triple expressor	5 (45.5%)	8 (27.6%)	13	
	Negative	5 (45.5%)	18 (62.1%)	23	
Stage at diagnosis	I-II-III	2 (18.2%)	14 (48.3%)	16	0.148
	IV	9 (81.8%)	15 (51.7%)	24	
Prior bendamustin	Yes	2 (18.2%)	2 (6.9%)	4	0.300
	No	9 (81.8%)	27 (93.1%)	36	
Prior ASCT	Yes	3 (27.3%)	5 (17.2%)	8	0.660

PATIENT ID	P1	P2	P3	P4	P5
AGE (years)	13	6	11	17	10
GENDER	M	F	F	M	M
DISEASE	rB-ALL	rB-ALL	rB-ALL	RB-ALL	rB-ALL
PREVIOUS HSCT	NO	YES	YES	NO	NO
Months to relapse		1.3	14.8		
PREVIOUS CD19 CAR-T	YES	YES	YES	NO	NO
Months to relapse	7	7	6.5		
OTHER PREVIOUS THERAPY	-	Inotuzumab	Carfilzomib (NCT02303821)	-	-
IMMUNOPHENOTYPE	CD19- CD22+	CD19- CD22low	CD19- CD22+	CD19lowCD22+ CD19+CD22low	CD19+ CD22+
BRIGDE THERAPY	ITT	Steroids	VCR	ARA-C MCP	HU Dexa
TUMOR BURDEN (%) PRE-LYMPHODEPLETION	0.01	4.5	5.32	87	75
LYMPHODEPLETION	FluCy600	FluCy600	FluCy600	FluCy900	FluCy500
DAYS OF PRODUCTION	9	11	10	11	10
DOSE (cells/kg)	3x1e6	3x1e6	3x1e6	1.5x1e6	7.5x1e5
FRESH INFUSSION	NO	NO	NO	YES	YES
CRS	YES	NO	NO	YES	YES
Max. grade (ASBMT)	1			3	3
Day of onset	1			0	5
Treatment	-			Tocilizumab	Siltuximab
				MP	MP
ICANS	NO	NO	NO	YES	YES
Max. grade (ASBMT)				3	3
Day of onset				6	7
Treatment				Siltuximab	Dexa
				Dexa	
HLH	NO	NO	NO	YES	YES
Day of onset				6	7
Treatment				Anakinra	Anakinra
				Dexa	Dexa
					Ruxo
PICU ADMISSION (days)	NO	NO	NO	YES (5)	YES (6)
RESPONSE DAY + 28	CR, MRD-	PD	CRi, MRD+	CR, MRD-	CR, MRD-
RELAPSE &	YES	-	-	NO	NO
TREATMENT	HSCT	Palliative	Reinfussion	HSCT	HSCT
STATUS &	A	PA	PA	A	A
FOLLOW-UP (months)	28	2	4.5	5	1

Conclusions: Our data confirm that OOS infusion is a feasible option, without any increase in terms of inflammatory and neurological toxicity. In consideration of the rapid progressivity of r/r DLBCL, a second manufacturing attempt with prolongation of apheresis-to-infusion time in case of OOS is not justifiable. Further data collection is desirable in order to confirm the non-inferiority OOS CAR-T in terms of efficacy, due to the small number of patients. Moreover, quality criteria of tisa-cel are still subject to continuous update, and larger cohorts of patients are required to establish which type of alteration from SOC may actually impact the outcome, possibly leading to further revision of OOS criteria.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P073

MANAGEMENT OF CRS AND ICANS WITH SILTUXIMAB AND ANAKINRA: A SYSTEMATIC REVIEW OF EVIDENCE TO INFORM SIES-GITMO-SIDEM RECOMMENDATIONS

Monia Marchetti[1], Annalisa Chiappella[2], Maria Guarino[3], Giorgia Gobbi[2], Massimo Martino[4], Andres JM Ferreri[5], Luca Fumagalli[6], Riccardo Saccardi[7], Mario Montanari[8], Maurizio Marchetti[9], Pierluigi Zinzani[10]

[1]Hematology and Transplant Unit, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, [2]Division of Hematology & Stem Cell Transplant, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [3]Neuro AOU, IRCCS Policlinico S'Orsola, Bologna, Italy, [4]Cell Transplantation and Cellular Therapies Unit, Grande

Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy, [5]Lymphoma Unit, Fondazione Centro San Raffaele, Milan, Italy, [6]Intensive Care Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [7]Azienda Ospedaliera Careggi, Florence, Italy, [8]OspedaliRiuniti Marche, Ancona, Italy, [9]Hematology, Azienda Ospedaliera Policlinico Umberto I, Sapienza University, Rome, Italy, [10]Lymphoma Unit, Istituto Seragnoli, Policlinico S'Orsola, University of Bologna, Bologna, Italy

Background: Patients with aggressive B-cell lymphomas may achieve prolonged survival after treatment with autologous chimeric antigen receptor T-cells (CAR-T). Nevertheless, after CAR-T infusion a relevant portion of the patients develop cytokine-related syndrome (CRS) and cytokine-mediated neurotoxicity (ICANS). Monoclonal agents anainst Interleukin-6 (IL6) receptor (namely tocilizumab) are standard of care for treating CRS, however, ICANS might be increased due to blood-brain bareeer blocking tocilizumab entrance. For the above reasons Siltuximab, a direct anti-IL6 monoclonal agent, and Anakinra, a monoclonal neutralizing antibody against interleukin-1 (IL1), have been tested in patients developing cytokine-related toxicities after CAR-T infusion. The present study is aimed at revising the available literature regarding Siltuximab and Anakinra use for the prevention or treatment of CRS and/or ICANS in order to support the development of evidence-based recommendations for the CAR-T guideline program started by three national scientific societies, namely SIE, GITMO and SIDEM.

Methods: On 1 December 2022 EMBASE, PubMed and Cochrane Library databases were scanned with standard queries in order to identify overall recordspublished since Jan 2019 and reporting the clinical outcomes of adult patients trated with CAR-T cell therapy for aggressive B-cell lymphomas. Out of 830identified records, those reporting Siltuximab or Anakinra use after CAR-T therapy were identified. The search also included studies presented uniquely in abstract form

Results: Fifteen studies reported the use of Anakinra in 132 patients with severe or steroid-refractory ICANS after CAR-T cell therapy (52% axi-cel), while 57 patients were enrolled into 3 prospective studies aimed at ICANS prevention. Grade 5 ICANS was reported in 4 out of 84 (4.7%) patients treated with Anakinra and amelioration of the neurological status was reported in 46-100% of the patients. Higher response rates were acieved with Anakinra doses higher than 200 mg per day and early mortality declined from 84% to 7% in patients receiving high vs low doses in one study. The rate of ICANS in patients receiving prophylaxis with Anakinra was 14% and only transient grade 3 ICANS developed.

Siltuximab use was detailed in overall 50 patients reported by 15 studies, but also in 4.4% of the 291 patients reported by the CART Consortium and CARICU studies. Most of the patients were treated with Siltuximab for tocilizumab-refractory CRS or concurrent CRS and ICANS. Unfortunately, specific outcomes of patients receiving Siltuximab were rarely reported. Overall no specific toxicity was alerted.

Conclusions: A growing body of evidence has been reporting the outcomes of Siltuximab and Anakinra in lymphoma patients who developed CRS or ICANS after CAR-T. Preliminary studies also tested an early adoption of Anakinra for the prevention of severe ICANS. The above systematic review confirms the need of randomized clinical trials to assess the effectiveness of Siltuximab and Anakinra in different patients subgroups, including those at high-risk of developing ICANS (see Rubin et al 2020).

Disclosure: MM (Gilead consultancy fees).

4 - CAR-based Cellular Therapy – Clinical

P074

EFFICACY OF EARLY LYMPHOPHERESIS TO IMPROVE CAR-T FITNESS AND PATIENT'S OUTCOMES IN HIGH RISK LARGE B CELL LYMPHOMA- A SINGLE CENTER, OPEN-LABEL PROSPECTIVE STUDY

Ron Ram[1], Odelia Amit[1], Chava Perry[1], David Hagin[1], Tal Freund[1], Yair Herishanu[1], Gil Fridberg[1], Nadav Sarid[2], Yakir Moshe[1], Uri Abadi[3], Noa Lavi[4], Shirley Shapira[3], Ofrat Beyar-Katz[4], Luiza Akria[5], Yafit Segman[6], Arie Apel[7], Shimrit Ringelstein-Harlev[4], Katrin Herzog Tzarfati[7], Tamir Shragai[1], Ronit Gold[1], Rinat Eshel[1], Irit Avivi[1]

[1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Wolfson Medical Center, Holon, Israel, [3]Meir Medical Center, Kefar Saba, Israel, [4]Rambam Medical Center, Heifa, Israel, [5]Galilee Medical Center, Nahariya, Israel, [6]Assuta Ashdod Hospital, Ashdod, Israel, [7]Shamir Medical Center, Rishon Leziyon, Israel

Background: Approximately 60%-70% of patients with relapse/refractory LBCL experience post anti CD-19 CAR-T disease progression that is partially related to the lack of CAR-T cell persistence and T cell exhaustion, attributed to T cell fitness at lymphopheresis. We hypothesized that early lymphopheresis (EL) in patients with high risk LBCL may improve CAR-T fitness and outcomes.

Methods: Patients with newly diagnosed high risk LBCL (defined as IPI ≥ 4, MYC + LBCL, a positive interim PET scan, evidence of progression of disease after 2 courses of first line treatment, or Richter's transformation) who signed informed consent were eligible to this study. Collection of cells was performed after ≤3 courses of first line therapy. Cells were sent for production of tisagenlecleucel, once patients were refractory to 2 lines of therapy and eligible to treatment. Prespecified interim analysis of collection and CAR-T product's characteristics was planned after the first 30 patients. We compared collection materials (T cell subpopulations and expression of exhaustion markers – HLA-DR and PD-1) and CAR-T products' characteristics between patients who underwent EL and patients who underwent standard lymphopheresis (SL) during same years.

Results: Between March, 2020 and November, 2022, 34 patients were recruited (IPI ≥ 4 (n = 6), MYC + LBCL (n = 25), positive interim PET scan/progression within 2 months (n = 1), and Richter's transformation (n = 2)). Median age was 66 (range, 33-80) years and in 31 (86%) patients collection was performed after 2 cycles of chemotherapy. Collection product was analyzed in all 34 patients. Median CD4/CD8 ratio and median % of naïve CD4 cells were both statistically significant higher in patients who underwent EL compared to those in the SL group (1.53 vs..59, p = .018, and 16.6% vs. 4.89%, p = .042, respectively), **Table**. Median expression of HLA-DR was statistically significant lower in the EL group in both the CD4 and the CD8 compartments (16.95% vs. 51.3%, p < .001, and 17.75% vs. 44.25%, p < .001, respectively) while median expression of anti PD-1 was statistically significant lower only in the CD4 compartment (32.46% vs. 52.8%, p = .021), **Table**. At a median follow-up of 22 (range, 3-35) months, 13 patients (38%) had a first disease progression with a median PFS of 30 (95% CI-22-38) months. Eight patients after second relapse/progression were given CAR-T. Characteristics of the CAR-T product of patients in the EL group showed statistically significant better transduction efficiency, higher % of cell viability, and increased CAR-positive viable cells, compared to patients in the SL group (p = .009, p = .042, and p = .042, respectively), **Table**. Incidence of grade 1-3 CRS was 100% (grade 3, 25%) and immune effector cell-associated neurotoxicity was documented in 25% of the patients (all grade 1). At 1 month post CAR-T infusion, overall response rate was

63% (CR = 4; PR = 1), and 2 patients had progressive disease. In 1 patient assessment of disease is pending.

Conclusions: Early lymphocyte collection in patients with high-risk LBCL is associated with high percentage of naiive T cells and low expression of exhaustion markers. This translates into superior specifications of the CAR-T product. This trial is still recruiting patients to test the toxicity profile and effectiveness of this approach.

Domain	Early Apheresis		Standard Apheresis		p Value
	Median	IQR	Median	IQR	
Apheresis material					
CD4/CD8	**1.53**	**.93-2.3**	**.59**	**.34—1.2**	**.018**
Naïve CD4, %	**16.6**	**11.7-31.2**	**4.89**	**1.7-11.6**	**.042**
HLA-DR CD4, %	**16.95**	**9.7-22.1**	**51.3**	**36.5-63.3**	**<.001**
PD1 CD4, %	**32.46**	**22.8-39.6**	**52.8**	**32.6-68.5**	**.021**
Naïve CD8, %	11.42	3.4-35.0	4.03	0.6-5.0	.052
HLA-DR CD8, %	**17.75**	**7.2-26.4**	**44.25**	**32.9-71.2**	**<.001**
PD1 CD8, %	28.40	20.9-33.6	31.3	29.3-35.5	.45
CAR-T product					
% of viable T cells	99.9	99.7-99.9	99.5	99.4-99.7	.33
Transduction efficiency	**.7**	**.35-.99**	**.25**	**.15-.39**	**.009**
% cell viability	**93.3**	**91.2-96.7**	**86.5**	**82.4-88.8**	**.042**
Total cell count (10^6/ml)	97.1	84.9-120	90.2	43.8-97.9	1
Number of viable cells (x10^6)	1700	1300-3300	1800	1050-2400	1
CAR-pos viable cells (x10^6)	**450**	**34-495**	**280**	**170-380**	**.042**
% CAR expression by flow	20.2	15.1-31.5	15.7	10.3-20.9	.16
Release of IFNg in response to CD19 (fg/transduced cells)	352	180-477	186	122-349	.16

Disclosure: Ron Ram. - Honoraria and speakers bureau: Novartis, Gilead; Ofrat Beyar-Katz - Honoraria: Novartis.

4 - CAR-based Cellular Therapy – Clinical

P075

A REAL-WORLD ANALYSIS OF CAR T-CELL CANCELLATIONS FROM A CANADIAN CELL THERAPY REFERRAL CENTRE

Eshrak Al-Shaibani[1], Rhida Bautista[1], Eshetu Atenafu[2], Andrew Winter[1], Anca Prica[1], Michael Crump[1], John Kuruvilla[1], Vishal Kukreti[1], Robert Kridel[1], Arjun Law[1], Ivan Pasic[1], Sam Saibil[1], Wilson Lam[1], Sita Bhella[1], Christine Chen[1]

[1]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Canada, Princess Margaret Cancer Centre, Toronto, Canada

Background: CAR T-cell therapy is a potentially curative treatment for aggressive large cell lymphoma. However, CAR T success in the real world can be constrained by restricted resources, systemic delays, manufacturing inefficiencies, and with few CAR T centres in Canada, the need to provide services across regional borders (out of province; OOP). These realities could contribute to CAR T delays and cancellations. We reviewed patient data from time of referral, initial assessment, cell collection and infusion, identifying causes for patient attrition.

Methods: We performed our first commercial CAR T in June 2020. At that time, there were only 3 CAR T centres in Canada using two CD19 CAR T products axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel). We analyzed 101 patients referred for CAR T to our centre from June 2020 to December 2021; 28 (28%) from OOP. Chi-square/Fisher test was used for categorical covariates and Kruskal-Wallis test for continuous variables comparing between patients receiving and not receiving CAR T infusion.

Results: Of the 101 patients referred for CAR T, median age was 61 years (22-81), lymphoma histologies included: DLBCL (51%), high grade lymphoma (21%), transformed lymphoma (18%), PMBCL (5%), other/missing (6%). 24% patients had double/triple-hit lymphoma, 54% refractory disease.

Of the 101 patients, 33 patients (33%) did not reach CAR T-cell infusion. 4/33 patients (12%) were declined at triage even before initial assessment due to: poor ECOG (1), CNS disease (1), unconfirmed relapse histology (1), alternative therapy favored (1). Of the remaining 29 patients who underwent initial assessment, 17 patients proceeded to T-cell collection (59%), 12 (41%) did not. Reasons for not proceeding at this point included: patient declined (4), disease progression (5), including 2 active CNS disease, severe comorbidity (1), and alternative therapy chosen (2).

Of the 17 patients who proceeded to T-cell collection, reasons for not proceeding to infusion included: failed manufacturing (n = 8; 7 tisa-cel, 1 axi-cel), disease progression (n = 8, 4 with active CNS disease), 1 declined. The 8 patients unable to reach cell infusion due to disease progression had high risk features at relapse (all stage IV, IPI score>2, high LDH), 50% double-hit disease, 75% refractory, 50% CNS disease. To identify a-priori predictors for cancellation amongst collected patients, we compared patient demographics, disease factors, and timeline metrics in patients who proceeded to CAR-T infusion to those who did not (Table 1). Aggressive disease features such as CNS involvement (active or previous) and double/triple-hit status predicted for failure to proceed to infusion. Lower absolute lymphocyte counts and elevated inflammatory markers at apheresis were increased in cancelled patients. Timeline metrics and proportion of OOP referrals were similar between the two groups.

Table 1: Comparison between collected patients who proceeded and did not proceed to CAR T-cell infusion

	CAR-T infusion N = 68	No CAR-T infusion N = 17	P value
Demographics			
Median age (range) at time of CAR T referral	60.6 (22-81)	64 (50.8-73.9)	0.22
Gender, n (%)			1
Female	26 (38.2%)	7 (41.2%)	
Male	42 (61.8%)	10 (58.8%)	
Referring center, n (%)			0.52
Within province	54 (79.4%)	12 (70.6%)	
Out of province (OOP)	14 (20.6%)	5 (29.4%)	
Diagnosis, n (%)			0.096
DLBCL	38 (55.9%)	8 (47.1%)	
High grade lymphoma	11 (16.2%)	8 (47.1%)	
Transformed follicular lymphoma	12 (17.6%)	1 (5.9%)	
Primary mediastinal B cell lymphoma (PMBCL)	5 (7.4%)	0	
Others	2 (2.9%)	0	

	CAR-T infusion N = 68	No CAR-T infusion N = 17	P value
Factors at time of relapse			
IPI score at relapse, n (%)			0.17
0-2	29 (42.7%)	4 (23.5%)	
>2	39 (57.4%)	13 (76.5%)	
CNS IPI at relapse, n (%)			0.28
Low	11 (16.4%)	2 (12.5%)	
Intermediate	44 (65.7%)	8 (50.0%)	
High	12 (17.9%)	7 (37.5%)	
Disease stage at relapse, n (%)			0.72
I-II	13 (19.1%)	2 (11.8%)	
III-IV	55 (80.9%)	15 (88.2%)	
High serum LDH at relapse, n (%)	55 (80.9%)	17 (100%)	0.06
Bulky disease at relapse, n (%)	35 (51.5%)	13 (76.5%)	0.099
Extra-nodal disease at relapse, n (%)	41 (60.3%)	9 (52.9%)	0.58
Prior CNS disease, n (%)	0	2 (11.8%)	**0.04**
Factors at time of CAR T referral			
Active CNS disease, n (%)	0	4 (23.5%)	**0.001**
Prior lines of therapy, median (range)	3 (2-5)	3 (1-4)	**0.28**
Disease status at referral for CAR-T, n (%)			**0.16**
Relapsed	33 (48.5%)	5 (29.4%)	
Refractory	35 (51.5%)	12 (70.6%)	
Double or triple hit lymphoma, n (%)	11 (16.2%)	8 (47.1%)	**0.006**
Karnofsky Performance Status (KPS), n (%)			**0.11**
≥80	53 (77.9%)	10 (58.8%)	
<80	15 (22.1%)	7 (41.2%)	
ECOG, n (%)			**0.15**
0-1	55 (80.9%)	11 (64.7%)	
≥2	13 (19.1%)	6 (35.3%)	
Hematopoietic cell transplant comorbidity index (HCT-CI), n (%)			**0.21**
0-1	48 (70.6%)	12 (70.6%)	
3-Feb	16 (23.5%)	2 (11.8%)	
>3	4 (5.9%)	3 (17.7%)	
Factors at time of apheresis cell collection			
Elevated ferritin level, n (%)	63 (92.7%)	11 (64.7%)	**0.0003**
Elevated serum C-reactive protein, n (%)	34 (50%)	8 (47%)	**0.016**
Median peripheral blood absolute lymphocyte count, 109/L (range)	0.9 (0.1-3.4)	0.5 (0.1-1.6)	**0.028**
Median peripheral blood CD3 counts/UL, median (range)	685.5 (16-3662)	308 (22-4916)	**0.057**
Bridging therapy (after apheresis), n (%)	53 (77.9%)	12 (75%)	**0.75**
Timeline metrics			
Median days from salvage treatment to apheresis (range)	19.5 (5-45)	19.5 (6-30)	0.77
Median days from initial visit to apheresis (range)	12 (2-35)	13 (1-33)	0.88

Conclusions: We report that one-third of referrals do not receive CAR T-cell infusion. Half of these cancel *before* cell collection, many due to aggressive disease progression and active CNS disease. CNS disease was also a primary reason for cancellation *after* collection, emphasizing the unmet need for improved CNS disease control through the CAR T process. Cancellations did not appear due to delays in timeline metrics for OOP referrals.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P076

EASIX AS A PREDICTOR INDEX FOR NEUROLOGICAL COMPLICATIONS AFTER ANTI-CD19 CAR-T CELL THERAPY IN AGGRESSIVE B-CELL LYMPHOMAS: A STUDY FROM THE GETH-TC GROUP

Marta Peña Domingo[1,2], Alberto Mussetti[1,2], Blanca Rius Sansalvador[2], Lucía Lopez-Corral[3], Mario Sanchez-Salinas[4], Pere Barba[4], Ana Benzaquén[5], Rafael Hernani[5], Manuel Guerreiro[6], Maria Perera[7], Anna Torrent[8], Antonio Perez-Martinez[9], Anna Sureda[1,2,10]

[1]Hospital Duran i Reynals-Institut Català d'Oncologia-Hospitalet, Hospitalet de Llobregat, Spain, [2]Institut d'Investigació biomèdica de Bellvitge (IDIBELL), Hospitalet de Llobregat, Spain, [3]Hospital Clínico Universitario de Salamanca, Salamanca, Spain, [4]University Hospital Vall d'Hebron, Barcelona, Spain, [5]Hospital Clínico Universitario de Valencia, INCLIVA Research Institute, Valencia, Spain, [6]Hospital La Fe, Valencia, Spain, [7]Hospital Universitario Doctor Negrin, Las Palmas de Gran Canaria, Spain, [8]Hospital Germans Trias i Pujol Institut Catala d'Oncologia-Badalona, Badalona, Spain, [9]Hospital Universitario La Paz, Madrid, Spain, [10]University of Barcelona, Barcelona, Spain

Background: Cytokine release syndrome (CRS) and immune-effector cells associated neurotoxicity (ICANS) due to chimeric antigen receptor T (CAR-T) cell therapy are associated to endothelial damage. This study evaluated the Endothelial Activation and Stress Index (EASIX) as a predictor for CRS and ICANS in patients treated with commercial CD19-directed CAR-T cells.

Methods: We retrospectively analyzed clinical data of 126 patients affected by aggressive B-cell lymphomas who received commercial-CD19 CAR-Ts (tisacel, axicel) from 7 centers in Spain. Inclusion period started from February 2019 to August 2022. Data were collected into the Grupo Español de Trasplante y Terapia Celular (GETH-TC) registry. CRS and ICANS were graded according to the ASTCT grading system. All patients received lymphodepleting chemotherapy with fludarabine and cyclophosphamide in doses determined according to the manufacturer. EASIX was calculated before the start of lymphodepletion (EASIX-PRE) and on the day of CAR-T administration (EASIX-d0). Log2 transformation was applied to reduce skew. Predictors of CRS and ICANS were identified using logistic regression analysis. Variables found to be significant (p-value < 0.05) in the univariate analysis and/or those considered clinically relevant for the study were included in the logistic multivariate analysis. Other outcome variables were overall survival (OS) and progression-free survival (PFS), calculated using the Kaplan-Meier estimator method, and non-relapse mortality (NRM) and relapse incidence/progression of disease (RI/POD) calculated as cumulative incidences.

Results: A total of 101 (80.2%) patients developed CRS of any grade. Of those, grade 3-4 CRS occurred in 6 (5.9%). A total of 36 (28.6%) patients developed ICANS, which happened to be grade 3-4 in 16 (44.4%). For CRS, ECOG score >1 was associated with a higher incidence of CRS grade 2-4 (Odds ratio [OR] 3.16, 95% confidence interval [CI] 1.08-9.27, p = 0.036) and day 0 C-reactive protein was associated with a higher incidence of CRS grade 3-4 (OR 1.09, 95% CI 1.02-1.17, p = 0.015). Neither Log2-EASIX-PRE nor log2-EASIX-d0 were found to be associated with grade 2-4 or

3-4 CRS. The use of axicel (OR 8.59, 95% CI 2.45-30.18, p = 0.001) and Log2-EASIX-d0 (OR = 1.66, 95% CI 1.23-2.25, p = 0.001) were associated to a higher incidence of ICANS grade 2-4. The same two factors maintained their negative prognostic role also for ICANS grade 3-4. Six patients died before day +30 (refractory disease, n = 4; CRS, n = 1; ICANS, n = 1). Median follow-up among survivors was 728 (range 84-1164) days. At 2-years, OS, PFS, NRM and RI/POD were 45% (95% CI 35-54%), 36% (95% CI, 28-45%), 8% (95% CI, 3-13%) and 55% (95% CI, 36-64%), respectively.

Conclusions: In our study, no association was found between Log2-EASIX-PRE or Log2-EASIX-d0 and CRS. However, Log2-EASIX-d0 was a strong prognostic factor for ICANS underlying the endothelial involvement in such complication. This index might help guiding preemptive strategies for those individuals at higher risk for ICANS.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P077

OUTCOMES OF CAR-T CELL THERAPY FOR LARGE B CELL LYMPHOMA IN PATIENTS OF 70 YEARS AND OLDER: MULTICENTRIC REAL WORLD EXPERIENCE

Rebeca Bailen[1,2], Mi Kwon[1,2], Gloria Iacoboni[3,4], Juan Luis Reguera[5], Lucia Lopez-Corral[6], Rafael Hernani[7], Valentin Ortiz-Maldonado[8], Manuel Guerreiro[9], Ana Carolina Caballero[10], Maria Luisa Guerra Dominguez[11], Jose Maria Sanchez Pina[12], Alberto Mmussetti[13], Juan Manuel Sancho[14], Mariana Bastos-Oreiro[1,2], Eva Catala[1], Javier Delgado[5], Hugo Luzardo Henriquez[11], Jaime Sanz[9], Maria Calbacho Robles[12], Cecilia Carpio[3], Jose Maria Ribera[14], Anna Sureda[13], Javier Briones[10], Juan Carlos Hernández-Boluda[7], Nuria Martinez-Cibrian[8], Jose Luis Diez-Martin[1,15,2], Alejandro Martin[6], Pere Barba[4,3]

[1]Hospital General Universitario Gregorio Maranon, Madrid, Spain, [2]Instituto de Investigacion Sanitaria Gregorio Maranon, Madrid, Spain, [3]Hospital Vall d'Hebron, Barcelona, Spain, [4]Universidad Autonoma de Barcelona, Barcelona, Spain, [5]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [6]Hospital Clinico Universitario de Salamanca, Salamanca, Spain, [7]Hospital Clínico Universitario de Valencia, Valencia, Spain, [8]Hospital Clinic de Barcelona, Barcelona, Spain, [9]Hospital Universitario La Fe, Valencia, Spain, [10]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [11]Hospital Universitario Doctor Negrin, Gran Canaria, Spain, [12]Hospital Universitario Doce de Octubre, Madrid, Spain, [13]Hospital Duran i Reynals, Instituto Catalán de Oncología, Barcelona, Spain, [14]Hospital Universitari Germans Trias i Pujol, Instituto Catalán de Oncología, Barcelona, Spain, [15]Universidad Complutense de Madrid, Madrid, Spain

Background: Median age at diagnosis of diffuse large B cell lymphoma (DLBCL) patients is 66 years; 40% of patients are diagnosed at an age greater than 70 years. CAR-T cell therapy is approved for the treatment of relapsed/refractory DLBCL patients; however, outcomes in patients older than 70 years are poorly reported. Our aim was to report outcomes of CAR-T cell therapy in this population as compared to those obtained in younger patient in the real world setting.

Methods: A subgroup analysis of our prior real life experience report (Kwon, Iacoboni et al. Haematologica 2022) was performed. Data from consecutive patients treated in Spain with commercial CAR-T products were retrospectively collected on behalf of GETH (Spanish Group of Stem Transplantation and Cell Therapy)-GELTAMO (Spanish Group of Lymphoma and Autologous Stem Cell Transplantation). Patients included were infused between November-2018 to August-2021. Last update of the cohort was performed in December-2021. Cytokine release syndrome (CRS) and Immune effector cell-associated neurotoxicity syndrome (ICANS) were graded with the ASTCT consensus criteria. Response was assessed according to the Lugano criteria.

Results: A total of 307 patients underwent apheresis for CAR-T cell therapy as 3rd of subsequent line. Fifty-four (18%) were 70 years or older. There were no differences between groups regarding product selection, proportion of patients infused, production failure and patients receiving bridging therapy. There were more patients with HCT-CI score ≥3 and a trend of higher proportion of patients with ECOG > 2 at apheresis in the older group (31% vs. 19%, p = 0.047; 9% vs. 5%, p = 0.054); the remaining baseline characteristics including gender, histology, disease stage, status, R-IPI and bulky disease, primary refractory disease, prior lines and prior transplant did not differ.

Among the infused population (n = 261), median time from apheresis to infusion was 49 days for patients ≥70 years (n = 45) and 47 for younger patients (n = 216) (p = 0.824). Regarding toxicity, the proportion of patients developing CRS and ICANS did not differ between groups (88% vs. 80%, p = 0.132 and 31% vs. 29%, p = 0.843). Similarly, the incidence of grade 3-4 CRS and ICANS was similar (11% vs. 6.5%, p = 0.277 and 18% vs. 10%, p = 0.146). Median duration of CRS (4 and 5 days, p = 0.150), ICANS (4 and 5 days, p = 0.540) and admission length (20 days for both groups, p = 0.995) did not differ between groups. There were not significant differences in the proportion of patients admitted to ICU (24% vs. 18%, p = 0.284); however, the proportion of patients developing infection in the first 6 months after infusion showed a trend to be higher in the older group (42% vs. 29%, p = 0.099). With a median follow-up of 9.2 months, estimated 12-m PFS was similar between groups (27% vs. 34%, p = 0.303); OS showed a trend to be lower in the older group (31 vs. 50%, p = 0.059).

Conclusions: In our real-life experience, CAR-T cell therapy in patients older than 70 years showed similar efficacy and safety than that observed in younger patients. Consequently, these patients should receive CAR-T cell therapy if treatment criteria are met.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P078

CORRELATION OF CAR-T EXPANSION WITH EARLY TUMOR RESPONSE AND TOXICITY OF CD19 CAR T THERAPY AMONG CHILDREN WITH RELAPSED/REFRACTORY B-ALL

Mariia Fadeeva[1], Dmitriy Pershin[1], Alexander Popov[1], Olga Molostova[1], Elena Kulakovskaya[1], Ekaterina Malahova[1], Viktoriya Vedmedskaya[1], Arina Rahteenko[1], Yakov Muzalevskiy[1], Alexey Kazachenok[1], Larisa Shelihova[1], Michael Maschan[1]

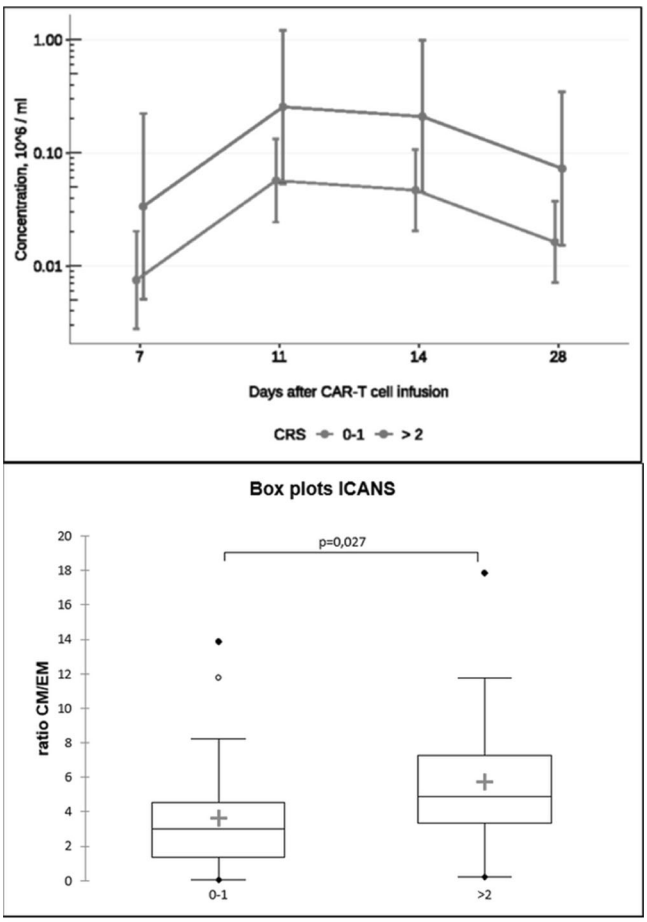
[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: Chimeric antigen receptor T-cell therapy (CAR-T therapy) is a novel immunotherapy for relapsed/refractory CD19+ lymphomas and leukemias. While clinical trials of CAR T cells have shown clear efficacy in CD19+ malignancies, life-

threating toxicities are possible. Different CAR T products are used in a variety of dosing regimens, product formulations and lymphodepletion schedules. Here we report on the correlation of early response and CAR-T toxicity with CAR-T expansion, based on a trial of CD19 CAR-T cells prepared with Prodigy platform.

Methods: From February 2018 through August 2020, we enrolled 57 pediatric patients with refractory B-cell ALL. All the patients had relapsed disease in response to their previous treatment. The purpose of the study was to assess the safety and the efficacy of CD19-CAR-T cells. Four CAR-T dose levels were used: 0.1, 0.5, 1, and 3*10^6/kg. Early response was defined as a negative status of minimal residual disease (MRD), assessed by flow cytometry on day 14 after CAR-T cells infusion. Treatment-related toxic effects were assessed according to ASTCT Consensus grading for CRS and neurologic toxicity. CAR-T cells persistence in peripheral blood (day 7, 11, 14, 28) and their functional differentiation were evaluated by flow cytometry.

Results: All the patients survived 21 days or more. One patient died on day 26 from severe CRS and multiorgan failure. 46 of 57 had early response on day 14. A status of complete remission with negative MRD was significantly associated with a higher peak CAR T-cell expansion ($p < 0.001$). Ten patients had grade 3-4 CRS and 18 had neurotoxic effects. The CAR T-cell expansion values on day 7, 11, 14 and 28 were significantly higher in patients with neurotoxic effects of grade 3-5 and with CRS of grade 2-4 than in those with toxic effects of lower grade 2 ($P = 0.042$). We found a significant association of severe neurotoxicity with predominance of central memory CD8 + CAR-T (CD197 + CD45RA-) cell phenotype ($p = 0.027$).



Disclosure: M.Maschan recieved lecturer's fee from Miltenyi Biotec

Conclusions: Our analyses show that high CAR-T expansion associated with greater toxicity. The main question is how the CD19 CAR-T cell therapy can be improved to prevent life-threating toxicities while maintaining effectiveness. One of possible way is to use split dose of CAR-T cells according to leukemia burden.

Disclosure: M.Maschan recieved lecturer's fee from Miltenyi Biotec.

4 - CAR-based Cellular Therapy – Clinical

P079

CELL AND GENE THERAPY FOR SOLID TUMORS

Patrizia Comoli[1], George Pentheroudakis[2], Annalisa Ruggeri[3], Ulrike Koehl[4], Florian Lordick[4], Jarl E. Mooyaart[5], Jorinde Hoogenboom[6], Alvaro Urbano-Ispizua[7], Solange Peters[8], Jurgen Kuball[9], Nicolaus Kroeger[10], Anna Sureda[11], Christian Chabannon[12], John Haanen[13], Paolo Pedrazzoli[1]

[1]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [2]University Hospital, Ioannina, Greece, [3]San Raffaele Hospital, Millan, Italy, [4]Universitatsklinikum, Leipzig, Germany, [5]EBMT Statistical Unit, Leipzig, Netherlands, [6]EBMT Leiden Study Unit, Leipzig, Netherlands, [7]Clinic University Hospital, Barcelona, Spain, [8]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [9]Center for Translational Immunology, UMC, Utrecht, Netherlands, [10]University Medical Center, Hamburg, Germany, [11]Institut Català d'Oncologia, Barcelona, Spain, [12]Institut Paoli-Calmettes, Marseille, France, [13]Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Among novel targeted treatment strategies, advanced therapy medicinal products (ATMPs) have gained new momentum, as encouraging results were observed in patients with hematologic malignancies who were treated with industry-manufactured gene therapies such as CAR-T Cells. So far, available information on ongoing studies in solid tumors (ST) is limited, due to the variety of programs and infrastructures involved in ATMP manufacturing and delivery.

Methods: The aim of this study was to describe the current landscape of ATMP developments for the treatment of ST from January 2018 to December 2020, by means of a web-based questionnaire circulated within the EBMT and the European Society of Medical Oncology (ESMO) centers.

Results: 149 questionnaires were returned from 53 countries, 23% of the respondents were involved in ATMP trials during the study period, and 15% indicated their intention to start a cell/gene therapy program in the future. The majority of centers involved in ATMP trials treated an approximate number of 1-5 adult patients, while a minority exclusively or partially treated children. Only 23% of the centers enrolled more than 20 pts. Among targeted tumors, melanoma and lung cancer were the most common, but GI tract tumors, gynecological cancers, bone sarcomas, head & neck and breast cancer were also targeted. Although increasingly used, T-cells gene-modified either with CAR sequence or TCR transgene represented no more than 51% of ATMPs employed in patients with ST, differently from the overwhelming prevalence of CAR gene therapy in the setting of hematological malignancies worldwide. Tumor-infiltrating lymphocytes were the most frequently used non-gene modified products. In 56% of the centers, ATMPs were combined with other treatment modalities, largely represented by immunotherapeutic or immunomodulatory

agents. Small-scale cell culture and gene engineering was largely performed in academic institutions, mainly by Point of Care manufacturing facilities. When looking at the sources of financial support, only a minority of the studies were supported by EU funding.

Conclusions: Our survey evidences that the development of ATMPs in medical oncology has not reached the same level of maturity than in hematology. Many clinical trials are still based on ATMP production by academic centers, although industry-sponsored trials are present in at least half of the centers. While waiting for breakthrough cellular products to treat solid tumors, that may have widespread distribution as observed for CD19-CART cells, the field may benefit from network models for ATMP production in academic centers.

Clinical Trial Registry: NA

Disclosure: All authors have no conflict of interest to declare.

4 - CAR-based Cellular Therapy – Clinical

P080

PREDICTIVE ROLE OF PRE-LYMPHODEPLETION ALC/AMC RATIO IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA RECEIVING CAR T-CELL THERAPY

Hannah Lust[1], Jenna Rossoff[1]

[1]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, United States

Background: The ratio of peripheral absolute lymphocyte count (ALC) to absolute monocyte count (AMC) can predict treatment response and outcomes in adult malignancies, including breast, colon, and lung cancer (Tibaldi et al, J. Can. Res. & Clin. Onc 2008; Stotz et al, Br. J. Canc 2014). Low ALC/AMC ratio prior to CD-19 chimeric antigen receptor T-cell therapy (CAR-T) for relapsed/refractory (R/R) non-Hodgkin lymphoma was associated with shorter EFS and OS (Zhang et al, JCO 2021). ALC/AMC ratio has not been assessed in pediatric patients with R/R acute lymphoblastic leukemia (ALL) receiving CAR-T.

Methods: We performed a retrospective review of 30 pediatric patients who received 32 infusions of CD19-directed CAR-T for R/R B-cell ALL at our institution between 2018 and 2022. Primary endpoints were relapse, loss of B-cell aplasia (BCA), death, and CAR-T-related toxicity in the form of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Receiver operator curve was generated using nominal logistic regression to predict toxicity and survival. Survival curves were calculated using Kaplan-Meier method.

Results: High ALC/AMC ratio ≥4.6 prior to lymphodepleting chemotherapy (LDC) (range D-25 to D-8) was associated with moderate to severe toxicity (grade ≥2) with a likelihood ratio of 1.62 (AUC 0.65, 95% CI 0.46-0.85, $P = 0.14$, Log-rank). High ALC/AMC ratio ≥4.6 prior to LDC was associated with improved OS (median survival low ratio 580 days, high ratio not reached, $P = 0.11$, Log-rank). Between patients with low and high ratio, there was no difference in 6-month relapse rate, development of ICANS, EFS, duration of BCA, or duration of remission. Though there was no significant difference in duration of BCA between the groups, duration plateaued after D + 100 in patients with a low ratio. Patients who did not achieve a response by D + 30 were excluded from analysis of duration of BCA. All patients, including those who received stem cell transplant in remission after CAR-T, were included in EFS analysis.

Table 1

Variable	All infusions (n = 32)	ALC/AMC < 4.6 (n = 15)	ALC/AMC > 4.6 (n = 17)
Age (yr), median (range)	13 (3-21)	13 (3-21)	13 (3-19)
High disease burden, n (%) (> 5% blasts on bone marrow, peripheral blasts, or CNS3 disease)	15 (47)	4 (27)	11 (65)
Relapse at any point, n (%)	11 (34)	5 (33)	6 (35)
Deaths, n (%)	10 (31)	7 (47)	3 (18)
CRS ≥2, n (%)	17 (53)	6 (40)	11 (65)
ICANS any grade, n (%)	12 (38)	5 (33)	7 (41)

Conclusions: High pre-LDC ALC/AMC ratio may be a useful tool in predicting pediatric patients with ALL who are more likely to experience moderate to severe CRS after CAR-T. Though we did not examine lymphocyte subsets, this ratio may suggest a more activated phenotype that is primed for inflammation. This may identify patients who would benefit from CRS prophylaxis. High ALC/AMC ratio was also associated with improved OS. This may reflect decreased impact of tumor-associated macrophages, derived from monocytes, in leukemic states as compared to the solid tumor microenvironment. Calculations are limited by small sample size, with 7 of 10 total deaths occurring in the low ratio group. However, the causes of death were not different between the low and high ratio groups. While the distribution of patients with high-disease burden may help explain the relationship between high ratio and increased toxicity, this does not account for the difference in survival. Given the availability of pre-LDC ALC/AMC ratio, these findings warrant further investigation in a larger population to determine validity as a clinical tool in risk-stratifying pediatric patients receiving CAR-T.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P081

CAR-T CELL DYNAMICS ARE ASSOCIATED WITH CLINICAL OUTCOME IN PATIENTS TREATED WITH ANTI-CD19 CAR-T CELL THERAPY FOR RELAPSED/REFRACTORY B-CELL MALIGNANCIES: A REAL-LIFE COHORT STUDY

Maddalena Noviello[1], Francesco De Felice[1], Gregorio Maria Bergonzi[2], Veronica Valtolina[1], Piera Angelillo[1], Raffaella Greco[1], Elisabetta Xue[1], Edoardo Campodonico[1], Maria Teresa Lupo-Stanghellini[1], Francesca Somai[2], Laura Falcone[1], Valeria Beretta[1], Elena Tassi[1], Jacopo Peccatori[1], Monica Casucci[1], Matteo Carrabba[1], Fabio Ciceri[2], Chiara Bonini[2]

[1]IRCCS Ospedale San Raffaele, Milan, Italy, [2]Università Vita-Salute San Raffaele, Milan, Italy

Background: Although anti-CD19 CAR-T cell therapy is highly effective in treating recurrent/refractory B-cell malignancies, the high rate of treatment related toxicities, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), and the significant rate of disease recurrence, still limit its overall impact. The purpose of this study was to shed light on the biological determinants associated with the short- and

long-term efficacy and toxicity of anti-CD19 CAR-T cell therapy in a real life setting.

Methods: The infused product (IP) was phenotypically characterized using a 24-color panel. In addition, fresh blood samples collected at several timepoints (+3, 7, 10, 14, 21, 30, 45, 60, 90, 180, 365 days) after the infusion were analyzed to assess the pharmacokinetics (PK) of CAR-T cells.

Results: Twenty-two patients were enrolled. Of these, 20 had aggressive B-cell lymphomas and 2 B-cell precursor acute lymphoblastic leukemia, all relapsed/refractory after previous therapies. Eight patients received axicabtagene ciloleucel (axi-cel), 4 brexucabtagene autoleucel (brexu-cel) and 10 tisagenlecleucel (tisa-cel). The Overall Response Rate at day +90, evaluable for all the patients enrolled, was 50%. Among the major toxicities, CRS was observed in 20 patients (n = 15 grade 1, n = 5 grade 2, none were grade 3 or 4), whereas ICANS was observed in 7 patients (n = 4 grade 1-2, n = 3 grade 3-4).

Despite distinct costimulatory domains and manufacturing process, no significant differences were observed between tisa-cel and axi-cel/brexu-cel products in terms of both T-cell differentiation and PK. Of note, the infusion of CAR-T cells at early stages of differentiation correlated with a more favorable clinical outcome, in terms of long-term (1 year) clinical response and toxicity. Interestingly, a higher proportion of central memory CD8+ CAR-T cells within IP was associated to a lower risk to develop severe neurotoxicity. Moreover, a high expression of the inhibitory receptor LAG-3 on infused CAR-T cells correlated with disease recurrence. The PK curves showed a significant association between higher counts of circulating CAR-T cells in the first 30 days and a favorable response to therapy evaluated for up to 1 year, threatened by a higher frequency of adverse events, mainly ICANS. Finally, a longitudinal in-depth phenotypic T-cell and myeloid characterization on frozen PBMC is ongoing in order to evaluate both CAR+ T cells and non-manipulated immune cells potentially involved in the development of adverse events and in the response to therapy.

Conclusions: Although preliminary, this study indicates the presence of biological biomarkers in the infusion product and in circulating CAR-T cells at early timepoints able to predict the clinical response, including the susceptibility to develop severe neurotoxicity.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P082

MANUFACTURING OF CAR T CELLS FROM PATIENTS WITH AUTO-IMMUNE DISEASES

Michael Aigner[1], Simon Völkl[1], Sascha Kretschmann[1], Hannah Reimann[1], Gloria Lutzny-Geier[1], Susanne Achenbach[1], Fabian Müller[1], Georg Schett[1], Andreas Mackensen[1]

[1]University Hospital Erlangen, Erlangen, Germany

Background: We have recently shown that robust manufacturing of autologous CD19 CAR T cells is possible for patients with systemic lupus erythematosus (SLE), despite a history of heavy immune-suppressive treatments. To broaden this approach, we have extended the manufacturing efforts to other auto-immune indications like systemic sclerosis (SSc) and dermatomyositis (DM), where patients could potentially also profit from CAR treatments.

Methods: We utilized aphereses of patients with SLE, SSc and DM and subsequently generated CAR T cell products under full GMP conditions in clinical scale using a closed, semi-automatic system. The cellular composition of the source materials, in-process controls and CAR T cell products were analyzed with special focus on T cells and B cell content.

Results: Despite heterogeneity of patients' aphereses, successful production of GMP grade CAR T cells in sufficient numbers for clinical application was achieved in all cases (N = SLE = 7, SSc=2, DM = 2). All CAR T products showed excellent viability and comparable, homogenous properties (cell numbers, product composition) regardless of the underlying disease, demonstrating both the T cell quality in the source materials as well as the robustness of the manufacturing process.

Conclusions: We were able to demonstrate that CAR T cell manufacturing is feasible for auto-immune patients beyond SLE and thus could offer a promising therapeutic option.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P083

LISOCABTAGENE MARALEUCEL FOR RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA: FEASIBILITY, SAFETY AND EFFICACY IN A REAL-WORLD SETTING

Andrew Portuguese[1], Emily Liang[1], Aya Albittar[2], Alexandre Hirayama[1], Brian Till[1], Ryan Cassaday[1], Ryan Lynch[1], Christina Poh[1], Filippo Milano[1], Aude Chapuis[1], Hans-Peter Kiem[1], David G. Maloney[1], Jordan Gauthier[1]

[1]Fred Hutchinson Cancer Center, Seattle, United States, [2]University of Washington Medical Center, Seattle, United States

Background: CD19-targeted chimeric antigen receptor (CAR) therapy with lisocabtagene maraleucel (liso-cel) has demonstrated impressive efficacy with manageable toxicity in patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) enrolled on the TRANSCEND clinical trial (NCT02631044; Abramson, *Lancet*, 2020). This led to the approval of liso-cel by the FDA for LBCL patients with R/R disease after 2 or more lines of prior therapy. We report outcomes of LBCL patients referred to our institution for liso-cel treatment in the non-trial setting.

Methods: We retrospectively analyzed the outcomes of all patients who arrived to the Bezos Family Immunotherapy Clinic at the Fred Hutchinson Cancer Center for planned treatment with liso-cel between 1/1/21 and 11/17/22 (intention-to-treat [ITT] group). Disease response was assessed by PET-CT imaging per Lugano 2014 criteria. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded using ASTCT criteria.

Results: Of 26 ITT patients, 25 (96.2%) underwent leukapheresis, 24 (92.3%) received lymphodepleting chemotherapy, and 23 (88.5%) received liso-cel. Six of 23 infused patients (26.1%) received an out-of-specification product on an expanded access protocol. The median time from leukapheresis to liso-cel infusion was 33 days (interquartile range [IQR] 30.5-39.5). In the ITT group, the median patient age was 67.6 years (IQR 62.2-72.3), ECOG performance status was 1 (IQR 1.0-1.0), and hematopoietic cell transplantation-specific comorbidity index (HCT-CI) was 1.5 (IQR 1.0-3.0, range 0-7). Fourteen of 26 ITT patients (53.8%) met eligibility criteria for the TRANSCEND trial. Reasons for ineligibility included: coronary artery disease (n = 3),

ECOG ≥ 2 (n = 3), significant central nervous system pathology (n = 3), recent history of prior malignancy (n = 1), and pulmonary dysfunction (n = 1). LBCL types included diffuse LBCL (DLBCL; 80.8%, n = 21), transformed DLBCL from indolent histologies (tDLBCL; 11.5%, n = 3), and high-grade B cell lymphoma (HGBCL; 7.7%, n = 2). Bulky and extranodal disease were present in 7 (26.9%) and 13 patients (50.0%), respectively.

Liso-cel was administered in the outpatient setting in 20 of 23 infused patients (87.0%). Among these, 15 (75%) required admission at a median of 4.5 days (IQR 2.0-6.0) with a median duration of hospitalization of 7.0 days (IQR 5.3-11.3). We observed CRS and ICANS after liso-cel infusion in 16 (69.6%; grade ≥3, none) and 7 patients (30.4%; grade ≥3, 13.0%), respectively. Tocilizumab and steroids were administered to 5 (21.7%) and 7 (30.4%), respectively.

Among infused patients (n = 23), the best overall response (ORR) and complete response rates were 78.3% (ITT, 69.2%) and 56.5% (ITT, 50.0%), respectively. After a median follow-up of 310 days (IQR 105-383) among infused patients, the 1-year duration of response (DOR), disease-free survival, and overall survival were 63.0%, 52.7%, and 90.3%, respectively. The median DOR was not reached. In an exploratory univariate logistic regression model, increasing vein-to-vein time was associated with a lower likelihood of response (odds ratio 0.72, 95% confidence interval 0.54 to 0.96, p = 0.02).

Conclusions: Our ITT analysis in an older patient population referred to our center for CD19 CAR-T therapy for R/R LBCL in the non-trial setting showed high rates of durable response after liso-cel with an acceptable safety profile.

Disclosure: Alexandre Hirayama: honoraria from Bristol Myers Squibb, Novartis; research funding from Juno Therapeutics, NanoString Technologies, Nektar Therapeutics.

Ryan Cassaday: honoraria from Amgen, Jazz, Kite/Gilead, Pfizer; consultancy or advisory role for Amgen; research funding from Pfizer, Amgen, Servier, Kite, and Vanda; DSMB for Pepromene Bio; independent response review committee for Autolus; and his spouse has been employed by and owned stock in Seagen. Brian Till: patent/royalties, research funding, and consulting from Mustang Bio; consulting for Proteios Technology, Inc.; research funding from BMS/Celgene.

Ryan Lynch: research funding from TG Therapeutics, Incyte, Bayer, Cyteir, Genentech, SeaGen, Rapt; consulting for Cancer Study Group, SeaGen, Foresight Diagnostics.

Christina Poh: research funding from Incyte and MorphoSys; advisory role for Acrotech.

David Maloney: Honoraria from BMS, Caribou Biosciences, Inc., Celgene, Genentech, Incyte, Juno Therapeutics, Kite, Lilly, Mustang Bio, Novartis, Umoja; research funding from Kite Pharma, Juno Therapeutics, Celgene, Legend Biotech, BMS; royalties from Juno Therapeutics/BMS; stock options from A2 Biotherapeutics, Navan Technologies; consultancy or advisory role for A2 Biotherapeutics, Navan Technologies, Chimeric Therapeutics, Genentech, BMS, ImmPACT Bio, Gilead Sciences, Interius.

4 - CAR-based Cellular Therapy – Clinical

P084

COMMERCIAL MANUFACTURING EXPERIENCE OF AXICABTAGENE CILOLEUCEL DELIVERY IN EUROPE: FROM THE FIRST 2 YEARS TO THE LATEST 2 YEARS

Didier Hallard[1], Louis van de Wiel[1], Jonathan Tsang[1], Suresh Vunnum[1], Lisa Mazzoni[1], Clare Spooner[1], Harry W. Smith[1], Jurjen Velthuis[1]

[1]Kite, a Gilead Company, Santa Monica, United States

Background: Axicabtagene ciloleucel (axi-cel), is a CD19-directed genetically modified autologous T-cell immunotherapy with a CD28 costimulatory domain that provides rapid and strong expansion and reprograms T cells to trigger target-specific cytotoxicity of cancer cells. Axi-cel was granted European marketing authorisation in August 2018 for the third-line treatment of adults with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) and primary mediastinal large B-cell lymphoma. Axi-cel is manufactured at 3 sites (El Segundo, CA, USA; Frederick, MD, USA; and Hoofddorp, Netherlands), and has a

Table. Patient characteristics (n = 26, all arrivals) and disease outcomes (n = 23, received CAR-T therapy).

Age, median (IQR)		67.6	(62.2-72.3)	**ICANS**, n (%)	0	16	69.6%
Sex, n (%)	Male	16	61.5%		Any	7	30.4%
ECOG, n (%)	0	4	15.4%		1	2	8.7%
	1	18	69.2%		2	2	8.7%
	2	3	11.5%		3	2	8.7%
	NA	1	3.8%		4	1	4.3%
HCT-CI, median (IQR)		1.5	(1.0-3.0)	**Admission**, n (%)		17	73.9%
Eligible for TRANSCEND, n (%)		14	53.8%	**Inpatient days**, median (IQR)		7.0	(2.0-6.0)
Disease, n (%)	DLBCL	21	80.8%	**ICU**, n (%)		1	4.3%
	tDLBCL	3	11.5%	**Inflammatory peak day**, median (IQR)	IL-6	6.0	(4.0-8.0)
	HGBCL	2	7.7%		CRP	7.0	(4.0-14.5)
Disease characteristics, n (%)	Bulky	7	26.9%	**Immunosuppression**, n (%)	Toci	5	21.7%
	Extranodal	13	50.0%		Steroid	7	30.4%
Out-of-spec product, n (%)		6	26.1%	**Best response**, n (%)	ORR	18	78.3%
Vein-to-vein days, median (IQR)		33	(30.5-39.5)		CR	13	56.5%
CRS, n (%)	0	7	30.4%		PR	5	21.7%
	Any	16	69.6%		PD	5	21.7%
	1	11	47.8%	**Relapse**, n (%)		8	34.8%
	2	5	21.7%	**Death**, n (%)		2	8.7%

treatment network of over 300 qualified centres worldwide, including over 180 centres in Europe. The manufacturing process has previously been described (Better M, et al. *Cell Gene Ther Insights*. 2017) as has the first 2 years' experience for patients in Europe (Van de Wiel L, et al. EBMT 2021. Poster 017). Here, we discuss commercial manufacturing experience for European patients with R/R DLBCL from the first 2 years to the latest 2 years.

Methods: This analysis includes data from 3701 European patients, including those from the European Union, Great Britain, Switzerland, and Israel, who were registered on Kite Konnect and leukapheresed during the 4-year period from 6 September 2018 to 5 September 2022 (Table). The manufacturing experience of the first 2 years was compared with the latest 2 years. If additional leukapheresis was needed, the first leukapheresis was considered for each patient and is subsequently referred to as that patient's lot. Delivery success rate is defined as the percentage of patient lots shipped (dispositioned as Qualified Person–released or Physician-released) out of the total number of patients leukapheresed in the time period (excluding those patient lots in process and patients withdrawn). Turnaround time is defined as time from date of leukapheresis to Qualified Person–release for lots using fresh material (excluding starts from re-leukapheresed lots, or for the latest 2 years' frozen peripheral blood mononuclear cells).

Results: For European patients who underwent leukapheresis between September 2020 and September 2022, median turnaround time was 19 days (range, 16-38). In total, 2398 patient lots were delivered to the treatment centres, resulting in a delivery success rate of 99%. Compared with data for European patients leukapheresed between September 2018 and September 2020, the current median turnaround time has reduced from 25 days to 19 days, respectively. An improvement in delivery success rate since the initial 2-year period (99% vs 96%) was also observed.

Conclusions: Patient outcomes are dependent on rapid and reliable manufacturing capability, as real-world experience has shown (Locke FL, et al. ASH 2022. Abstract 3345). Results from the latest 2 years' experience demonstrate a consistent and robust commercial axi-cel manufacturing capability with high delivery success rates and improved turnaround time for European patients with R/R DLBCL.

Table

	First 2 years' experience	Latest 2 years' experience (as of 30Nov22)
Date range (with final lot disposition available)	6 September 2018 – 5 September 2020	6 September 2020 – 5 September 2022
Patients registered on Kite Konnect and leukapheresed[a]	1155	2546
Median turnaround time[b]	25 days	19 days
Delivery success rate	96% (1072/1115)	99% (2398/2432)

[a] Includes patients from the European Union, Great Britain, Switzerland, and Israel. [b] Based on primary peripheral blood mononuclear cell (PBMC) process. A frozen PBMC process was used in the first 2 years' experience, and a fresh PBMC process was used in the latest 2 years' experience.

Clinical Trial Registry: N/A

Disclosure: **DH:** employment with and travel support from Kite, a Gilead Company; and stock or other ownership in Gilead. **LvdW:** employment with and travel support from Kite Pharma EU B.V.; and stock or other ownership in Gilead. **JT:** employment with Kite, a Gilead Company; stock or other ownership in Bayer, BioMarin, Bristol Myers Squibb, and Gilead; and travel support from Gilead. **SV:** employment with and travel support from Kite, a Gilead Company; and stock or other ownership in Gilead Sciences. **LM:** employment with Kite, a Gilead Company; and stock or other ownership with Baxter, Gilead, and Roche. **CS:** employee with Kite, a Gilead Company; and stock or other ownership in Gilead Sciences. **HWS:** employment with and stock or other ownership in Kite, a Gilead Company. **JV:** employment with and travel support from Kite Pharma EU B.V.; and stock or other ownership in Gilead (self) and Johnson and Johnson (spouse).

4 - CAR-based Cellular Therapy – Clinical

P085

DEVELOPING IN-HOUSE, POINT-OF-CARE MANUFACTURED ANTI-CD19 CHIMAERIC ANTIGEN RECEPTOR (CAR)-T CELLS

Nelson Chun Ngai Chan[1], Sandra Loaiza[1], Shab Uddin[1], Edward Aina[1], Lucy Cook[2,3], Renuka Palanicawandar[2], Anna Bara[4], Eduardo Olavarria[2,3], Jane Apperley[3,2], Anastasios Karadimitris[3,2]

[1]John Goldman Centre for Cellular Therapies, Imperial College Healthcare NHS Trust, London, United Kingdom, Imperial College Healthcare NHS Trust, London, United Kingdom, [3]Centre for Haematology, Imperial College London, London, United Kingdom, [4]National Institute of Health Research Imperial Clinical Research Facility, London, United Kingdom

Background: Multiple anti-CD19 CAR-T cells have been granted marketing approval and established as the standards of care for the treatment of relapsed/refractory B cell lineage haematological neoplasms. Nevertheless, the timely administration of CART-T cells remains a clinical challenge. Experience from the United Kingdom national CAR-T program revealed the median time from CAR-T approval to infusion was 57 days while 87% of patients required bridging therapy and 26% of patients were unable to receive infusion due to disease progression. In part, this is attributable to intercontinental transport of cellular products between leukapheresis facilities and central current good manufacturing practice (cGMP) compliant cell processing facilities. Here, we propose and validate an alternative model of manufacturing, where clinical grade CAR-T cells are produced at the point-of-care (POC).

Methods: Peripheral blood mononuclear cells (PBMC) were harvested on-site from three healthy volunteers as starting materials. Each harvest was processed in-house using CliniMACS® Prodigy with a 12-day manufacturing protocol which involves T cell enrichment, transduction with lentiviral vectors and cell culture to generate anti-CD19 CAR-T cells in accordance with cGMP standards in a closed system. The starting materials, and the final drug products were characterized and validated against pre-defined product release criteria.

Results: Three anti-CD19 CAR-T cell products were harvested after 12 days of production. Characteristics of the starting materials and final drug products were summarized in Table 1. In summary, all pre-defined product release criteria including transduction frequency, CAR-T cell dose, safety and purity parameters were achieved and clinical grade CAR-T cells were manufactured.

Table 1: Characterization of starting materials and final drug products in POC CAR-T manufacturing

Validation	1	2	3
Starting material			
Total viable T cells	4.20 x10^9	3.54 x10^9	2.88 x10^9
Percentage of CD3+ T cellsamong CD45+ viable events	49.8%	49.1%	49.7%
T cell subsets			
• CD4+ T cells	58.9%	54.8%	46.9%
• CD8+ T cells	35.9%	32.9%	47.4%
• CD4+CD8+ T cells	2.5%	1.7%	2.0%
• CD4+CD8+ T cells	2.7%	10.5%	3.7%
Multiplicity of infection	20	20	20
Final drug product			
Total viable T cells	3.29 x10^9	4.48 x10^9	3.92 x10^9
Percentage of CD3+ T cells among CD45+ viable events* *(Acceptance ≥ 80%)*	93.3%	97.1%	94.7%
Total CD3+ CAR-T cells	1.96 x10^9	2.5 x10^9	1.59 x10^9
Transduction frequency (%)* *(Acceptance: ≥ 10%)*	54.02	58.43	42.67
Dose (CD3+CAR+ cells/kg) * *(Acceptance: ≥ 2.0 x10^6/kg)*	2.61 x10^7	3.58 x10^7	1.98 x10^7
CAR+ T cell subsets			
• CD4+ T cells	39.8%	66.0%	22.0%
• CD8+ T cells	53.5%	28.6%	71.7%
• CD4+CD8+ T cells	6.6%	5.3%	6.2%
• CD4-CD8- T cells	0.1%	0.1%	0.1%
Vector copy number (Copies) * *(Acceptance: < 5 Copies)*	2.28	1.95	1.54
Sterility*† *(Acceptance: Negative)*	Negative	Negative	Negative
Mycoplasma* ‡ *(Acceptance: Negative)*	Negative	Negative	Negative
Endotoxin (EU/mL) * *(Acceptance: < 5 EU/mL)*	< 5	< 5	< 5

** Product release criteria*
† Detection of microbial growth after 14 days culture
‡ Detection of mycoplasma by cell culture method
EU, Endotoxin units; PBMC: Peripheral blood mononuclear cells

Conclusions: This validation provides a proof of concept for POC manufacturing of clinical grade CAR-T cells using a 12-day manufacturing protocol within the capacity of an Academic Health Science Centre. Moreover, it enables further clinical studies to evaluate the efficacy of POC manufactured CAR-T cells, the effect of cryopreservation on CAR-T cells and the impact of shortened leukapheresis to infusion lead time in the treatment of patients with advanced B cell neoplasms.

To address the clinical safety of this investigational anti-CD19 CAR-T therapy, a phase I clinical study is in the pipeline. Specific challenges were encountered which underpin the complexity for clinical academics to navigate through the regulatory approval process of Advanced Therapy Investigational Medicinal Product (ATIMP). More importantly, they highlighted the potential of an enhanced Trust and College ATIMP clinical trial approval system and the invaluable input from pharmacy and clinical services. Early engagement of regulatory authorities cannot be overemphasized.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P086

OUTCOMES OF IDECABTAGENE VICLEUCEL IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA PREVIOUSLY TREATED WITH BELANTAMAB MAFODOTIN

Megan Melody[1], Daniel Przybylski[1], Adam Robinson[1], Adam Lin[1], Leo Gordon[1], Kehinde Adekola[1], Seema Singhal[1], Jayesh Mehta[1], Jonathan Moreira[1]

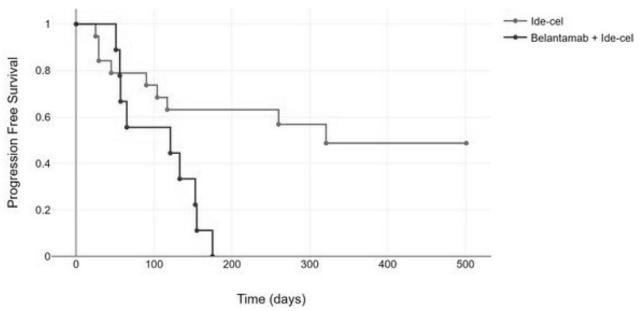
[1]Northwestern University Feinberg School of Medicine, Chicago, United States

Background: Belantamab mafodotin is an immunoconjugate comprised of an anti-BCMA monoclonal antibody conjugated to a microtubule-disrupting agent. Idecabtagene Vicleucel (Ide-cel) is a BCMA-directed chimeric antigen receptor (CAR) T-cell therapy. Both are used for management of relapsed/refractory (R/R) multiple myeloma (MM) after 4 lines of therapy. The pivotal study of Ide-cel for R/R MM excluded patients previously treated with BCMA-targeted therapy. We studied the outcome of patients treated with Ide-cel and the impact of prior exposure to Belantamab.

Methods: Utilizing the NMH Stem Cell Transplantation and Cell Therapy Program database, we identified 28 patients treated with Ide-cel between June 2021 and May 2022. Group A patients (n = 9) were treated with Belantamab prior to Ide-cel, and Group B (n = 19) had not received Belantamb prior to Ide-cel therapy. Treatment response, disease progression, and survival were assessed. Fisher's exact test of independence and two-sample t-test with equal variances were utilized to determine the statistical significance of the difference between variables.

Results: Group A had received a median of 8 (range, 5-10) prior lines of therapy and a median of 4 (1-13) dose of Belantamab. Eight out of nine patients responded to Belantamab therapy. Median time from last dose of Belantamab to Ide-cel infusion was 225 (19-484) days. Group B had received a median of 6 (3-13) prior lines of therapy. There was no difference in the incidence and severity of CRS and ICANS between the groups. Response rates in Groups A and B were 33% vs 53% (CR), 44% vs 42% (PR) and 22% vs 5% (NR/PD) respectively. Median PFS of group A patients was 127 (51-175) days versus 291 (25-501) in group B (p = 0.020). There was no difference in OS between patients in Group A vs Group B with a median OS of 277 (179-452) vs 291 (67-516), respectively (p = 0.77).

0.77).



Conclusions: Our data suggest that prior exposure to BCMA-directed therapy adversely impacts the duration of response to Ide-cel therapy but does not appear to affect overall survival. Given the limited patient numbers, it is difficult to draw definitive conclusions regarding response to therapy. With the advent of new BCMA-directed therapies such as teclistamab, further studies

are needed to evaluate the sequencing of therapy with BCMA-directed CAR-T cells.

Disclosure: None.

4 - CAR-based Cellular Therapy – Clinical

P087

DURABLE RESPONSES FOLLOWING CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN PATIENTS WITH RELAPSED/ REFRACTORY LARGE B-CELL LYMPHOMA AFTER MULTIPLE LINES OF TREATMENT: THE HELLENIC REAL-WORLD EXPERIENCE

Vasiliki Bampali[1], Panagiotis Dolgyras[2], Angelos Matheakakis[3], Alexandros Alexandropoulos[4], Ioannis Tsonis[1], Eleni Gavriilaki[2], Ifigeneia Tzannou[1], Ioannis Batsis[2], Tatiana Tzenou[1], Despina Mallouri[2], Maria Bouzani[1], Anna Vardi[2], Achilles Anagnostopoulos[2], Stavros Gigantes[1], Damianos Sotiropoulos[2], Dimitrios Karakasis[1], Ioannis Baltadakis[1], Ioanna Sakellari[2]

Evangelismos Hospital, Athens, Greece, George Papanikolaou General Hospital, Thessaloniki, Greece, University Hospital of Heraklion, Heraklion-Crete, Greece, Division of Hematology, Laikon General Hospital, Athens, Greece

Background: Chimeric Antigen Receptor (CAR)-T cells are an approved therapy for relapsed/refractory aggressive B-cell lymphomas. However, their implementation into clinical practice is associated with several challenges regarding proper selection of patients, optimization of efficacy and amelioration of toxicity. The aim of study was to analyze the experience with the application of CAR-T therapy at two national referral centers and to identify areas for improvement.

Methods: Enrolled in the study were consecutive adult patients who received CAR-T infusion as 3rd or greater line of treatment for Large B-Cell Lymphoma (LBCL) at the first two accredited centers in Greece. All patients received lymphodepleting conditioning with cyclophosphamide/fludarabine. The severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) was assessed according to the American Society for Transplantation and Cellular Therapy Consensus Grading. For toxicity management, the European Blood and Marrow Transplantation Group guidelines were followed. Responses were assessed as per Lugano 2014 classification. Progression-free (PFS) and overall survival (OS) were estimated by Kaplan-Meier analysis and were correlated with patient and disease characteristics by log-rank test.

Results: Between 01/2020-11/2022, 40 patients (female/male: 15/25) underwent CAR-T therapy at a median age of 46 (range, 20-69) years. Histologic subtypes were diffuse large B-cell lymphoma (DLBCL) in 30 (75%) patients, transformed follicular lymphoma (TFL) in 6 (15%), primary mediastinal B-cell lymphoma (PMBCL) in 3 (7.5%) and high-grade B-cell lymphoma (HGBCL) in 1 (2.5%). Patients were administered either axicabtagene ciloleucel ($n = 22$) or tisagenlecleucel ($n = 18$). The median number of prior lines of therapy was 3 (range, 2-9). Seven (17.5%) patients had received autologous stem cell transplantation. CRS occurred in 33 (82.5%) patients and was severe (grade 3) in 9 (22.5%). Ten (25%) patients developed ICANS, which was severe (grade 3) in 4 (10%). Tocilizumab was administered in 28, and steroids in 17 patients. Transfer to the Intensive Care Unit was required in 8 cases with a median duration of stay of 9.5 (range, 4-14) days. An objective response was observed in 25 (65.8%) of 38 evaluable patients, with complete response (CR) in 17 (44.7%). With a median follow-up of 15 months (range, 1.5-35), PFS and OS at 1 year were 36.1% and 58.7%, respectively. A single treatment-related death was noted 4.7 months after infusion due to infection. Elevated baseline LDH levels were associated with inferior OS ($p = 0.005$) and PFS ($p = 0.038$). In addition, 3 or more prior lines of treatment were also correlated with worse OS ($p = 0.039$) and PFS ($p = 0.029$). Treatments administered for relapse/progression after CAR-T infusion included chemoimmunotherapy, lenalidomide/rituximab, bispecific T-cell engager (glofitamab), pembrolizumab, and selinexor. Notably, 2 of 6 patients who received glofitamab, achieved complete remission and are scheduled for an allogeneic transplant.

Conclusions: CAR-T cell therapy is a viable option in relapsed/refractory LBCL, and results in durable remissions in a considerable subgroup of patients. The major limitation of the procedure is disease progression following CAR-T infusion, which is associated with pre-treatment disease burden and the number of prior lines of therapy. Therefore, moving CAR-T cells to earlier lines of treatment may enhance their therapeutic potential.

Disclosure: Ioannis Tsonis: Honoraria, Eleni Gavriilaki: Honoraria, Ifigeneia Tzannou: Honoraria, Ioannis Batsis: Honoraria, Maria Bouzani: Honoraria, Dimitrios Karakasis: Honoraria/Advisory Board, Ioannis Baltadakis: Honoraria/Advisory Board, Ioanna Sakellari: Honoraria/Advisory Board.

4 - CAR-based Cellular Therapy – Clinical

P088

BREXUCABTAGENE AUTOLEUCEL FOR ADULT PATIENTS WITH B-ACUTE LYMPHOBLASTIC LEUKEMIA - THE ITALIAN REAL LIFE FROM THE COMPASSIONATE USE PROGRAM

Federica Sorà[1,2], Eugenio Galli[1,2], Elisabetta Xue[3], Fabio Giglio[3], Francesco Restuccia[4], Francesco Autore[2], Alberto Fresa[1,2], Maria Assunta Limongiello[2], Elisabetta Metafuni[2], Idanna Innocenti[2], Sabrina Giammarco[2], Ilaria Pansini[1], Luca Laurenti[1,2], Patrizia Chiusolo[1,2], Andrea Bacigalupo[1,2], Prassede Salutari[4], Fabio Ciceri[3], Simona Sica[1,2]

[1]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Rome, Italy, [2]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [3]UO Ematologia e Trapianto Midollo Osseo, IRCCS Ospedale San Raffaele, Milan, Italy, [4]Dipartimento di Oncologia ed Ematologia, UOC Ematologia, Ospedale Civile Spirito Santo, Pescara, Italy

Background: Chimeric antigen receptor (CAR) T-cell therapy, approved in the pediatric setting for B-cell acute lymphoblastic leukemia (B-ALL), currently represents one of the most promising immunotherapeutic approaches for hematologic malignancies. In January 2021 Kite/Gilead started a Brexucabtagene autoleucel (brexu-cel) compassionate use program dedicated to adults affected by B-ALL relapsed or resistant to all lines of therapy according to national current practice.

Methods: We report the Italian experience with the compassionate use program of brexu-cel in 10 R/R B-ALL adults treated from February 2021 to October 2022. This observational study based on retrospective data collection and analysis was approved by the ethical committee.

Results: The median age was 40.5 years (range 32-65), 5 were male, 6 showed a common B phenotype, 6 were Philadelphia positive, median number of prior lines were 3 (range 2-6), and 7 patients had received a previous allogeneic HSCT.

Five out of 10 (50%) patients were refractory to the last treatment at the time of CAR-T eligibility. Patients had been exposed to blinatumomab and inotuzumab before leukapheresis in 4 (40 %) and 5 (50%) cases, two had received both. All patients had CD19+ blasts at the enrolment. ECOG performance status score was 0 in 6 patients, and 1 in the others. All patients received bridging therapy.

Lymphodepletion was administered with Flu-Cy regimen, according to ZUMA-3 trial schedule; none experienced progression during bridging therapy and all received CAR-T infusion. The median time from leukapheresis to CAR-T reinfusion was 68 days (range 37-122). Two patients (20%) experienced a manufacturing failure, and a second leukapheresis was then successfully performed.

CRS was observed in 9 patients after 7 median days (range 4-9): CRS was usually mild, with grade 1 in 8 patients (80%) and grade 2 in 1 (10%) patient. ICANS was observed in 2 (20%) patients after 7.5 median days (range 6-9), graded 1 in one patient and 2 in the other. Tocilizumab was administered in 3 patients and high-dose steroids was required in 1 patient. No patients developed consumptive coagulopathy, and macrophage activation syndrome was recorded in 1 patient. Other adverse events included transient transaminase elevation (n = 2) and deep venous thrombosis (n = 1). None required Intensive Care Unit admission.

Median follow-up was 178 days (32-424); nine out of 10 patients were in MRD negative CR at day +30, while one patient progressed before day 30. Of six patients evaluable 6 months after treatment, three were in MRD negative CR, two had progressed and received salvage therapy with blinatumomab, and one had positive MRD with persistent morphological CR, received preemptive TKI and subsequent allo-HSCT. At last FU, one patient deceased due to relapse.

Conclusions: In our series of 10 infused heavily pretreated adult B-ALL patients, brexu-cel was well tolerated and effective.

The incidence of CRS, ICANS, and other toxicities was very low. ORR at day+30 after infusion is very promising, despite a longer follow-up and further study are necessary to confirm these data.

Disclosure:

4 - CAR-based Cellular Therapy – Clinical

P089

VIRAL REACTIVATION AFTER CAR-T CELL THERAPY: ACTIVE SURVEILLANCE, PROPHYLAXIS AND TREATMENT STRATEGIES

ELISABETTA XUE[1], Edoardo Campodonico[1], Maria Teresa Lupo Stanghellini[1], Chiara Oltolini[1], Piera Angelillo[1], Elisa Diral[1], Francesca Farina[1], Daniela Clerici[1], Consuelo Corti[1], Jacopo Peccatori[1], Fabio Ciceri[1], Matteo Giovanni Carrabba[1], Raffaella Greco[1]

[1]*San Raffaele Hospital, Milan, Italy*

Background: CD19-targeted chimeric antigen receptor (CAR)-T cell therapy provides a valid treatment option for B-cell haematological malignancies, with substantial disease remission rate. However, CAR-T cells on-target effects can determine B-cell aplasia and hypogammaglobulinemia which expose patients to prolonged infectious risk.

Methods: We retrospectively collected data on viral infections and immune-reconstitution in patients treated with CD19 CAR-T cell therapy. Fludarabine-cyclophosphamide based lymphodepletion was given to all patients. Routine viral PCR monitoring on peripheral blood after CAR-T cell therapy included CMV, HSV6 and EBV. Patients received prophylactic acyclovir. Starting on May 2022, all patients received antii-SarsCov2 prophylaxis with tixagevimab/cilgavimab. Lymphocyte counts were monitored on +30, +90 and +180 days. Patients with a minimum of 3 months of follow-up were analysed; data were censored at disease relapse.

Results: Twenty-eight CAR-T cell recipients treated between December 2019 and July 2022 were analysed (**Table1**). Median follow-up was 362 days (range 91-1005). Twenty-one and three patients achieved complete and partial response, respectively; of these, ten eventually relapsed after a median of 124 days (range 74-466). Four never responded.

Median CD4 values at 1 months were 196/mcl (range 21-1127), at 3 months were 215/mcl (range 11-481), at 6 months were 284/mcl (range 9-535). Median CD8 values at 1 months were 365/mcl (range 81-1047), at 3 months were 447/mcl (range 14-1518), at 6 months were 587/mcl (range 62-1418). Median NK values at 1 months were 95 (range 6-462), at 3 months were 91 (range 36-152), at 6 months were 85 (range 29-394). B-cell aplasia was still present at 6 months in more than 50% of evaluable cases.

CMV, EBV and HSV6 reactivations occurred in 8, 2 and 1 patient, respectively. CMV reactivated after a median of 26 days (range 10-167); in five cases the viremia spontaneously resolved, whereas in three the reactivation was clinically significant and occurred within the first month; one developed CMV-related pneumoniae and one developed concomitant hepatitis. EBV and HSV6 reactivation were non-clinically significant and spontaneously resolved. None had VZV reactivation.

Nine patients developed Covid-19 after a median of 15 months (range 2-32); six had received post-CAR-T vaccination, one had received tixagevimab/cilgavimab prophylaxis. Seven had minor respiratory symptoms: of these, three received nirmatrelvir/ritonavir and one sotrovimab. Two developed Covid-19-related pneumoniae at 32 and 17 months after CAR-T, respectively; both were Covid-19 vaccinated and in disease remission; one received nirmatrelvir/ritonavir, the other received remdesivir plus sotrovimab, with clinical resolution. One patient had persistent viral shedding. Both had B-cell aplasia and CD4 < 200/mcl at the time of infection.

Patients characteristics N = 28	
Primary Disease	DLBCL n = 15, PMBCL n = 2, HG BCL n = 2, MCL n = 4, ALL n = 5
Prior treatment lines	2 lines n = 8, 3 lines or more n = 20
Prior transplant	Auto n = 8, Allo n = 5, None n = 16
Disease status at CAR T	PD n = 17, CR/PR n = 9, SD n = 2
CAR T Product	Axi-Cel n = 6, Tisa-Cel n = 15, Brexu-Cel n = 7
Cytokine release syndrome	Grade 1-2 n = 23 Grade 3 or more – none
Neurotoxicity	Grade 1-2 n = 3 Grade 3 or more n = 3

Conclusions: Despite not frequent, clinically significant viral reactivations can occur after CAR-T cell therapy, confirming the importance of active monitoring of herpes-viruses reactivation including CMV and EBV within the first six months after treatment. Role of additional viruses like HHV-6 needs further investigation in this setting. Covid-19 can have severe presentations also long-time after CAR-T administration; several studies suggested CAR-T recipients had an attenuated immune response to SARS-CoV-2 vaccination compared with healthy individuals. In this setting, the risk of severe Covid-19 presentation can be minimized by prophylaxis strategies and early treatment.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P090

OUTCOMES WITH AXICABTAGENE CILOLEUCEL IN RELAPSE/ REFRACTORY FOLLICULAR LYMPHOMA: PILOT STUDY OF A NOVEL COMPOSITE ENDPOINT OF TOXICITY AND PROGRESSION-FREE SURVIVAL

Razan Mohty[1], Julio Chavez[1], Sameh Gaballa[1], Sepideh Mokhtari[1], Rawan Faramand[1], Hayder Saeed[1], Christina Bachmeier[1], Bijal Shah[1], Taiga Nishihori[1], Frederick Locke[1], Michael Jain[1], Aleksandr Lazaryan[1]

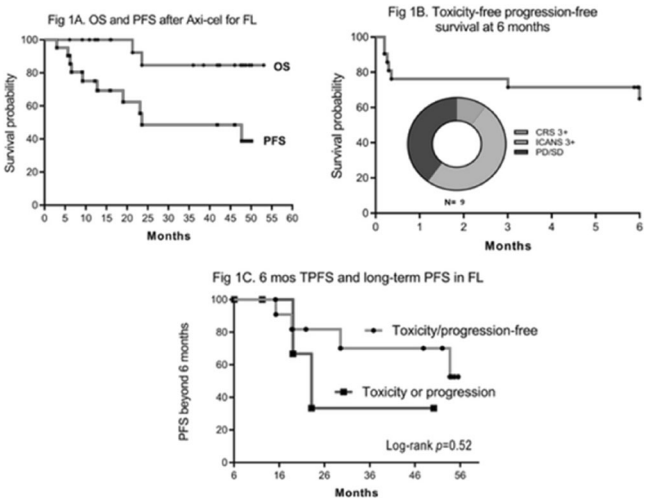
[1]H. Lee Moffitt Cancer Center, Tampa, United States

Background: Axicabtagene Ciloleucel (axi-cel) is an FDA approved anti-CD19 chimeric antigen receptor T cell (CAR T) therapy for relapsed/refractory (R/R) follicular lymphoma (FL) after 2 or more lines of therapy. This approval was based on the results of ZUMA-5 trial (Neelapu et al. ASH 2022) showing high overall response rate (ORR, 94%), complete remission (CR, 79%), and prolonged progression free survival (median PFS = 40.2 months; 3-years PFS = 54.4%).

Methods: In this single-center retrospective study, we examined the outcomes (safety, responses, and survival) following axi-cel for R/R FL and focused on a novel composite endpoint of toxicity and progression-free survival (TPFS) defined as absence of severe (Grade 3+) cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), lymphoma progression/no response, and non-relapse mortality within 6 months after CAR T cell infusion. Both CRS and ICANS were graded according to ASTCT Consensus grading.

Results: A total of 21 consecutive patients (June 2018-Dec 2021) were included in this study. Baseline patient characteristics are summarized in Table 1 and divided in 2 groups: 1) patients with TPFS at 6-months (N = 12, 57%); 2) patients with toxicity and/or progression at 6 months (N = 9, 43%). The median age was 61 years. Most patients had high-risk disease with 62% (N = 13) of the patients having FL international prognostic index (FLIPI) > 2 and 76% (N = 16) had POD24. With a median follow-up of 36 months for the entire population, 2-year overall survival (OS) and PFS were 84.6% and 48.5%, respectively (Fig 1A). At 6 months, the ORR and CR rates were 81% and 76%, respectively. The best ORR and CR rates were 95% and the median duration of response was 15.9 months. Any grade and severe CRS occurred in 18 (85.7%) and 1 (4.8%) patients, respectively. Any grade and severe ICANS occurred in 14 (66.7%) and 5 (23.8%) patients, respectively. The 6-months TPFS was 57% (Fig 1B). Of patients with 6 months toxicity and/or progression, 1 had severe CRS and progressive disease, 5 had severe ICANS, and 3 had progressive or stable disease (Fig 1B). There was no non-relapse mortality within 6 months. In the landmark analysis of long-term PFS, 6 months TPFS did not appear to have prognostic significance in this pilot analysis albeit limited by number of survival endpoints (only 2 deaths and 9 progression events) ($p = 0.52$, Fig 1C).

	All patients N = 21	Toxicity/ Progression-free at 6 months N = 12	Toxicity and/or progression at 6 months N = 9
Age, median (range)	61 (42-79)	61 (42-79)	61 (49-79)
Male, N (%)	12 (57%)	5 (42%)	5 (56%)
Histologic grade			
Grade 1-2	17 (81%)	9 (75%)	8 (89%)
Grade 3a	4 (19%)	3 (25%)	1 (11%)
Follicular Lymphoma International Prognostic Index			
Low risk (0-1)	2 (10%)	0	2 (22%)
Intermediate Risk (2)	6 (29%)	4 (33%)	2 (22%)
High Risk (≥3)	13 (62%)	8 (67%)	5 (56%)
Bulky disease (≥10 cm)	2 (10%)	1 (8%)	1 (11%)
Previous lines of therapy, median (range)	4 (2-9)	4 (2-6)	4 (2-9)
≥3 lines of therapy	15 (71%)	8 (67%)	7 (78%)
Previous Pi3K inhibitor	7 (33%)	5 (42%)	2 (22%)
Previous bendamustin	12 (57%)	6 (50%)	6 (67%)
Previous lenalidomide	7 (33%)	4 (33%)	3 (33%)
Previous autologous stem cell transplantation	2 (10%)	0	2 (22%)
Refractory to last line of therapy at time of CAR T	14 (67%)	9 (75%)	5 (56%)
POD24 from first anti-CD20 therapy	16 (76%)	8 (67%)	8 (89%)



Conclusions: Our safety and efficacy outcomes with axi-cel in R/R FL were largely aligned with the results of the pivotal ZUMA-5 trial. We analyzed a novel composite end point, TPFS, which reflects the major complications of CAR T therapy. Using this new end point, 57% of axi-cel recipients with R/R FL survived at 6 months without experiencing a TPFS-defining event. Since each TPFS component is clinically meaningful, this endpoint may represent an ideal recovery outcome after CAR T therapy as it measures initial success without progression, major morbidity or

mortality. Thus, TPFS can serve as a uniform safety and efficacy endpoint for comparing different CAR T products in future larger studies among patients with R/R FL.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P091

CYTOKINE-BASED MODELS FOR EFFICIENT DIFFERENTIATION OF INFECTION AND CYTOKINE RELEASE SYNDROME IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

Linqin Wang[1,2], Yuqi Lv[1,2], Linghui Zhou[1,2], Shenghao Wu[3], Yuanyuan Zhu[1,3], Shan Fu[1,2], Shuyi Ding[1], Ruimin Hong[1,2], Mingming Zhang[1,2], Hanjing Yu[4], Alex H. Chang[5], Guoqing Wei[1,2], Yongxian Hu[1,2], He Huang[1,2]

[1]The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, [2]Zhejiang University Medical Center, Hangzhou, China, [3]Wenzhou Central Hospital, Dingli Clinical College of Wenzhou Medical University, Wenzhou, China, [4]Hangzhou Medical College, Hangzhou, China, [5]Shanghai YaKe Biotechnology Ltd., Shanghai, China

Background: Although the promising efficacy of chimeric antigen receptor (CAR)-T cell therapy has been demonstrated widely in clinical trials, the complexity and severity of toxicities largely hampered the widespread clinical application. Cytokine release syndrome (CRS) is the most common toxicity after CAR-T cell infusion, characterized by fever and various symptoms of multiple organ involvements. Nonetheless, these profiles have substantial overlaps with infection. Worse still, routine blood culture and radiological examinations show limited efficiency in quick diagnosis, which would influence the accurate clinical intervention. Therefore, it's necessary to build an efficient and feasible diagnosis model.

Methods: This study included 95 patients with relapsed or refractory B cell hematologic malignancies who developed CRS-related fever after CAR-T cell infusion (ChiCTR1800017404, ChiCTR-ORN-16008948, ChiCTR1800017402, ChiCTR1800015575), as well as 80 patients who suffered from infective fever in our center between January, 2017 and June, 2022. After fully informed consent, blood were collected from patients during the episode of fever (> 38°C).

To build the clinical model, patients were chronologically divided into training cohort (n = 130) and external validation cohort (n = 45) approximately at the proportion of 3:1. In training cohort, forty-four serum cytokines during fever were detected and log-transformed before analysis. Two cytokine-based models were obtained via classification tree algorithm and stepwise logistic regression analysis, respectively. Based on that, two new cytokine panels containing targeted cytokines were tested in validation cohort. Sensitivity, specificity and receiver operating characteristic (ROC) curve were used to validate the accuracy of models.

Results: A feasible decision tree model was obtained based on three cytokines with moderate accuracy. It identified that high levels of IFN-β, GRO-α, and low IP-10 were predominant indicators for infection. The area under curve (AUC) reaches around 0.94, and the sensitivity is no less than 90% both in training and validation cohort.

In contrast, a seven-cytokine based predictive model demonstrated higher accuracy through stepwise regression analysis. The equation model converts the logistic regression score into a modeled probability. Patients with high cumulative score (å 0.610) would be recognized as a "infection" case. Consistent with decision tree model, this model identified high level of IP-10 as an indicator for CRS, accompanied with MIP-3b, MIP-1a and VEGF. Moreover, it indicated that high level of Eotaxin, MIP-3a and IL-4 were indicators for infection. Of note, in validation cohort, this could completely divide infective and CRS case in a accurate way.

Conclusions: Based on the profiles of serum cytokine during fever, our study developed feasible and accurate clinical models for efficiently differentiate infection from CRS, which could prompt the early diagnose and early intervention of infective cases. Moreover, the observation of wide-spectrum serum cytokines could facilitate the understanding of the mechanism of CRS or infection initiated fever.

Clinical Trial Registry: ChiCTR1800017404, ChiCTR-ORN-16008948, ChiCTR1800017402, ChiCTR1800015575

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P092

CAR-T CELL EXPANSION DYNAMICS AND THEIR CLINICAL IMPLICATIONS IN LYMPHOMA PATIENTS TREATED WITH AXICABTAGEN CILOLEUCEL AND TISAGENLECLEUCEL

Diego Carbonell[1,2], Eva Catalá[1,2], Ana Pérez-Corral[1,2], Gillen Oarbeascoa[1,2], Rebeca Bailén[1,2], Ignacio Gómez-Centurión[1,2], José Luis Díez Martín[1,2,3], Jorge Gayoso[1,2], Mi Kwon[1,2], Javier Anguita[1,2]

[1]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain, School of Medicine, Complutense University of Madrid, Madrid, Spain

Background: CD19-targeted chimeric antigen receptor (CAR)-T cell is a treatment for B-cell lymphoma patients. CAR-T cell monitoring is important to ensure a correct follow-up, being multiparametric flow cytometry (MFC) the actual gold standard technique. However, clinical implications of CAR-T dynamics are not fully elucidated. Here, we aimed to analyze potential associations between CAR-T cell levels and post-infusion complications.

Methods: Seventy-seven patients affected by B-cell lymphoma treated with axicabtagen ciloleucel (axi-cel -n = 48-) and tisagenlecleucel (tisa-cel -n = 29-) between September 2019 and July 2022 were included in the study. MFC analysis was performed on a DxFLEX cytometer (Beckman Coulter), using CD19 (20-291) protein-FITC (ACRO Biosystems). Comparison between axi-cel and tisa-cel CAR-T cell levels at different time points was performed using Mann-Whitney U test. Associations between main post-CAR-T therapy complications (cytokine release syndrome -CRS-, immune effector cell-associated neurotoxicity syndrome -ICANS-, relapse and exitus) and CAR-T cell levels (on different post-CAR-T days and at maximum peak of expansion) were analyzed by cumulative incidence using Fine-Gray test, based on cut-off points obtained from ROC curves. Statistical tests were performed with R (3.3.2 version) and Graphpad Prism (8.0.1 version).

Results: Median values of CAR-T cells at different days post-infusion of axi-cel and tisa-cel were different only on day 3 post-infusion (Mann-Whitney U test, <0.001). No significant differences were found between axi-cel and tisa-cel in terms of clinical complications, except for ICANS, which was greater in axi-cel group (CI 53% vs. 18%, p = 0.006). Respecting CAR-T complications and CAR-T cell expansion dynamics, absence of CAR-T cells at day +3 was associated with an increased risk of developing ICANS in patients treated with axi-cel (CI 73% vs. 18%, p = 0.007.

Conclusions: Based on the results obtained, levels of CAR-T cells in peripheral blood at day 3 after infusion could be a potential biomarker to predict ICANS in patients treated with axicel, a common complication in this CAR-T cell therapy. Further studies are needed to confirm these results.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P093

FROM MNC COLLECTION TO CAR T CELL INFUSION: EXPERIENCE OF A CELLULAR THERAPY CENTRE

Susana Roncon[1], Catarina Pinho[1], Sérgio Lopes[1], Filipa Bordalo[1], Sara Ferreira[1], Fátima Amado[1]

[1]Instituto Português de Oncologia do Porto, Porto, Portugal

Background: T cells engineered to express chimeric antigen receptors (CAR) are capable of inducing clinical responses in selected patients with relapsed/refractory hematologic malignancies. However, not all are eligible to receive these cell therapies, as manufacture presents unique challenges and patients aggressive diseases. Our goal was to characterize the population of patients treated with CAR T cells in our hospital and to analyze the real time of the circuit from collection to infusion.

Methods: We retrospectively studied 52 adult patients proposed for CAR T therapy (April/2019-November/2022), with statistical analysis of clinical data. All patients performed collection of mononuclear cells (MNC) by leukapheresis using Spectra Optia with a continuous method and citrate as single anticoagulant (ratio 1:12-1:14). MNC were shipped to manufacturing site and CAR T final product was received and stored at -150ºC until infusion.

Results: Nineteen female and 33 male patients with a median age of 50(18-70)years, weight of 80(47-185)kg, volemia of 5.390(3.290-12.950)ml, diagnosis of Diffuse Large B-Cell Lymphoma (n = 48), Acute Lymphoblastic Leukemia (n = 3) or Mantle Cell Lymphoma (n = 1), followed at our hospital (n = 26) or referred by another (n = 26), were proposed to therapy with Tisa-cel (n = 29), Axi-cel (n = 22) or Brexu-cel (n = 1).

During pre-leukapheresis screening, we noted that patients had previously received 2 or more (≤ 6) chemotherapy lines. Nineteen collected peripheral blood stem cells, but only 8 were transplanted with an autologous graft 28(6-118)months before; 7 with progressive disease and 3 poor mobilizers were no longer considered eligible for transplantation; 1 was transplanted 20 months after CAR T infusion. Two young adults performed allogeneic transplant (one familiar, one unrelated) 16 months before. Regarding infectious disease marker reactivity, we reported that 6 were positive for Hepatitis B and C and syphilis, but with no active infection.

Following EBMT criteria, all but one had >1.000 nucleated cells/ul [4.900(900-17.000)/ul] and all presented >200 CD3+ cells/ul in the peripheral blood [900(240-2.890)/ul] immediately before leukapheresis.

Patients processed 13.919(5.762-32.749)ml of total blood, equivalent to 2.3(1.2-7.9) of blood volemias, with a flow rate of 55(35-79)ml/min during 226 (119-783)minutes. All of them performed a one-day collection, except one that required two days, by peripheral vein (n = 28) or central venous catheter (n = 24).

Leukapheresis products released for Tisa-cel production were shipped cryopreserved (n = 28) with a median number of 12.8(5.0-76.6)x10^9 nucleated cells and 5.8(1.6-19.4)x10^9 CD3+ cells; other products (n = 23) were sent "fresh"; one is stored waiting for new clinical indication and further manufacturing.

We received and stored 42 compliant CAR T products and 3 out-of-specification (1 low viability, 1 low dose and 1 with residual beads) but with no contraindication for administration; 6 productions were cancelled due to patient death. We infused 42 and 3 are still cryopreserved (2 patients are in complete remission, 1 is waiting for infusion).

Median (minimum-maximum) time between the main steps of CAR T circuit

1st clinical evaluation → MNC collection: 8 (1-46) days

MNC collection → CAR T storage: 32 (21-177) days

CAR T storage → CAR T infusion: 11 (0-116) days

End of CAR T thawing → start of CAR T infusion: 12 (7-55*) minutes (* only one patient exceeded 30 minutes due to catheter malfunction).

Conclusions: In our department, CAR T circuit is fully implemented; traceability and chain of custody are well guaranteed. However, some improvements should be made to simplify logistical issues. In order to offer these innovative therapies to a greater number of patients in a timely manner, academic CAR T cells should also be considered.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P094

ACCESS BARRIERS FOR ANTI-CD19+ CHIMERIC ANTIGEN RECEPTOR T (CAR-T) CELL THERAPY FOR NON-HODGKIN LYMPHOMA (NHL) ACROSS A LARGE COMMUNITY TRANSPLANT AND CELLULAR THERAPY NETWORK

Minoo Battiwalla[1], Michael Tees[2], Ian W. Flinn[1], Jeremy Pantin[1], Jesus Berdeja[1], Tara Gregory[2], Michael Maris[2], Vikas Bhushan[3], Estil Vance III[3], John Mathews[3], Carlos Bachier[4], Paul J. Shaughnessy[4], Aravind Ramakrishnan[5], Shahbaz Malik[5], Shahram Mori[6], Rocky Billups[7], Betsy Blunk[7], C. Fred LeMaistre[7], Navneet Majhail[7]

[1]Sarah Cannon Transplant and Cellular Therapy Program at TriStar Centennial Medical Center, Nashville, United States, [2]Colorado Blood Cancer Institute at HealthONEs Sarah Cannon Cancer Institute at Presbyterian/St. Luke's Medical Center, Denver, United States, [3]Texas Oncology, PA, Dallas, United States, [4]Adult Blood and Marrow Transplant, Sarah Cannon Transplant and Cellular Therapy Program at Methodist Hospital, San Antonio, United States, [5]Sarah Cannon Transplant and Cellular Therapy Program at St. David's South Austin Medical Center, Austin, United States, [6]Sarah Cannon Transplant and Cellular Therapy Program at Mountain View Hospital, Las Vegas, United States, [7]Sarah Cannon Cancer Institute, Nashville, United States

Background: Anti-CD19+ CAR-T cell utilization has accelerated in the US after FDA-approval for several indications in B-cell NHL. The current generation of CAR-T therapies is complicated by high cost, a lengthy manufacturing process, and acute toxicities requiring administration at specialized centers. The Sarah Cannon Transplant and Cellular Therapy Network (SCTCTN) implemented a coordinated approach to streamline the utilization of these complex therapies. We conducted a retrospective

review to identify barriers to delivery of anti-CD19+ CAR-T cells for NHL.

Methods: All patients referred to SCTCTN for CAR-T were tracked in our prospective registry (Stafa-CT). We identified 254 patients referred to 5 SCTCTN centers who were intended recipients of FDA-approved anti-CD19+ CAR-T through 9/5/22.

Results: The 254 patients were categorized as follows:

1. 96 patients (38%) were screened but did not proceed or were not eligible because of disease progression (14), decline in clinical status (7), insurance denial (8), other treatment including CAR-T clinical trials (17), or other reasons (50).
2. 22 patients (9%) were collected but did not infuse because of disease progression (4), decline in clinical status (7), manufacturing issues (5), other treatment (2), other reasons (4).
3. 29 patients (11%) are approved and currently awaiting collection or infusion.
4. 107 patients (42%) were collected and received infusion of IECT.

For the whole cohort, median age at referral was 61 years (range 23-87), 65% were male, referral year was prior to 2019 (5%), 2019 (12%), 2020 (16%), 2021 (34%), and 2022 (33%). The diagnosis was diffuse large B-cell (68%), mantle cell (18%), follicular (10%), or other (4%) lymphoma. 59% were privately insured, 33% had Medicare, 3% had Medicaid, 1% had other (eg. VA), 4% missing. Median time from referral to consultation was 4 days. For eligible patients, the median time from referral to infusion was 143 days. Among the 107 infused, product was Axicel (56%), Brexu-cel (18%), Liso-cel (13%) and Tisa-cel (13%). Infused patients had a median age of 61 (range 23-82), 70% were male, and 60% had private insurance.

Conclusions: Despite prompt evaluation at the time of referral, 47% of patients did not ultimately receive CAR-T therapy for NHL. Disease-related factors were the primary reason, while age and financial coverage were not major contributors. Ongoing analyses will review the impact of other health determinants such as race and socioeconomic vulnerability. The complexity of the current generation of CAR-T involves authorization, apheresis, and manufacturing steps which practically result in a duration of >3 months till CAR-T infusion. Implications of our findings include the necessity for reducing manufacturing time, education efforts to support early referral, and routine planning for interim bridging strategies.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P095

ADDITION OF NIVOLUMAB TO ANTI-CD-19 CAR-T CELLS IN PATIENTS WITH STABLE/PROGRESSIVE DLBCL AT LYMPHODEPLETION – A SINGLE ARM, PHASE 2, PROSPECTIVE INTERVENTIONAL STUDY

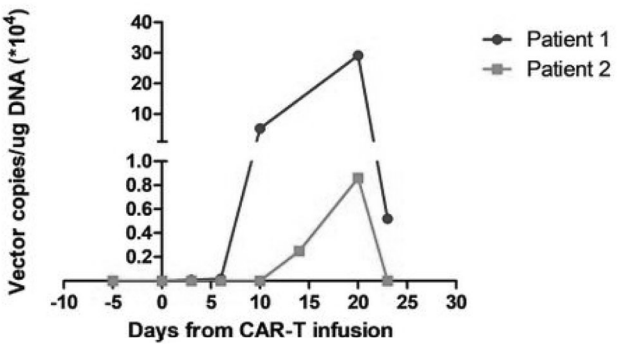
Ron Ram[1], Odelia Amit[1], Chava Perry[1], Yair Herishanu[2], Irit Avivi[1], Nadav Sarid[2], Arie Apel[3], Meir Price[4], Ariel Aviv[5], Ronit Gold[1], Chen Glait-Santar[1], Sigi Kay[1], Rivi Hertz-Levi[6], Dina Rosenberg[6], Ofrat Beyar-Katz[6]

[1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Wolfson Medical Center, Holon, Israel, [3]Shamir Medical Center, Rishon Leziyon, Israel, [4]Carmel Medical Center, Heifa, Israel, [5]Haemek Medical Center, Afula, Israel, [6]Rambam Medical Center, Heifa, Israel

Background: Progression of DLBCL is the major cause of failure of CAR-T therapy and those with stable or progressive disease (SD/PD) at the time of lymphodepletion have a dismal 6 month PFS of 20-30%. Improved in-vivo expansion of CAR-T cells may overcome this grave prognosis and may result in better PFS. Based on our recent published analyses, day +7 CAR-T concentrations analyzed by flow cytometry can predict response in this population. We thus hypothesized that the addition of nivolumab will improve clinical response by "switching on" the immune system and inducing greater CAR-T cell expansion.

Methods: Patients with SD/PD DLBCL documented by PETCT prior to lymphodepletion were recruited to this prospective phase 2 trial (NCT05385263). Patients who did not present active CRS/ICANS were assigned to receive nivolumab (3mg/kg) on day +5. Those with <100 CAR-T cells/microL on day +7 were then given an additional dose of nivolumab on day +19. Endpoints included assessment of disease response at 1 and 3 months, response duration, and overall safety of the protocol. This trial is planned to recruit 20 patients and the current analysis aimed to test feasibility.

Figure – CAR-T blood concentrations measured by PCR during the first month of treatment



Results: As of November, 2022, 8 patients were recruited and received anti-CD19 CAR-T (Axicabtagene ciloleucel, n = 5 and tisagenlecleucel, n = 3). Median age was 63 (range, 47-77) years. Of them, 4 were not eligible to receive nivolumab due to ongoing active CRS (n = 4) and ICANS (n = 1). Day +7 CAR-T concentrations were higher in patients not eligible for nivolumab infusion compared to those eligible (range, 87-724 cells/microL vs. range 1-26 cells/microL). Three patients received the full 2 doses of nivolumab, while 1 patient withdrew consent after the first dose. Six non-hematologic AEs were noted (CRS grade 1-2, n = 3 and CRS grade 3, n = 1; fever, n = 1 and folliculitis, n = 1) and 2 SAEs (neutropenia grade 4, n = 1 and pseudomonas skin infection, n = 1). Of these, 5 AEs were attributed to nivolumab. Three patients received tociluzumab and 2 patients, in addition, received systemic steroids. No patients required ICU admission. There was no difference in the median duration of severe neutropenia and severe thrombocytopenia between patients who received nivolumab and those who were excluded (p = .34 and p = .37, respectively). In 2 patients who received the 2 doses of nivolumab, serial PCR CAR-T concentrations showed a shift from the standard day +7 peak concentrations to day +21, **Figure**. Disease response, documented by PETCT at 1-month showed PR, n = 2, SD, n = 1, and PD, n = 1. Both PETCT PRs converted to CR in subsequent 3-month PETCT. PETCT re-evaluation of the 3rd patient with SD is pending.

Conclusions: Interim data from this risk-for-relapse-adopted administration of nivolumab suggest feasibility with a reasonable toxicity profile. Assessment of disease response at 1 month may be premature at this time. Recruitment for this trial is ongoing.

Clinical Trial Registry: NCT05385263

Disclosure: Ron Ram. - Honoraria and speakers bureau: Novartis, Gilead; Ofrat Beyar-Katz - Honoraria: Novartis

4 - CAR-based Cellular Therapy – Clinical

P096

COST-EFFECTIVENESS AND BUDGET IMPACT ANALYSES OF AXICABTAGENE CILOLEUCEL VS SALVAGE CHEMOTHERAPY IN ADULTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA FROM SINGAPORE'S HEALTHCARE SYSTEM PERSPECTIVE

Francesca Lorraine Wei Inng Lim[1], Tza-Kai Diong[2], Graeme Ball[3], Soon Thye Lim[4], Hian Li Esther Chan[5], Colin Phipps Diong[6], Zi Yi Lim[7], David Champion[8], Devi Raman[8], William Ying Khee Hwang[9]

[1]Singapore General Hospital, Singapore, Singapore, [2]Kite Gilead Science, Singapore, Singapore, [3]Gilead Sciences Canada Inc, Mississaga, Canada, [4]National Cancer Centre, Singapore, Singapore, [5]National University Cancer Institute, National University Health System, Singapore, Singapore, [6]Mount Elizabeth Medical Centre, Parkway Cancer Center, Singapore, Singapore, [7]Center for Clinical Haematology, Singapore, Singapore, [8]Ansea Consultants Pte Ltd, Singapore, Singapore, [9]National University Cancer Institute, Singapore, Singapore

Background: Patients with relapsed or refractory large B-cell lymphoma (R/R LBCL) have limited treatment options and a poor prognosis in Singapore. Axicabtagene ciloleucel (axi-cel) has demonstrated improved clinical outcomes in the ZUMA-1 trial but its clinical and economic value to Singapore's multi-payer healthcare system is currently unknown. Hence, in this study, our objective is to evaluate the cost-effectiveness and budget impact of axi-cel versus salvage chemotherapy (SC) for treating R/R LBCL patients who have failed at least 2 lines of systemic therapies from Singapore's public healthcare system perspective.

Methods: Over a life-time horizon, a mixture-cure partition survival model was developed to evaluate the cost-effectiveness of axi-cel vs. SC. Clinical data for axi-cel and SC were derived from ZUMA-1 (5-year follow-up) and the SCHOLAR-1 retrospective cohort study, respectively. Outcomes included quality-adjusted life-years (QALYs), health-related quality of life (HRQoL), costs and incremental cost-effectiveness ratios (ICERs). Direct costs for conditioning chemotherapy, hospitalisation, drugs and management of adverse events were included. Sensitivity analysis and scenario analyses were conducted. The financial implication of introducing axi-cel in Singapore was analysed comparing the current treatment pathway (without axi-cel) with a future scenario (with axi-cel) over 5 years.

Results: In the base case analysis over a lifetime horizon, compared with SC, axi-cel generated 4.86 incremental quality adjusted life year (QALYs) at an incremental cost of S$454,358 (US$326,876), resulting in an ICER of S$93,440 (US$67,223) per QALY gained. The projected annual incremental budget impact ranged from S$2.29 million (US$1.65 million) to S$10.91 million (US$7.85 million) during the first 5 years of introduction of axi-cel.

Conclusions: At commonly accepted ICER thresholds, results of this analysis suggest that axi-cel can be considered a cost-effective allocation of resources with manageable budget impact compared with SC for the treatment of adult patients with R/R LBCL after 2 or more lines of systemic therapy in Singapore.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P097

POSSIBLE EFFECT OF PRE CAR-T RADIOTHERAPY ON TIME-TO-RELAPSE: A MONOCENTRIC EXPERIENCE

Massimiliano Gambella[1], Anna Maria Raiola[1], Chiara Ghiggi[1], Livia Giannoni[1], Alessandra Bo[1], Salvina Barra[1], Emanuele Angelucci[1]

[1]IRCCS Ospedale Policlinico San Martino, Genova, Italy

Background: Metabolic persistence of lymphoma 1 month after CAR-T therapy (PET-1) is challenging: some patients will achieve complete remission thereafter; the majority will progress in an unpredictable time. We sought to analyse the impact of pre CAR-T radiotherapy in patients still with evidence of disease 1 month following treatment.

Methods: Twenty-five consecutive patients affected by aggressive B cell lymphoma, treated at our center from October 2020 to July 2022 with anti-CD19 CAR-T therapy (tisagenlecleucel or axicabtagene ciloleucel) were analyzed. Patients with complete metabolic response or with disease progression at PET-1 were excluded. Involved-field radiation therapy (IFRT) was delivered as part of the bridging-therapy with remission purposes. Criteria for IFRT were mediastinal and/or bulky disease. For each patient, areas of active disease were still present before CAR-T in addition to the irradiated ones. Progression-free survival was calculated from PET-1 thorugh the Kaplan Meier estimator, with progression and death considered as events; patients still in remission at last follow-up were censored; Log-rank test was employed for comparison among groups.

Results: Nine patients fulfilled the pre-specified criteria, 6 with partial remission and 3 with stable disease at PET-1; 5 patients received radiotherapy before CAR-T therapy (2/5 for mediastinal, 3/5 for non-mediastinal bulky masses). Eight of nine (89%) patients progressed following PET-1. Median progression-free survival was 127 days (95% CI: 0 - 444) for patients who received pre CAR-T radiotherapy and 33 days (95% CI: 31.04 – 34.9) for those who did not ($p = 0.036$). Among the former, one patient is still in remission and two relapsed beyond 6 months from CAR-T; among the latter, all progressed after PET-1, three of whom within 1 month. No significative differences were depicted among the two groups for variables associated with tumor burden or inflammation, as evaluated before CAR-T (Table). Relapse in patients who received radiotherapy occurred in areas other than those irradiat.

Table. Pre CAR-T variables associated with tumor burden or inflammation, comparison among groups.

Variable	No Radiation Therapy (N = 5)	Radiation Therapy (N = 5)	Significance (p)
IPI int-high / high	2/4	2/5	0.7
Bulky ≥ 10 cm	1/4	1/5	0.8
Refractory to last line	3/4	4/5	0.8
B symptoms	1/4	2/5	0.1
LDH > UNL	2/4	4/5	0.3
LDH (U/L), median	235	244	0.9
Ferritin (mcg/L), median	233	310	0.5
CRP (mg/L), median	3,3	4,9	0.5

IPI international prognostic ndex; *LDH* lactate dehydrogenase; *UNL* upper normal limit; *CRP* C-reactive protein.

Conclusions: Almost all patients who still retain metabolically active disease at PET-1 subsequently progress, representing an ultra-high-risk group. Radiotherapy before CAR-T may prolong the progression free survival and consent additional salvage treatments (i.e. bispecific antibodies, allogeneic transplant). We conclude that radiation therapy is a per-se useful strategy to limit progression in relevant areas of disease (metabolically active, bulky masses) and should be systematically integrated in the bridging-strategy. Lack of relapse in irradiated areas also suggests biological interactions with CAR-T activity that should be explored.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P098

CD19 CAR-T-CELL THERAPY IN POST HSCT RELAPSE OF MIXED PHENOTYPE ACUTE LEUKEMIA (MPAL) WITH PHENOTYPIC LINEAGE SWITCH FROM MYELOID TO LYMPHOID CLONE

Aleksandra Oszer[1], Bartłomiej Pawlik[1,2], Paweł Marschollek[3], Natalia Ćwilichowska[4], Julia Kołodrubiec[1], Justyna Jakubowska[1], Maciej Zdunek[1], Karolina Liszka[3], Joanna Trelińska[1], Szymon Janczar[1], Krzysztof Kałwak[3], Marcin Poręba[4], Wojciech Młynarski[1]

[1]Medical University of Lodz, Lodz, Poland, [2]Medical University of Warsaw, Warsaw, Poland, [3]Wroclaw Medical University, Wroclaw, Poland, [4]Wroclaw University of Science and Technology, Wroclaw, Poland

Background: This is questionable whether CD19 CAR-T-cell therapy is effective in mixed phenotype acute leukemia (MPAL) because of the clonal plasticity of the disease. Here we report a case of an 11-years-old girl with MPAL who was successfully treated with CAR-T cells.

Methods: Evaluation of the phenotypic lineage switch from myeloid blasts to lymphoid blasts was shown by flow cytometry. The percentage of CAR T cells was counted at apheresis time, 7, 28, and 60 days after CAR-T cells infusion by cytometry by time of flight (CyTOF), using Maxpar Direct Immune Profiling Assay (Standard BioTools) for deep immunophenotyping and in-house 169Tm-conjugated monoclonal anti-FMC63 scFv antibody (ACRO-BIOSYSTEMS Inc.). Additionally, quantitative polymerase chain reaction was used to enumerate integrated CAR transgene in CAR-T cells in peripheral blood at leukapheresis time, 7 and 28 days after CAR-T cells infusion. The study was reviewed and approved by the human research ethics committee of the Medical University of Lodz. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. No personal or identifiable data were included in the paper.

Results: MPAL was diagnosed based on immunophenotyping of bone marrow showing 94.7% of monocytic cells with abnormal phenotype: CD45dim+, CD34+, cytMPO+, CD7-, cytCD3-, CD3-,CD19+, CD79a-, HLA-DR+, CD117-, CD10-, CD11b+, CD13+, CD14+, IREM2-, CD15+, CD16-, CD33+, CD36-, CD64+, CD4-, CD56-, CD71-, NG2-, CD41-, CD42b-. Genetic diagnostics revealed *TCF3-ZNF384* fusion and *FLT3* (NM_004119.3):c.2505T>A (p. Asp835Glu) mutation. The patient was treated with AML-BFM 2019 protocol, subsequently underwent an allogeneic hematopoietic stem cell transplantation but relapsed within 9 months after HSCT with phenotypic lineage switch to lymphoid clone with persistent *TCF3-ZNF384* fusion and *FLT3* mutation. She started treatment according to IntreALL HR 2010 protocol, achieving cytologic remission within 5 weeks, but with remaining positive PCR-MRD < 5 x 10^{-4}. Then, after leukapheresis she was treated with sorafenib and 6-MP/MTX as a bridging therapy and was subjected to CD19-targeted CAR-T cells (tisagenlecleucel). CyTOF-based immunophenotyping allowed us to count the percentage of CAR-T cells in peripheral blood, which reached 21.14% on day 7 after CAR-T infusion and sustained concentration on day 28 and 60 after CAR-T infusion – 0.05-0.07%. The presence of CAR-T cells in peripheral blood was also confirmed using qPCR. Persistent complete molecular remission at 90 days post-CAR T cells infusion was confirmed (PCR-MRD negative with sensitivity 10^{-4}).

Conclusions: This case study shows an example of a successful CD19 CAR-T-cell therapy for relapsed mixed phenotype acute leukemia (MPAL) with a phenotypic lineage switch from myeloid clone to lymphoid. Further follow-up is needed to confirm the sustained effect of the therapy.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P099

VALIDATION OF DIGITAL PCR-BASED MONITORING OF TISAGENLECLEUCEL EXPANSION AND PERSISTENCE IN CLINICAL SAMPLES - A SINGLE CENTRE EXPERIENCE IN SINGAPORE

Gee Fung How[1], Aloysius Ho[1], Yeh Ching Linn[1], William Hwang[1], Jeffrey Quek[1], Yunxin Chen[1], Lawrence Ng[1], Melinda Tan[1], Yeow Tee Goh[1], Chandramouli Nagarajan[1], Shin Yeu Ong[1], Christopher Tham[1], Jing Jing Lee[1], Angeline Tan[1], Francesca Lim[1], Hein Than[1]

[1]Singapore General Hospital, Singapore, Singapore

Background: Chimeric antigen receptor (CAR) T-cell therapy has now been established in the treatment of relapsed/refractory B-cell acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL). Durability of clinical response after infusion of tisagenlecleucel (Tisa-cel) has been linked to expansion and persistence of CAR in the blood and marrow samples of patients. Quantification of CAR has been done via flow cytometry or real time quantitative polymerase chain reaction (qPCR) in clinical trials, but is not standardized in real-world clinical practice.

Methods: CAR quantification was performed in the peripheral blood samples collected from adult relapsed/refractory DLBCL patients treated with Tisa-cel in Singapore General Hospital from January 2021 to October 2022. Genomic DNA samples were extracted using QIAamp DNA blood mini kits (QIAGEN). Probe-based assays targeting the junction of the 4-1BB costimulatory domain and the CD3-zeta signaling region of Tisa-cel transgene were developed. The ubiquitously expressed housekeeping *CDKN1A* gene was used as a control for variability in DNA quality and quantity in each clinical sample. Digital PCR (dPCR) reactions consisting of 150-300 ng DNA as template per reaction were performed on two platforms for comparison: QIAcuity Digital PCR System (QIAGEN) and QuantStudio Absolute Q Digital PCR System (ThermoFisher Scientific). Both systems were plate-based with similar workflows. Copies of transgene and *CDKN1A* gene were determined in each reaction using the respective system software. Results of dPCR were expressed as ratio percentages of transgene copies to *CDKN1A* copies, and correlated with flow cytometric data and clinical response.

Results: Forty-six clinical samples longitudinally collected from twelve patients at different time points were available for analysis. CAR transgene percentages detected by the two dPCR platforms, the QIAcuity and Absolute Q™ showed an excellent agreement ($R^2 = 0.998$, $p < 0.01$). Both sets of dPCR results also exhibited a strong correlation with flow cytometric data ($R^2 = 0.9473$ for QIAcuity, and $R^2 = 0.9771$ for Absolute Q™). Longitudinal dPCR results from the two methods showed similar trends with an expansion of CAR-T cells peaking around day 7 post-infusion. Persistence of CAR-T cells beyond 6 months after infusion of Tisa-cel was consistently detected by dPCR in the patients with durable clinical response.

Conclusions: The results from our study show that the current dPCR protocol provides an accurate and reliable means of monitoring kinetics of CAR-T cells. The dPCR platform is potentially superior to real time qPCR which is restricted by the standard curve for its reproducibility, and also to flow cytometry which is limited by the target population size, total event count and sample quality. With further refinement and detailed analytical validation, the dPCR protocol can be established for routine clinical monitoring of CAR-T cells.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P100

BREXUCABTAGENE AUTOLEUCEL THERAPY FOR ADULT PATIENTS AFFECTED BY RELAPSED/ REFRACTORY B-ACUTE LYMPHOBLASTIC LEUKEMIA: THE ITALIAN REAL LIFE EXPERIENCE IN A CONTEXT OF THE NAMED PATIENT USE

Federica Sorà[1], Eugenio Galli[2], Elisabetta Xue[3], Francesco Restuccia[4], Ilaria Pansini[1], Sabrina Giammarco[2], Idanna Innocenti[2], Elisabetta Metafuni[2], Fabio Giglio[3], Francesco Autore[2], Alberto Fresa[2], Andrea Bacigalupo[1], Patrizia Chiusolo[1], Luca Laurenti[1], Prassede Salutari[4], Fabio Ciceri[3], Simona Sica[1]

[1]Università Cattolica del Sacro Cuore, Rome, Italy, [2]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [3]San Raffaele Hospital, Milan, Italy, [4]Ospedale Civile Spirito Santo, Pescara, Italy

Background: Relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) in adult patients is associated with poor prognosis after salvage chemotherapy. Chimeric antigen receptor (CAR) T-cell therapy, approved in the pediatric setting, currently represents one of the most promising immunotherapeutic approaches for hematologic malignancies.

Methods: Since January 2021 10 adult patient affected by B-ALL relapsed or resistant to all lines of therapy according to national current practice were treated with Kite/Gilead Brexucabtagene autoleucel (brexu-cel) in a context of a named patient use in three different italian transplant centres. This is a observational study based on retrospective data collection and analysis approved by the ethical committe.

Results: Their clinical characteristics were collected: median age was 40.5 years (range 32-65), 5 were male, 6 showed a common B phenotype, 6 were Philadelphia positive, median number of prior lines were 3 (range 2-6), and 7 patients had received a previous allogeneic HSCT.

Five out of 10 (50%) patients were refractory to the last treatment at the time of CAR-T eligibility. Patients had been exposed to blinatumomab and inotuzumab before leukoapheresis in 4 (40%) and 5 (50%) cases, two had received both. All patients had CD19+ blasts at the enrolment[EX1]. ECOG performance status score was 0 in 6 patients, and 1 in the others.

All received lymphodepleting Flu-Cy according to ZUMA-3 trial schedule; none experienced progression during bridging therapy and all received CAR-T infusion. Median time from leukapheresis to CAR-T reinfusion was 68 days (range 37-122). Two patients (20%) experienced a manufacturing failure, and a second leukapheresis was then successfully performed.

CRS was observed in 9 patients after 7 days (range 4-9): CRS was usually mild, with grade 1 in 8 patients (80%) and grade 2 in 1 (10%) patient. ICANS was observed in 2 (20%) patients after 7.5 days (range 6-9), graded 1 in one patient and 2 in the other. Tocilizumab was administered in 3 patients and high-dose steroids was required in 1 patient. None developed consumptive coagulopaty, and macrophage activation syndrome (MAS) was recorded in 1 patient. Other adverse events included transient transaminase elevation ($n = 2$) and deep venous thrombosis ($n = 1$). None required Intensive Care Unit admission.

Median follow-up [EX3] was 178 days (32-424); nine out of 10 patients were in MRD negative CR at day +30, while one patient progressed before day 30. Of six patients evaluable 6 months after treatment, three were in MRD negative CR, two had progressed and received salvage therapy with blinatumomab, and one had positive MRD with persistent morphological CR, received pre-emptive TKI and subsequent allo-HSCT. At last FU, one patient deceased due to relapse.

Conclusions: In our series of 10 infused heavily pretreated adult B-ALL patients, brexu-cel was effective and well tolerated.

The incidence of CRS, ICANS, and other toxicities was very low. ORR at day+30 after infusion is very promising, despite a longer follow-up and further study are necessary to confirm these data.

Disclosure: "Nothing to declare".

4 - CAR-based Cellular Therapy – Clinical

P101

CAR-T THERAPY IN LATIN AMERICA: REALITY AND EXPECTATIONS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION CENTERS

Fernando Barroso Duarte[1], Luciana Maria Barros Carlos[2], Nelson Hamerschlak[3], Lucila Kerbauy[3], Carmem Bonfim[4], Marco Aurelio Salvino[5], Amado Karduss[6], Alvaro Urbano Ispizua[7], Manel Juan Otero[7], Andrés Gómez De León[8], Juan Ramon Navarro Cabrera[9], Ana Lisa Basquiera[10], Juan Carlos Serrano Casas[11], Mariana Stevenazzi[12], Talyta Ellen Jesus Santos[13]

[1]Hospital Universitário Walter Cantídio, Fortaleza, Brazil, [2]Centro de Hematologia e Hemoterapia do Ceara-HEMOCE, Fortaleza, Brazil, [3]Hospital Israelita Albert Einstein, Sao Paulo, Brazil, [4]Hospital Pequeno Príncipe, Curitiba, Brazil, [5]Universidade Federal da Bahia, Salvador, Brazil, [6]Instituto de Cancerologia Las Americas-AUNA, Medellin, Colombia, [7]Hospital Clínic de Barcelona, Barcelona, Spain, [8]Universidad Autónoma de Nuevo León, Hospital Universitario Dr Jose Eleuterio González, Monterrey, Mexico, [9]Hospital Edgardo Rebagliati Marints, Jesús María, Peru, [10]Hospital Privado Universitario de Cordoba, Cordoba, Argentina, [11]Clinica Cancerologica del Norte de Santander, Norte de Santander, Colombia, [12]Integral Medical Service, Montevideo, Uruguay, [13]Laboratório Central de Análises Clínicas, Fortaleza, Brazil

Background: Recently, CAR-T cell has emerged as a necessary and well-established treatment strategy, especially for refractory haematological diseases. Latin America (LA) comprises 20 countries: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica,

Cuba, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Dominican Republic, Uruguay, and Venezuela and the estimated population is 569 million inhabitants who primarily speak Spanish and Portuguese. A very important aspect is the availability of Hematopoietic Stem Cell Transplantation (HSCT) centres in this region. Currently, there are 16 active HSCT countries and no reports of HSCTs in Nicaragua, El Salvador, Honduras, and Guatemala. In October 2021, the Latin American Bone Marrow Transplantation Group (LABMT) reported a total of 230 centres in LA, with the highest number in Brazil (120) and the lowest in Ecuador (1). In this region, some peculiarities exist, including limited access to unrelated allogeneic HSCT and the availability of paediatric HSCT centres. Due to the complexity of the CAR-T cell procedure, there is a premise that teams with experience in allogeneic HSCT are better prepared to take care of the patients. The chain of this process ranges from lymphocyte collection, cryopreservation, and infusion of CAR-T cells to clinical complications such as Cytokine-Release Syndrome (CRS) or Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), besides the need for Good Manufacture Practices experience.

Methods: We conducted an informal poll, including some groups of haematologists and transplant HSCT physicians, about possible CAR-T cell initiatives.

Results: No CAR-T cell development activities exist in Colombia, Venezuela, Peru, and Uruguay. In Mexico, there is one university initiative. In Argentina, three centres are participating in the CARTITUDE-5 study. There are ongoing industry and academic projects in Brazil. In São Paulo, the following initiatives are active: CAR T Prodigy Platform for CD19 haematological diseases, CD19 CAR-T for B cell Lymphomas, and CARTITUDE-5, all at the Albert Einstein Hospital; Hub for CAR-T production Prodigy System at the Butantan Institute; Belinda Phase III trial at the Albert Einstein Hospital and San Raphael Hospital (Bahia). In the Northeast of Brazil (Fortaleza), CAR T Prodigy Platform is in development at the Federal University of Ceara (HEMOCE/HUWC). An Agreement among the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy, LABMT, and the Clinical Hospital of Barcelona was created to improve access to CAR-T cell therapies in this region.

Conclusions: CAR-T cell indications are increasing in LA, but access is still the biggest problem. Initiatives by specialists from medical societies are fundamental for implementing this treatment in countries with limited resources. It is necessary to join efforts to serve our patients better and define specific roles for each centre within this process. These efforts are more relevant in countries with continental dimensions, such as Brazil, where HSCT activity is not evenly distributed across all regions. The emergence of rapidly growing CAR-T cell activity in restricted- resources countries will need support from international HSCT societies to ensure the best use of the limited resources available in this region.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P102

CHALLENGES IN OPTIMIZING CELL COLLECTION FOR MANUFACTURING OF CART-T CELLS IN RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA

Sanja Mazić[1], Ines Bojanić[1], Maja Pavlović[1], Koraljka Gojčeta[1], Vladimira Rimac[1], Milica Liker[1], Ernest Bilić[1], Branka Golubić Ćepulić[1]

[1]UHC Zagreb, Zagreb, Croatia

Background: Chimeric antigen receptor modified T-cells (CAR-T) offer a therapeutic possibility in pediatric relapsed acute lymphoblastic leukemia (ALL). Prerequisite to production of CAR-Ts is a collection of the target number of autologous T-cells that comply with manufacturer's requirements ($>1x10^9$ CD3+ cells, $>2x10^9$ TNC, >3% CD3+ cells for tisagenlecleucel - Kymriah®, Novartis). However, a leukapheresis procedure in active relapsed disease presents a challenge and here we describe our center's first experience with such a patient.

Methods: At our pediatric hematology department 10 years old girl was treated for pre-B ALL with translocation 4:11. She received induction phase and 2 high risk (HR) cycles according to ALL IC BFM 2009 protocol. Before HR1 cycle she was in complete remission, and before HR2 she had 1% of leukemic cells in bone marrow. Just before third HR cycle, she presented with hyperleukocitosys ($156x10^9$/L) with 71% blasts and thrombocytopenia ($43x10^9$/L). Bone marrow aspiration confirmed relapse of the disesase with 81% blasts. Femoral central line was placed before her transfer to apheresis unit. CD3+ percentage in peripheral blood was 1,01% and count $1579x10^6$/L.

Results: Leukapheresis was performed using Spectra Optia, cMNC procedure, AC:WB ratio was increased from 12:1 to 24:1. The patient weighted 44 kg with haemoglobin 92 g/L and hematocrit 0.274 L/L and a blood prime was not required. Due to the hyperleukocytosis, the procedure started with collect pump rate set at 3.0 mL/min and was lowered to 1.0 mL/min after product was sampled. During 180 minutes a total of 7360 mL of blood was processed (2,7 TBV). Product was sampled after 73 minutes (V 180 mL, CD3+ 1,57%, count $5271x10^6$/L, total CD3+ $0,95x10^9$) and 120 minutes (V 280 mL, CD3+ 1,92%, count $5907x10^6$/L, total CD3+ $1,65x10^9$) which estimated that we will be able to reach target numbers. Apheresis procedure was well tolerated and uneventful. Since it was an evening procedure going into a night shift cryopreservation, leukapheresis was completed after 180 min. Final volume of apheresis product was 296 mL, TNC $80,24x10^9$, CD3+ 2,25%, count $6060x10^6$/L, total CD3+ $1,81x10^9$ that was cryopreserved in 4 bags. The product met the target cell numbers for TNC and CD3+cells but the percentage of CD3+ was lower then required. After consultation with Novartis team, apheresis product was accepted for the manufacturing. CAR-T product passed quality control and the patient was infused with $2,6x10^6$ CAR positive viable T-cells. The CAR-Ts were successfully engrafted, but severe case of immune effector cell-associated neurotoxicity syndrome occurred.

Conclusions: Collection of target CD3+ cells is challenging in relapsed pediatric ALL patients due to need to balance the urgency of the collection, delay of chemotherapy in case of disease rapid progression and organisational issues such as central line placement and availability of trained apheresis and cryopreservation staff, all happening, very likely, outside regular working hours. Optimizing cell collection in the case when patient's peripheral blood is highly burdened with blasts is difficult since the algorithm normally used to determine the target blood volume to process is not reliable in such a setting.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

P103

LYMPHOCYTE APHERESIS IN HEALTHY DONORS FOR VALIDATING CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS PRODUCTION

Yandy Marx Castillo-Aleman[1,2], Loubna Abdel-Hadi[1], John Dearborn Philips[1], Yendry Ventura-Carmenate[1,2], May Ann

Martinez[1], Antonio Alfonso Bencomo-Hernandez[1], Samira Hasan-Sheikh[1], Carlos Agustin Villegas-Valverde[1], Rene Antonio Rivero-Jimenez[1], Nameer Abdul Raheem Al-Saadawi[1,2], Inas El-Najjar[1,2], Fatema M. Al-Kaabi[1,2]

[1]Abu Dhabi Stem Cells Center, Abu Dhabi, United Arab Emirates, [2]Yas Clinic Khalifa City Hospital, Abu Dhabi, United Arab Emirates

Background: The emerging chimeric antigen receptor T cell (CAR-T) therapies require strict validation before they can be introduced into the relevant clinical studies that support their marketing authorization. Lymphocyte apheresis provides the starting material for CAR-T cell manufacturing; therefore, this collection is critical for the success of those studies or treatments in clinical settings. Interestingly, apheresis parameters showed high variability, and clinical guidelines are currently lacking. We report the first lymphocyte aphereses undertaken in healthy donors for CAR-T cell validation studies in the United Arab Emirates performed at Abu Dhabi Stem Cells Center (ADSCC).

Methods: Apheresis procedures were performed on the Amicus Blue™ Separator System running software v6.0 (Fresenius Kabi, Germany) using peripheral venous access. A 12:1 whole blood (WB) to ACD-A anticoagulant ratio was used, with an average citrate infusion rate of 1.25 mg/kg/min, maximum WB draw rate of 55 mL/min, and 8 cycles. The mononuclear cells (MNC) offset was set at 1.5 mL, red blood cells (RBC) offset to 6.8 mL, with a mean of cycle volume of 900 mL, and plasma storage fluid of 50 mL. Lymphocyte collection was considered based on absolute lymphocyte count of peripheral blood cells that was higher than 1,500/μL in nonmobilized, healthy volunteers with normal complete blood counts, coagulation, electrolytes, metabolic, renal, and liver profiles, along with negative infectious disease screening within one week of apheresis. The collection goal was set at a minimum of 1.0 x 10^9 lymphocytes and 0.6 x 10^9 $CD3^+$ cells with a target of 3.0 x 10^9 lymphocytes and 2.0 x 10^9 $CD3^+$ cells required for the validation trials.

Results: Five healthy male donors (34–61 years old) were eligible for apheresis and signed an informed consent form for CAR-T clinical validation. The procedures were performed between September 2021 and September 2022 by a qualified apheresis team.

The five cell products were each collected in single procedures, received by the ADSCC Stem Cells Processing Laboratory, and met the requirements for manufacturing CAR-T cells. All cell products exceeded the collection target for lymphocyte and $CD3^+$ cell thresholds. **Table 1** summarizes the means of peripheral blood/collection cell counts and apheresis parameters.

Table 1. Means of peripheral blood/collection cell counts and procedural parameters (n = 5)

Parameters	Peripheral blood * (range)	Collection (range)
HGB: Hemoglobin (g/dL)	14.7 (13.5–16.6)	2.9 (2.1–3.8)
PLT: Platelets (10^9/L)	268 (200–356)	1019 (389–2125)
WBC: White blood cells (10^9/L)	7.9 (5.4–9.2)	67.8 (56.0–79.6)
NE: Neutrophils (10^9/L)	4.8 (3.0–6.0)	5.4 (1.4–12.2)
LY: Lymphocytes (10^9/L)	2.3 (1.6–3.5)	45.4 (34.9–54.6)
MO: Monocytes (10^9/L)	0.5 (0.4–0.7)	16.4 (12.2–18.4)
MNC: Mononuclear cells (10^9/L)	2.9 (2.0–4.2)	61.8 (50.9–71.6)
Procedure parameters	**Mean (range)**	
TBV: Total blood volume (mL)	5000 (4436–6823)	
WB processed (mL)	6546 (4693–8441)	
TBV processed (ratio)	1.31 (1.02–1.90)	
AC used (mL)	518 (336–655)	
Duration (minutes)	247 (109–356)	
Product volume (mL)	129 (102–161)	
LY-CE_2 (%)	45.2 (24.0–67.7)	
LY-FE (ratio)	20.9 (14.9–32.8)	
LY-CT (mL/min)	13.8 (4.2–22.8)	
LY collected (10^9)	5.9 (4.0–8.4)	
$CD3^+$ T cells collected (10^9)	4.6 (2.1–7.9)	

* Pre-apheresis counts

CE_2 Collection efficiency 2; *FE* fold enrichment; *CT* collection throughput

All donors tolerated apheresis without undergoing any serious adverse events or technical incidents. Prophylactic intravenous calcium gluconate (1,000 mg) was administered in all procedures per institutional protocol with no reports of citrate-related events.

The most common adverse events (CTCAE v.5.0) were grade 1 pain at the needle insertion site in 3/5 donors (60%) followed by grade 1 diminished inlet flow rate (lower than 30 mL/min) in 2/5 donors (40%), grade 1 chills in one volunteer (20%), and grade 1 headache in one donor (20%).

Conclusions: Despite the heterogeneity of procedures and cell products collected from healthy donors, the Amicus Blue™ Separator System showed a favorable safety profile, and the collection efficiency in a single low-volume apheresis was adequate for the CAR-T cell validation studies.

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to declare.

3 - CAR-based Cellular Therapy–Preclinical

P104

INHIBITION OF MITOCHONDRIAL ISOCITRATE DEHYDROGENASE ENHANCES CAR-T CELL IMMUNOTHERAPY BY PROMOTING ANTIOXIDANT ACTIVITY

Mi Shao[1], Xiaohui Si[1], Xinyi Teng[1], Yue Huang[1], Gang Xiao[2], He Huang[1]

[1]The First Affiliated Hospital of Zhejiang University of Medicine, Hangzhou, China, [2]Zhejiang University Medical Center, Hangzhou, China

Background: Chimeric antigen receptor (CAR)-T cells are engineered to initiate immune response to specific antigens that mark target cells. CAR-T cell therapy was approved for clinical practice for its remarkable efficacy particularly in treating B-cell malignancies. However, several obstacles are limiting the long-term efficacy and restraining the application in broader cancer types of CAR-T therapy. Besides antigen escape, poor tumor infiltration and toxicity, CAR-T cell exhaustion and short persistence are major challenges affect treatment success. In addition, nutrient-deprived

tumor microenvironment (TME) has been found to render CAR-T cell dysfunction through impairment of metabolic fitness.

Methods: we performed mitochondria-related compound library screen in CAR-T cells and CAR-T cells post killing via expansion assay and flow cytometry. Further analysis were performed to detect cell phenotypes including cell differentiation (CD62L, CD45RO), cell exhaustion (PD-1, LAG-3, TIM-3) and cell apoptosis (Annexin-V). Luciferase-based cytotoxicity assays was employed to evaluate the cytolytic ability. We used NCG mice to validate the antitumor of CAR-T in vivo. Metabolomic and transcriptomic analyses were used to reveal the effect of IDH2 inhibitors on metabolic reprogramming of CAR-T cells.

Results: Firstly, we found that the IDH2 inhibitor enasidenib could significantly increase the proportion of its naïve and central memory population without affecting the proliferation of CAR-T cells by compound screening. Further in vitro experiments demonstrated that enasidenib treatment reduced exhaustion (measured by expression of inhibitory receptors PD-1, TIM-3 and LAG-3) and terminal differentiation of CAR-T cells and increased their killing capacity, both in the co-stimulatory domain of 4-1BB and CD28. Secondly, we further demonstrated in NCG mice that enasidenib-pretreated CAR-T cells exhibited better antitumor function in vivo, as evidenced by lower tumor burden and longer survival in mice. More interestingly, enasidenib pretreatment combined with in vivo gavage administration group showed optimal outcome. What is more, by combined transcriptomic and metabolomic analysis, we found the suppression of IDH2 results in a reduction of the TCA cycle activity and dramatically rewired glucose utilization into pentose phosphate pathway (PPP) that provides anti-oxidant capacity.

Conclusions: We screened out enasidenib, a mutant and wild-type IDH2 inhibitor approved by the US FDA, from 157 mitochondria-related compound library. Enasidenib was able to enhance anti-tumor functionality of CAR-T cells via metabolic reprogramming. Enasidenib treatment during CAR-T cell culture process not only augmented long-lived memory CAR-T cell production, but also promoted survival and sustained cytotoxicity. Our studies also provide insights into the metabolic regulation of CAR-T cells. The PPP plays a pivotal role in CAR-T cell memory formation and persist function. We simultaneously developed a potential combination therapy using IDH2 inhibition and CAR-T cell immunotherapy.

Clinical Trial Registry: Not involved

Disclosure: Nothing to declare.

3 - CAR-based Cellular Therapy–Preclinical

P105

THE CHOICE OF CO-STIMULATION DETERMINES THE FATE OF CD5 TARGETING CAR-NK CELLS

May Daher[1], Rafet Basar[1], Nadima Uprety[1], Emily Ensley[1], Sunil Acharya[1], Mayra Shanley[1], Pinaki Banerjee[1], Ana Karen Nunez Cortes[1], Ye Li[1], Bin Liu[1], Enli Liu[1], Vakul Mohanty[1], Merve Dede[1], Jinzhuang Dou[1], Ken Chen[1], Richard Champlin[1], David Marin[1], Elizabeth Shpall[1], Katy Rezvani[1]

[1]UT MD Anderson Cancer Center, Houston, United States

Background: Relapsed/refractory T-cell malignancies have a particularly poor prognosis and novel therapies are direly needed. CD5 is a great candidate for adoptive cellular therapy to target T-cell malignancies since it is ubiquitously expressed on T cells with restricted expression on other hematopoietic cells. NK cells are an attractive platform for CAR engineering to target CD5 since, unlike T cells, they do not express CD5 on their surface, which eliminates the risk of fratricide. Another advantage of NK cells for CAR engineering is their safety profile; in contrast to T cells, they do not cause cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) and they are not associated with graft-versus-host disease (GVHD) in the allogeneic setting, opening the potential for a completely off-the-shelf cellular product to be used at point of care. Therefore, we sought to develop CD5 targeting CAR-NK cells for the treatment of T-cell malignancies.

Methods: Multiple studies have demonstrated that the choice of co-stimulatory domain in CAR-T cells influences their function, persistence and metabolic profile. In the field of CAR-NK cells, the first constructs tested in the clinic have incorporated CD28, a T cell specific co-stimulatory domain, borrowing from the design of CAR-T cells. There is a sparsity of data regarding the impact of co-stimulatory domains on the proliferation, transcriptomic and proteomic profile, polyfunctionality, metabolism and fitness of CAR-NK cells. In this study, we aimed to do so, by comprehensively studying the impact of co-stimulatory domains including some that are more relevant for NK cell biology, namely DNAX-activating Protein 10 (DAP10), a major adaptor protein and the exclusive signaling intermediate of NKG2D in human NK cells, DNAX-activating Protein 12 (DAP12), an important adaptor molecule that associates with multiple activating receptors (e.g. NKG2C, NKp44, activating KIRs) and NKG2D, one of the most potent NK cytotoxicity receptors which is essential for anti-tumor immunity.

Results: Our results show that CD5 CAR-NK cells with DAP10 co-stimulatory domain show enhanced cytotoxicity against CD5+ T-cell leukemia targets even after multiple tumor rechallenges in an Incucyte live-cell imaging assay. They also show augmented polyfunctionality compared to CD5 CAR-NK cells with other co-stimulatory domains in an Isoplexis single-cell secretome assay. Moreover, DAP10 co-stimulation endowed CD5 CAR-NK cells with enhanced metabolic fitness as evidenced by increased oxidative phosphorylation compared to other co-stimulatory molecules. At the epigenetic level, CD5 CAR-NK cells with DAP10 co-stimulation interrogated by sc-ATACseq show enrichment in AP-1 complex and BATF transcription factors related to memory formation and exhaustion resistance. This translates to better in vivo performance as CD5 CAR-NK cells with DAP10 co-stimulatory domain significantly improve tumor control and survival in an NSG mouse model of CD5+ T-cell leukemia (CCRF-CEM) and show evidence of recall response following tumor rechallenge.

Conclusions: In conclusion, our data show that DAP10 co-stimulation induces epigenetic reprogramming of CD5 CAR-NK cells leading to enhanced cellular fitness and memory formation ensuing better anti-tumor potential. Based on these preclinical data, a Phase I/II clinical trial evaluating the safety and efficacy of CD5 CAR-NK cells for the treatment of CD5+ malignancies is in preparation.

Clinical Trial Registry: NCT05110742
https://clinicaltrials.gov/ct2/show/NCT05110742?term=CD5+CAR+NK&draw=2&rank=1

Disclosure: M.Daher, R.Basar, P.Banerjee, E.Liu, E.Shpall, D.Marin, and K.Rezvani and The University of Texas MD Anderson Cancer Center (MDACC) have an institutional financial conflict of interest with Takeda Pharmaceutical for the licensing of CAR-NK cell technology.

3 - CAR-based Cellular Therapy – Preclinical

P106

INHIBITION OF CD38 ENZYMATIC ACTIVITY ENHANCES CAR-T CELL IMMUNOTHERAPEUTIC FUNCTIONS

Yue Huang[1], Mi Shao[1], Xinyi Teng[1], Xiaohui Si[1], Longyuan Wu[1], Yongxian Hu[1], Pengxu Qian[2], He Huang[1]

[1]Bone Marrow Transplantation Center The First Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China, [2]Institute of Hematology Zhejiang University, Hangzhou, China

Background: The impressive efficacy of CAR-T therapy for treating acute lymphoblastic leukemia, non-Hodgkin lymphoma, and multiple myeloma leads to FDA marketing approval of CAR-T products. Nonetheless, less than 50% of patients achieve sustainable disease control and others experience inadequate T cell potency to eradicate solid tumor cells. T cell exhaustion hinders the efficacy of CAR-T cells driven by excessive CAR signaling due to a high antigen burden or by constant signaling resulting from the CAR receptor aggregation in an antigen-independent manner. Omics-based analyses of in vitro exhausted T cell models and patient-derived tumor-infiltrating lymphocytes (TILs) have identified a series of genes that regulate T cell exhaustion. Genome-wide CRISPR-Cas9 knockout and knockin screening have also demonstrated potential targets to regulate CAR-T cells' durability and long-term cytotoxic function.

Methods: We pretreated CAR-T cells with small molecule CD38 inhibitors for 72h after CAR-T cell sorting. Flow cytometry was performed to detect cell phenotypes including cell differentiation (CD62L, CD45RO), cell activation (CD25, CD69), and cell exhaustion (PD-1, LAG-3, TIM-3). Luciferase-based cytotoxicity assay was employed to evaluate the cytolytic ability of CAR-T. We established the B-ALL NSG mice model with the inoculation of 1×10^6 luciferase/GFP/Nalm6 cells by tail vein injection followed by intravenous injection of 1×10^6 mCherry/CAR-T cells 5 days later. Leukemia progression was measured weekly by bioluminescence imaging.

Results: First, we re-analyzed our recently published scATAC-seq data from two patient-derived CAR-T cells at the expansion peak stage and the later declining stage. CD38 is highly expressed together with other widely defined key factors including TOX, CTL4, BATF, and IRF4 in exhausted CD8+ cells, and is positively correlated with exhaustion score. We employed two different in-vitro culture systems to mimic CAR-T exhaustion induced by tonic signaling or tumor antigens. Expression of CD38 was significantly increased both during the natural culture procedure and after two times of consecutive tumor stimulation.

Then we treated CD19-41BBζ, CD19-28ζ, and HA-28ζ CAR-T cells with small molecule CD38 inhibitors. All three inhibitors enable CAR-T cells to maintain the naïve state (Tn) and central memory state (Tcm). CD38 inhibitors also endowed CAR-T cells with lower expression of activation markers CD25 and CD69, and inhibitory receptors PD-1, TIM-3, and LAG-3. When facing an exhaustion-inducing condition (low E:T ratio at 1:10 and multiple rounds of tumor challenge), CD38-inhibited CAR-T cells demonstrated significantly marked enhancement in cytotoxicity.

In a model wherein NSG mice were inoculated with Nalm6-GFP leukemic cells and 5 days later infused with CD38-inhibited CD19-41BBζ CAR-T cells, we observed enhanced tumor control and prolonged survival. The superiorly expanded CAR-T cells were endowed with fewer exhaustion characteristics, representing diminished co-expression of multiple inhibitory receptor markers. Finally, we found that the CD38 inhibitor could encounter CAR-T cell exhaustion and improve therapeutic efficacy via CD38-cADPR-Ca2+ signaling downregulation.

Conclusions: We present evidence that CD38 may serve as a potential molecular target for regulating CAR-T cell exhaustion. CD38 inhibition encounters CART cell exhaustion and significantly boosts the efficacy of CAR-T cells against hematological malignancies in vitro and in vivo, which constitutes a promising option for CAR-T function enhancement.

Disclosure: Nothing to declare.

3 - CAR-based Cellular Therapy – Preclinical

P107

GENERATION OF EX VIVO AUTOLOGOUS HEMATOPOIETIC STEM CELL-DERIVED T LYMPHOCYTES FOR OFF-THE-SHELF CANCER IMMUNOTHERAPY

Kajornkiat Maneechai[1], Wannakorn Khopanlert[1], Panarat Noiperm[1], Phakaporn Udomsak[1], Pongtep Viboonjuntra[1], Jakrawadee Julamanee[1]

[1]Prince of Songkla University, Hat Yai, Thailand

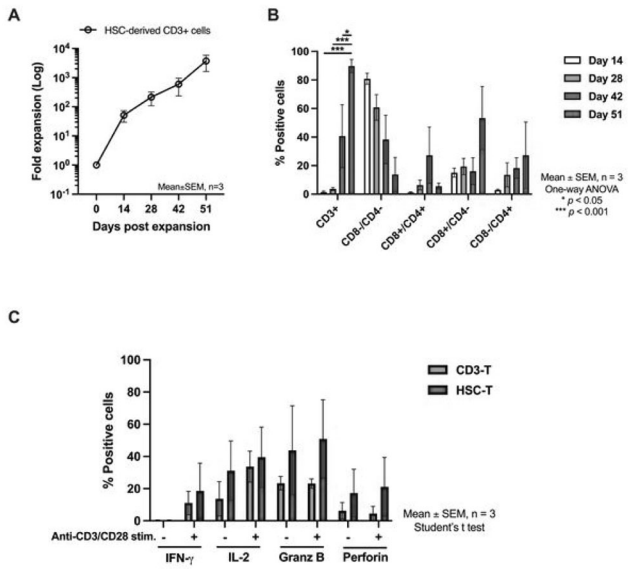
Background: Hematopoietic stem cells (HSCs) contain self-renewal and differentiative capacities. The hematopoietic stem cell transplantation is currently a standard of care to cure various malignancies. Recently, adoptive T-cell therapy, especially anti-CD19CAR T-cell which demonstrated promising results from various clinical trials, becomes an alternative curative approach for B-cell malignancies. Despite widespread enthusiasm for CAR-T cells, there are still unmet needs in the current autologous CAR-T cell therapy such as the poor T-cell function in heavily-pretreated patients which expresses exhausted phenotypes or inadequate T-cell number collection for therapeutic purposes. To overcome such limitations, we investigated the feasibility of "off-the-shelf" HSC-derived T-cells as an alternative T-cell source for CAR-T cell-based immunotherapy.

Methods: The autologous mobilized peripheral blood HSCs from myeloma or lymphoma patients were collected and isolated for $CD34^+$ and $CD3^+$ cells. $CD34^+$ cells were cultured using a StemSpan™ T-cell generation kit composed of 2 steps: lymphoid progenitor differentiation phase (day 0–14) and T-cell progenitor maturation phase (day 15–42). On day 42, progenitor T-cells were stimulated with anti-CD3/CD28 beads and cultured with IL-2 to induce the final stage of differentiation and functional maturity. HSC-derived T-cells (HSC-T) were harvested on day 51 for downstream functional assays to compare with pre-isolated $CD3^+$ cells (CD3-T). T-cell viability was assessed by trypan blue staining and the immunophenotypes were analyzed using flow cytometry at indicated time points. The CD3-derived and HSC-derived CD19CAR-T cells were also generated to assess T-cell applications.

Results: HSC-derived T-cells were successfully generated using HSCs from one myeloma and two lymphoma patients. Notably, robust HSC-T cell generation was observed for 3735 times fold expansion (Figure 1A). The purity of isolated $CD34^+$ and $CD3^+$ before expansion were 91.8% and 86.1%, respectively. After 14 days of culture, $CD34^+$ cells significantly decreased; whereas, $CD5^+$ and $CD7^+$ cells dramatically increased (65–84%). $CD3^+$ cells were significantly matured for 40% and 90% on days 42 and 51, sequentially (Figure 1B). The CD8:CD4 ratio was 2:1 and the naïve T-cell phenotype was the majority population of HSC-T (73%) compared to CD3-T cells (34%). However, TIM-3^+ cells were predominantly observed in HSC-T cells. To evaluate T-cell functions, T-cells were stimulated with anti-CD3/CD28 beads. Using intracellular cytokine staining, we observed higher IFN-γ, IL-2, granzyme B, and perforin in HSC-T compared to CD3-T cells (Figure 1C). For T-cell proliferation, we did not observe the difference among T-cell types after culture for 2 weeks. To assess cancer immunotherapy application, HSC-derived and CD3-derived CD19CAR-T cells were generated. The preliminary data demonstrated the higher cytokine production capacity of HSC-derived CD19CAR-T cells after being stimulated with CD19-K562 cells. In

terms of cytotoxicity, we observed a trend of superior specific cytolysis against primary mantle cell lymphoma and NALM-6 cells in HSC-derived compared to CD3-derived CD19CAR-T cells at all E:T ratios. In the chronic antigen stimulation assay, we did not observe the difference in T-cell proliferation, T-cell subsets, or T-cell exhaustion phenotypes among CAR-T cell types.

Figure 1. (A) HSC-derived T-cell fold expansion. (B) HSC-derived T-cell maturation. (C) Intracellular cytokine staining assay.



Conclusions: HSC-derived T-cells were successfully generated with preserved T-cell efficacy. The autologous HSC-T cells are a potential off-the-shelf cellular product for cancer immunotherapy.

Disclosure: Nothing to declare.

3 - CAR-based Cellular Therapy – Preclinical

P108

BLOCKADE OF CD95/CD95L PATHWAY ENHANCES CAR T CELL PERSISTENCE AND ANTI-TUMOR EFFICACY IN VITRO AND IN VIVO

Bailin He[1], Marina Scheller[1], Lei Wang[1], Brigitte Neuber[1], Anita Schmitt[1], Susanne Hofmann[1], Carsten Müller-Tidow[1], Michael Schmitt[1]

[1]Heidelberg University Hospital, Heidelberg, Germany

Background: CAR T cell persistence remains a major clinical challenge. Activation-induced cell death (AICD) is a programmed cell death caused by the interaction of CD95 and CD95L. Through specific blocking of the CD95-CD95L pathway, the CD95L inhibitor APG101 (asunercept®, obtained by Apogenix AG, Heidelberg) could prevent activated T cells from AICD. Therefore, we evaluated whether a blockade of the CD95L pathway through APG101 can improve CAR T cell persistence and enhance antitumor efficacy.

Methods: Human CAR T cells generated from were co-cultured with tumor cells at a 1:1 E:T ratio (round I) in the presence of APG101. Additional tumor cells were supplied to the co-culture every 24 hours. After 3 rounds (72 hr) of stimulation, tumor cells ($CD3^-CD19^+$) and CAR T cells ($CD3^+CD19^-$) were harvested for FACS analysis. To assess the antigen-induced CAR T cell proliferation, CAR T cells were preloaded with Cell Trace Violet cytosolic dye and cocultured with tumor cells for 72 hours. NSG mice were inoculated with CD19+ Nalm6 cells 0.5 x 10^5/mouse and an equal number of CD19.CART cells, followed by treatment of mice by APG101: 1mg/mouse, twice a weeks, i.v.

Results: Significant AICD of CAR T cells was observed after repeated antigenic stimulation, accompanied by an increased CD95L expression. $CD4^+$ CAR T cells were more susceptible to AICD compared with $CD8^+$ CAR T cells, although there was no difference in the expression of CD95L between $CD4^+$ and $CD8^+$ CAR T cells. Interestingly, addition of APG101 significantly inhibited CD95L expression and resulted in a lower level of CAR T cell death. Importantly, APG101 did not hamper the activation and proliferation of CAR T cells but was able to restore CAR T cell viability. The expression of PD1, TIM3 and LAG3 were also up-regulated after successive stimulation, however, their expression on CAR T cells were not influenced by APG101. After 3 days of co-culture, the number of CAR T cells were increased in the presence of APG101 (7.9 x 10^5 vs 6.0 x 10^5, $P = 0.01$) and residual tumor cells were dramatically reduced (1.7 x 10^5 vs 2.7 x 10^5, $P = 0.02$). Of note, APG101 itself showed no impact on CAR T cells or tumor cells when cultured separately. Moreover, the central memory CAR T (T_{CM}) cell subset showed higher CD95L expression after coculturing which could be inhibited by APG101. Therefore, the addition of APG101 to the coculture resulted in a significant accumulation of T_{CM} subset after APG101 treatment. In mice, addition of APG to CAR T cell treatment of Nalm6 inoculated mice resulted in a significantly better survival of the animals: all mice receiving solely CAR T cells were dead by day 32, whereas 50% of the animals obtaining additionally APG101 survived day 60 ($P < 0.01$).

Conclusions: Upregulation of CD95L after repeated antigen stimulation was reversed by APG101. CD95L blockade enhanced CAR T cell survival and promoted killing of tumor cells in vitro. Combining CAR T cell therapy with CD95L inhibitor improved CAR T cell persistence in vivo and thus enhanced the effect of CAR T cell therapy.

Disclosure: Asunercept®, obtained by Apogenix AG, Heidelberg.

3 - CAR-based Cellular Therapy – Preclinical

P109

SUPERIOR ANTI-TUMOR EFFICACY OF $CD4^+$ CAR-T CELLS IN HEMATOLOGICAL MALIGNANCIES

Qian Chen[1], Lei Wang[1], Min Lin[1], David Sedloev[1], Hao Yao[1], Marina Scheller[1], Volker Eckstein[1], Stefanie Hofmann[1], Huixiu Han[1], Yuntian Ding[1], Anna Keib[1], Genqiao Jiang[1], Dominik Hoffmann[1], Hannes Heilmann[1], Julia Unglaub[1], Anita Schmitt[1], Carsten Müller-Tidow[1], Michael Schmitt[1], Tim Sauer[1]

[1]Heidelberg University, Heidelberg, Germany

Background: Chimeric antigen receptor T-cell (CART) therapy has shown promising therapeutic efficacy in several hematological malignancies. However, current CART therapies still face major hurdles leading to primary or secondary resistance and relapse. The optimization of CART treatment requires a better understanding of the characteristics of the administered cell products, including the appropriate ratio between $CD4^+$ and $CD8^+$ T-cell subsets. In most reported trials, CART products contain a random, donor-dependent composition of $CD4^+$ and $CD8^+$ T cells, with only a few clinical trials implementing products with a defined 1:1 ratio of $CD4^+$ and $CD8^+$ T cells which were proposed to be the most beneficial composition. The aim of our study was to further

investigate the functionality of CD4 and CD8 expressing CARTs targeting different hematologic malignancies.

Methods: Healthy donor derived, activated T cells were transduced with CAR constructs targeting CD33 (CD33.CD28.41BB.zeta), CD19 (CD19.CD28.41BB.zeta) and CD70 (CD27.zeta) using a gamma retroviral vector system. Fluorescence Activated Cell Sorting (FACS) was used to purify CD4+ and CD8+ CARTs before they were mixed at various CD4/CD8 ratios and co-cultured with target antigen expressing tumor cell lines. Serial re-stimulation with tumor cells was performed every 72 hours[TS1]. Cytokine secretion was measured by flow cytometry (LEGENDplex kit) and CART proliferation using CSFE staining. For in-vivo studies, NSG mice were injected with luciferase expressing tumor cells, that could be detected by bioluminescence imaging, and were subsequently treated with CART products containing different CD4/CD8 ratios.

Results: In our serial co-culture screen, we observed an incremental anti-tumor-efficacy of all CART products with increasing CD4/CD8 for all ratios which was mainly related to an enhanced proliferative capacity of CART products with higher CD4 + T cell content. Indeed, pure $CD4^+$ CARTs exhibited a superior anti-tumor efficacy compared to a mixture of $CD4^+$ and $CD8^+$ CARTs even though the mixed product contained a higher total number of T cells suggesting that the addition of $CD8^+$ CARTs even diminished the functionality of $CD4^+$ CARTs. On the other hand, $CD4^+$ CARTs could improve the proliferation of $CD8^+$ CARTs, in particular at high CD4/CD8 ratios. We measured cytokine secretion upon antigen stimulation and found that CART products with increasing CD4/CD8 ratios secreted higher levels of Th1 and Th2 cytokines compared to products containing a higher percentage of CD8+ CARTs, namely IL-2, TNF-α, IL-4, IL-6, and IL-10. Further mechanistic studies revealed that cytokines secreted by $CD4^+$ CARTs could enhance the functionality of CD8+ CARTs whereas the coapplied CD8+ CARTs hampered the cytolytic and proliferative potential of $CD4^+$ CARTs. Using NSG xenograft models, we confirmed the superior anti-tumor efficacy of pure $CD4^+$ over mixed $CD4^+/CD8^+$ or $CD8^+$ CART products in-vivo.

Conclusions: Our data suggest that the CD4/CD8 ratio of CART products is crucial for their functionality and that $CD4^+$ containing T cell products have superior anti-tumor efficacy over $CD8^+$ CARTs. Our results warrant further exploration of pure $CD4^+$ CAR T-cell products within future clinical trials.

Disclosure: Nothing to declare.

3 - CAR-based Cellular Therapy – Preclinical

P110

EXTRACORPOREAL PHOTOPHERESIS CONSTITUTES A PROMISING STRATEGY FOR THE TREATMENT OF GVHD AFTER CAR-T CELL THERAPY

Huixiu Han[1], Lei Wang[1], Brigitte Neuber[1], Yuntian Ding[1], Min Lin[1], Hao Yao[1], Qian Chen[1], Bailin He[1,2], Sanmei Wang[1,3], Tim Sauer[1], Maria-Luisa Schubert[1], Alexander Kunz[1], Angela Hückelhoven-Krauss[1], Anna Keib[1], Christian Kleist[1], Carsten Müller-Tidow[1,4], Peter Dreger[1,4], Michael Schmitt[1,4], Anita Schmitt[1]

[1]Heidelberg University, Heidelberg, Germany, [2]Southern Medical University, Guangzhou, China, [3]Nanjing Medical University, Nanjing, China, [4]German Cancer Consortium (DKTK), Heidelberg, Germany

Background: Anti-CD19 chimeric antigen receptor transduced T (CAR-T) cell therapy has attracted much attention in the treatment of $CD19^+$ leukemia or lymphoma. Next to their potent antitumor activity, however, CAR-T cells give rise to significant side effects as well. Besides the well-known adverse events such as cytokine release syndrome (CRS) and immune-effector cell-associated neurotoxicity syndrome (ICANS), graft-versus-host disease (GvHD) also occurred in 10-30% of the patients receiving "autologous" CAR-T cells after preceding allogeneic transplantation due to the substantial amount of untransduced and alloreactive T cells.

Extracorporeal photopheresis (ECP), a cell-based photoimmunotherapy, shows very promising clinical outcomes in the treatment of GvHD and organ rejection. Since it selectively modulates alloreactive T cells without hampering anti-tumor and anti-virus effects, an interesting question arises whether ECP might constitute a new way to treat patients with GvHD after CAR-T cell therapy without having a negative influence on CAR-T cell function.

Methods: The 3rd generation CD19-specific CAR-T cells were generated using healthy donor PBMCs. To establish an in vitro ECP protocol according to ECP treatment the BIO-LINK crosslinker™ was used and for this treatment medium, cell concentration and UV-A dose were investigated.

The phenotype of CAR-T cells after ECP was evaluated by a multi-color flow cytometry. Moreover, the quantity and quality in terms of cell apoptosis, killing capacity, cytokine release, proliferation and persistence were assessed in CAR-T cells after ECP in two different models. Besides a "non-dilution model" (NDM) mimicking the situation of GvHD in the early period after CAR-T cell infusion, a "dilution model" (DM), i.e., CAR-T cells were diluted with B cell depleted auto-PBMCs, was established to imitate GvHD at a later time period.

Results: Principal components analysis based on cell components and the inhibitory marker expression showed no distinct difference between different UV-A dosages, while cell viability decreased in an UV-A dose dependent manner. Since 2 J/cm^2 is used clinically, this UVA dose is chosen for the ECP treatment protocol.

In the NDM, ECP hampered short-term cytotoxicity of CAR-T cells. The average killing efficiency decreased from 79% to 53.9%. Moreover, proinflammatory cytokines decreased significantly 24 hours after the ECP. The IL-6 decreased from 151 ± 55 to 82 ± 15 pg/mL. The IL-17A decreased from 87 ± 41 to 34 ± 20 pg/mL.

In contrast, in the DM, CAR-T cells diluted with auto-PBMCs maintained a high CAR-T cell viability after ECP, when compared to the NDM (76.4 ± 0.8 in DM and 69.6 ± 3.5 in NDM). Moreover, ECP in the DM had an immunemodulating effect by increasing cytokines as IL2 and IL10 with immunemodulating function and decreasing the proinflammatory cytokines such as IL-6 and IL-17A without negative effect on the short- and long-term cytotoxicity of CAR-T cells.

Conclusions: Our data suggest that ECP constitutes an effective promising treatment strategy for patients suffering from GvHD also in the situation after allo-HSCT and CAR-T cell transfusion, as ECP does obviously not affect the quantity and quality of CAR-T cells.

Disclosure: This study was financially supported by Mallinckrodt Pharmaceuticals through an external collaborative research grant to A.S and M.S.

3 - CAR-based Cellular Therapy – Preclinical

P111

PROTEASOMAL INHIBITION SENSITIZES AML CELLS TO CAR NK-CELL MEDIATED KILLING

David Sedloev[1], Qian Chen[1], Dominik Hoffmann[1], Anna Keib[1], Anita Schmitt[1], Michael Schmitt[1], Carsten Müller-Tidow[1], Tim Sauer[1]

[1]University Clinic Heidelberg, Heidelberg, Germany

Background: The prognosis of patients with relapsed and refractory acute myeloid leukemia (AML) remains dismal. Natural killer (NK) cell-based immunotherapy is emerging as a promising strategy for cancer treatment. However, in AML, patients' responses to activated allogeneic NK cells have been only moderate.

Proteasome inhibitors (PIs), such as Bortezomib (BTZ) and Carfilzomib (CFZ) have been shown to downregulate the expression of HLA class I molecules and increase the presentation of NKG2D ligands on tumor cells, hereby potentially enhancing the functionality of NK cells.

The goal of this study was to determine the potential of BTZ and CFZ to improve the susceptibility of AML cells to NK-cell mediated killing.

Methods: After establishing their IC50 concentration against a panel of AML cell lines, the effects of BTZ and CFZ treatment on the expression of HLA class I molecules and stress-induced proteins by AML cells were determined using multiparameter flow cytometry. Activated NK cells derived from healthy donors were retrovirally transduced with two AML-specific CARs (CD33/CD70). AML cells were treated with BTZ and CFZ either prior to or simultaneously with the addition of CAR- or non-CAR-transduced NK cells. We measured NK-cell mediated short term toxicity against PI treated target cells using a 24-hour co-culture assay as well as their long-term proliferation and killing capabilities in a serial co-culture assay.

Results: Ten of twelve cell lines measured, as well as all six primary AML samples were highly susceptible to proteasomal inhibition, with IC50 values in the low nanomolar range. Resistance to Venetoclax/Azacytidin did not confer resistance to proteasome inhibitors. BTZ and CFZ treatment at the IC50 concentration decreased HLA class I molecule expression by a median of 34% and increased NKG2D ligand and death receptor expression in the majority of tested AML cell lines. We show that these effects are mediated by different mechanisms and do not occur concurrently or peak at the same dose. Pre-treatment of AML cells with PIs significantly enhanced the anti-tumor efficacy of NK cells against AML cells in a short-term cytotoxicity assay ($p < 0.001$). Transduction of NK cells with AML-specific CARs further improved their functionality in vitro, reducing the number of surviving targets by over 80%, as compared to non-CAR transduced, but activated NK cell controls[SD3]. The combinatorial treatment of PIs and CAR-NK cells effectively eliminated AML cell lines resistant to Venetoclax/Azacitidin treatment, as well as primary AML samples. We investigated the mechanism of action of proteasomal inhibitors in AML and found that both NFkB inhibition and cFLIP downregulation as well as transcriptional upregulation of ULBPs are responsible for the enhanced tumor elimination.

Conclusions: Pre-treatment of AML cells with PIs significantly sensitizes them to NK-cell mediated killing and CAR-expression further enhances the anti-tumor efficacy of activated NK cells. AML cell lines, refractory to conventional chemotherapy treatment are still susceptible to both proteasomal inhibition and NK-mediated killing. Studies aiming to confirm these promising results in-vivo are ongoing.

Disclosure: No conflict of interest disclosed.

3 - CAR-based Cellular Therapy – Preclinical

P112

PD-1 CHECKPOINT INHIBITION IMPROVES FUNCTIONALITY OF TOLEROGENIC CD19-CAR-INKT CELLS AGAINST CD19 + MALIGNANCIES

Emmanuelle Moraes Ribeiro[1], Anton Wesle[1], Kathy-Ann Secker[1], Anita Schmitt[2], Hildegard Keppeler[1], Corina Schneidawind[1], Michael Schmitt[2], Dominik Schneidawind[1]

[1]University Hospital Tübingen, Tübingen, Germany, [2]University Hospital Heidelberg, Heidelberg, Germany

Background: Invariant natural killer (iNKT) T cells are a small T-cell population with robust immunoregulatory and antitumor properties. We recently demonstrated that human culture-expanded iNKT cells hinder allo-T-cell activation and proliferation while exerting tumor control. Hence, iNKT cells expressing a chimeric antigen receptor (CAR) are interesting cytotherapeutic candidates to treat relapse after allogeneic HCT since they also prevent GVHD. Here, we focused on evaluating the immunoregulatory and cytotoxic properties of CD19-CAR-iNKT cells in combination with the PD-1 inhibitor nivolumab to further enhance functionality.

Methods: iNKT cells were immunomagnetically isolated from PBMCs, transduced with an anti-CD19-CAR retrovirus and expanded in vitro. Cytotoxicity and proliferation of CD19-CAR-iNKT cells were assessed by flow cytometry, image stream analysis and multiplex analysis in single- or repeated-stimulation assays. Moreover, immunoregulatory properties of CD19-CAR-iNKT cells were analyzed in apoptosis and transactivation assays and in mixed lymphocyte reactions (MLR). The effect of checkpoint inhibition through nivolumab was analyzed in both settings.

Results: Robust cytotoxicity could be observed against both CD19 + CD1d- and CD19 + CD1d+ engineered K562 cells. Also, acute lymphocytic leukemia (ALL) and Burkitt lymphoma (BL) cells were highly susceptible to CD19-CAR-iNKT cells. Cell interactions and apoptosis of cancer cells could be confirmed by image stream analysis. Multiplex analysis revealed a robust release of cytotoxic factors such as IFN-γ and granzyme A. The interaction with BL cells induced a higher expression of PD-1 by CD19-CAR-iNKT cells in comparison to non-transduced iNKT cells. CD19-CAR-iNKT-cell function was impaired when challenged with lymphoma cells engineered to overexpress PD-L1/2, which could be partially reversed through nivolumab-treatment. Alloreactivity assays revealed that CD19-CAR-iNKT cells also maintain their ability to induce DC apoptosis and hinder allo-T-cell activation and proliferation even upon treatment with nivolumab.

Conclusions: We showed that CD19-CAR-iNKT cells promote effective lysis of CD19+ tumor cells through their CAR while preventing alloreactive T cell responses. Checkpoint inhibition may further enhance their cytotoxic activity without exacerbating the risk of GVHD after allogeneic HCT making them an ideal cytotherapeutic to treat relapse in this challenging clinical setting.

Disclosure: No conflict of interest to disclosure

3 - CAR-based Cellular Therapy – Preclinical

P113

INDIGENOUS DEVELOPMENT OF NEXT-GENERATION CAR MOLECULES TO OVERCOME ANTIGEN LOSS AND LIMITED IN-VIVO PERSISTENCE OF CONVENTIONAL CAR-T CELLS, CHALLENGES AND SUCCESSES: INITIAL EXPERIENCE FROM INDIA

Gaurav Kharya[1,2], Sivaprakash Ramalingam[3], Aditya Iyer[3], Pragya Gupta[3], Vinod Sarvanakumar[3], Md Imam Faizan[4], Areej Akhtar[4], Iqbal Azmi[4], Sufyan Ansari[4], Tanveer Ahmed[4]

[1]Centre for Bone Marrow Transplant & Cellular Therapy, Indraprastha Apollo Hospital, Delhi, India, [2]Cellogen Therapeutics Pvt Ltd, Delhi, India, [3]CSIR – IGIB, Counsel of Industrial and Scientific Research –

Institute of Genomics and Integrative Biology, Delhi, India, [4]Multi-disciplinary Center for Advanced Research and Studies, Jamia Millia Islamia, Delhi, India

Background: CD19 directed chimeric antigen receptor (CAR)-T cells have shown impressive results against B-cell related malignancies. However, CD19 antigen loss (30 - 70% of B-ALL patients; *Maude SL, et al. N Engl J Med. 2018*) and lower persistence of conventional 2nd generation CAR T cells is a common mechanism leading to relapse observed in a subset of patients.

Methods: To overcome these underlying limitations, we have designed and functionally screened 42 CARs consisting of a single (mono) or combinatorial (tandem) scFVs ectodomains (CD19, CD20 and/or CD22) with co-stimulatory domains based on CD28 and/or 4-1BB and/or ICOS and/or OX40 in various combinations. We screened these CAR designs in T cells to find CARs with optimal anti-tumor killing activity.

Results: Based on this initial screening, we found ICOS/4-1BB co-stimulatory domains with tandem CD20/CD19 or CD22/CD19 exhibit the most robust anti-tumor activity against CD19/20/22 triple positive cells as well as cells with either CD19 negative, CD20 negative or CD22 negative antigens, mimicking in vivo antigen loss. Upon comparing with the conventional 2nd generation CARs with either 4-1BB or CD28, we found that ICOS/4-1BB based co-stimulatory domains CAR-T (CAR-$T^{ICOS+4\text{-}1BB}$) cells (either CD20/19 or CD22/19 scFv ectodomain) have comparable effector and activation function but persisted longer, with better proliferation rate, and cytokine response. Notably, CAR-$T^{ICOS+4\text{-}1BB}$ displayed an increased memory phenotype than conventional CARs, a feature critical for the long-term in-vivo persistence of these cells. Currently, these CAR-$T^{ICOS+4\text{-}1BB}$ with bi-specific or tri-specific tandem ectodomains are being evaluated in-vivo in xenograft models which also mimic the respective tumor antigen loss.

Conclusions: Our pre-clinical work demonstrates that bi-specific (20-19/22-19) tandem CAR-$T^{ICOS+4\text{-}1BB}$ displayed better proliferation and persistence. Owing to its bi-specificity, they are expected to mitigate tumor relapse by antigen loss/escape as well. Based on our ongoing in-vivo work, the best performing construct shall be taken forward to Phase-1 trial. This is the 1st known indigenous bi-specific 3rd generation CAR molecule development from India.

Clinical Trial Registry: This work was funded by Cellogen Therapeutics Pvt ltd (Cell & Gene Therapy Start-up).

Disclosure: Nothing to declare.

3 - CAR-based Cellular Therapy – Preclinical

P114

CHANGES IN PHENOTYPE OF T CELLS / CD19 CAR-T CELLS IN THE COURSE OF PATIENT TREATMENT

Jonas Wißkirchen[1], Anna-Lena Seebald[1], Diana Wolff[1], Beate Hauptrock[1], Matthias Theobald[1], Eva Wagner-Drouet[1]

[1]Universitätsmedizin Mainz, Mainz, Germany

Background: Relapse after CAR-T-cell therapy occurs in almost half of all patients and can be divided into 2 modes: CD19-negative and CD19-positive relapse. Mechanisms for the latter remain unclear.

High proliferative and cytotoxic capacity of CAR-T-cells are fundamental for tumor control and may correlate with differentiation status and expression of exhaustion markers.

We examined initial T-cells and CAR-T-cells to determine how differentiation status and expression of exhaustion markers influence clinical outcome.

Methods: We analyzed blood samples from 22 lymphoma patients before lymphapheresis, 1 and 2 weeks after CAR-T-cell infusion and a backwash of the CAR-T-cell bag by flow cytometry.

T-cells were divided into CD4 and CD8 subsets as well as naive (CD45RA + CCR7 +), central memory (CD45RA-CCR7 +), effector memory (CD45RA-CCR7-) and effector (CD45RA + CCR7-) T-cells.

T-cell exhaustion was examined by expression of CD160, LAG-3, PD-1, TIGIT and TIM-3.

Results: 20 patients suffered from DLBCL, 2 had mantle-cell lymphoma. 12 received axi-cel, 8 tisa-cel and 2 brexu-cel. Before apheresis CD45RA + CCR7- T-cells were the major subset counting for > 50% of all T-cells in most patients. Within the final product almost all T-cells were CD45RA-CCR7- effector memory type (CAR-T-cells and non-CAR-T-cells). At d + 7 about 20% of CAR-T-cells are CD45RA + CCD7- and this increased further on d + 14. At apheresis in all patients less than 20% of T-cells expressed TIM-3. At least 60% of CAR-T-cells obtained from the bag expressed TIM-3. Expression of PD-1 and TIGIT was more prevalent on T-cells before apheresis but here we also observed significant increases especially within the CAR-T-cell population.

There was no significant difference between the different CAR-T-cell products, patient age or sex. Previous chemotherapy had no influence on the initial T-cell phenotype (no patient received Bendamustine).

In 21 patients we had sufficient data to compare CAR-T-cell frequency in patients with and without relapse respectively. Patients without relapse had a greater percentage of CAR-T-cells of their total T-cells at all timepoints (figure 1).

We observed a trend of higher expression of some checkpoint receptors in patients with relapse.

Patients with relapse had a higher expression of LAG-3 before apheresis (24,4% vs 15,1%) and on day

+8 (23,6% vs 9,4%) on their CD4 T-cells. Expression of TIM-3 and TIGIT was increased on both CD4

(71,0% vs 59,5% and 89,1% vs 83,1 respectively) and CD8 T-cells (86,2% vs 76,1% and 84,9% vs 67,8% respectively) in patients with relapse.

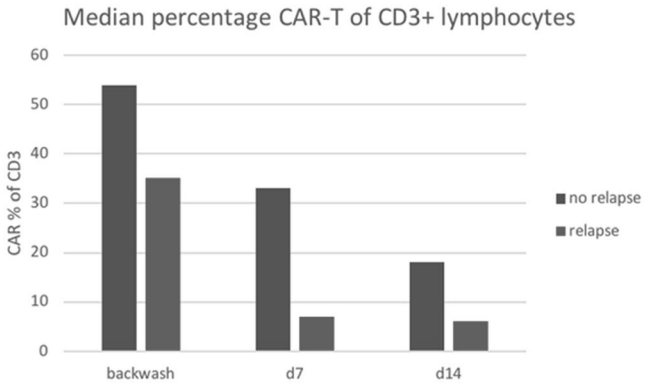


figure 1

Conclusions: We observed that the production process of CAR-T-cells itself causes a change from predominately CD45RA + CCD7- effector T-cells to effector memory T-cells. In vivo some of these develop into terminally differentiated effector T-cells.

Our data suggests a greater percentage of CAR-T-cells in the product and a better expansion of CAR-T-cells in patients without relapse. This may be the consequence of the differential upregulation of 3 checkpoint receptors and downregulation of two other checkpoint receptors.

Further phenotyping for these checkpoints may lead to prediction of clinical outcomes, or new therapeutic options in the course of CAR-T-cell therapy or optimizing the production process.

Disclosure: Advisory Board Celgene and Kite/Gilead.

3 - CAR-based Cellular Therapy – Preclinical

P115

A PERSONALIZED BIOMARKER-TARGETED CAR-T THERAPY IS POSSIBLE BASED ON IMMUNOPHENOTYPE FOR ACUTE MYELOID LEUKEMIA PATIENTS

Meiwei Gong[1], Hui Wang[1]

[1]*Hebei Yanda Lu Daopei Hospital, Langfang, China*

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has resulted in remarkable efficacy for certain patients with hematological malignancies. However, it is difficult to find an high-expression biomarker with good specificity for acute myeloid leukemia (AML) due to the strong heterogeneity of AML tumor cells. Here, we explored biomarker expression among AML patients to facilitate a personalized target CAR-T therapy approach.

Methods: From August 1, 2022 to November 12, 2022, of 671 AML patients tested for minimal residual disease (MRD) by flow cytometry (FCM) at the Hebei Yanda Lu Daopei Hospital, 174 were MRD positive. Among these MRD+ cases, there were 98 males and 76 females. The median age was 32 years (range: 1-76 years) and the median tumor blast proportion was 7.85% (range: 0.01%-97.83%). Biomarkers analyzed included CD34, CD117, CD45, HLA-DR, CD33, CD13, CD11b, CD7, CD56, CD38, and other biomarkers were selected according to the patient's subtype. In some cases, CD96, CD19, CD371(CLL1), LILRB4(CD85k), CD123, CD15, CD64, CD14, Tim-3,were also tested. Expression intensity of tumor cells was defined as follows: Bright = Score 5. Medium intensity expression = Score 4; Weak expression = Score 3, Partial bright/partial expression =Score 2; Part dim = Score 1; No expression = Score 0. Each marker has its own positive control.

Results: The overall expression rate and the rate of patients with expression intensity Score ≥3 for CD7, CD38, CD371, CD123, CD96, LILRB4, Tim3 and CD19 were 36.21%(63/174)/16.09%(28/174), 96.27%(155/161)/93.78%(151/161), 88.35%(91/103)/65.04%(67/103), 94.11%(96/102)/90.2%(92/102), 55.28%(68/123)/44.72%(55/123), 24.51%(25/102)/12.75%(13/102), 72.28%(73/101)/48.51%(49/101), and 11.21%(13/116)/5.17%(6/116).

We assumed that patients with expression Score ≥3 could receive CAR-T therapy. In terms of expression intensity, the sequence was CD38, CD123, CD371, tim3, CD96, CD7, LILRRB4, and CD19. However, CD38 and CD371 were expressed in various hematopoietic cells, may lead to greater off target effects and side effects. targeting CD123 is not likely to lead to high efficacy because of its weak expression intensity. If considering using dual targeted CAR-T for AML, the expression rates of CD7/CD38, CD7/CD371, CD7/CD123, CD38/CD123 and CD371/CD123 were 90.80% (158/174), 45.40% (79/174), 36.78% (67/174), 98.78% (163/165), 95.19% (99/104), respectively. Combining these dual targeted CAR T therapies with CD96/Tim-3/CD85k/CD19 CAR-T, the expression rate could be further improved.

Conclusions: Combined with the advantages of multi-parameter flow cytometry immunotyping, we expect that AML can be divided into various subtypes according to the expression of potential CAR-T targets and select individualized CAR-T.

Clinical Trial Registry: no.

Disclosure: Nothing to declare.

3 - CAR-based Cellular Therapy – Preclinical

P116

NK CELLS ENGINEERING USING ADVANCED LENTIVIRAL VECTORS QUALITY AND DESIGN

Regis Gayon[1], Florence Borot[2], Christine Duthoit[1], Nicolas Martin[1], Florine Samain[1], Alexandra Iche[1], Pascale Bouille[1]

[1]*Flash Therapeutics, Toulouse, France,* [2]*Columbia, New York, United States*

Background: The emergence of targeted immunotherapy, especially chimeric antigen receptor (CAR) T-cell therapy, has opened new possibilities, demonstrating tremendous success for patients with lymphoblastic leukemia. Natural Killer (NK) cells are other key immune effector cells which, contrary to T cells, do not require antigen priming and are at a low risk of Graft-Versus-Host Disease (GVHD), therefore offering the potential of an allogenic "off-the-shelf" therapeutic product. Nevertheless, primary NK cells exhibit a high resistance to lentiviral transduction, hampering transgene expression and consequently the generation of CAR-NK cells.

Methods: Pre-clinical and clinical CAR-NK cells manufacturing requires to be performed using the same process. Here we show a manufacturing process of highly purified and concentrated third generation lentiviral vectors, available for a continuum going from Discovery to Clinic phases, integrating a control plan, allowing for the development and for the good manufacturing practices (GMP) production of custom lentiviral batches dedicated to clinical applications. Human primary NK cells, previously activated by artificial antigen-presenting cells (APC) are transduced with such highly purified and concentrated Lentiviral vectors prior to be evaluated by in vitro cytotoxic assays and in vivo engraftments into mouse model.

Results: In this collaborative work, we show that the use of highly purified and concentrated self-inactivating lentiviral vectors in combination with an optimized transduction protocol, allows up to 65% of trasnduced human cord blood derived NK cells. Also, we show that transduction does not lead to viability nor phenotypic alterations of the transduced NK cells. Our approach not only achieves high transduction efficiency, leading to strong and stable transgene expression, but also preserves the cytotoxic function of the NK cells, in vitro and in vivo.

Conclusions: Many obstacles exist for clinical development of a CAR-based cellular therapy product, which requires efficient and safe delivery technologies, as well as gene expression level and duration tailoring. It's possible to achieve this, through the use of delivery tools, which allow highly efficient gene transfer while maintaining transduced cell viability and phenotype. Here we propose a novel method allowing for the generation and production of lentiviral vector engineered primary NK cells, thus circumventing the problem of poor autologous CAR-T cell efficiency and gamma retrovirus associated risks. This work lays the groundwork for novel cellular therapies based on lentivirally transduced primary NK cells. All these factors, as well as the ability to produce lentiviral vectors using Flash Therapeutics' GMP compliant production platform, offer additional safety considerations for clinical development and human use.

Disclosure: NONE.

3 - CAR-based Cellular Therapy – Preclinical

P117

A NOVEL MULTICOLOR FLUORESCENT SPOT ASSAY FOR THE FUNCTIONAL ASSESSMENT OF CAR T CELL PRODUCTS

Thierry Iraguha[1], Destiny Omili[1], Etse Gebru[1], Nancy Hardy[1], Tim Luetkens[1], Aaron Rapoport[1], Djordje Atanackovic[1]

[1]*University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, United States*

Background: Chimeric antigen receptor (CAR) T cell therapies are powerful anti-tumor immunotherapies and have revolutionized the treatment of B cell lymphomas. Unfortunately, recurrent disease after CAR T cell therapy remains a clinical problem with up to 50% early relapses after CD19-targeted CAR T cells. Therefore, there is a critical need for novel assays that are able to predict durable responses and will help to guide the optimization of CAR T cell therapies.

Methods: We developed a novel multicolor fluorescent spot assay (MFSA) for the functional assessment of CAR T Cell products on a single-cell level combining the numerical assessment of CAR T cell products with their functional characterization.

Results: We first used a standard single-cell interferon (IFN)g ELISPOT assay to measure CD19-targeted CAR T cell responses to CD19-coated beads or to beads coated with an irrelevant target. Beads coated with anti-CD3/anti-CD28 antibodies were used as a positive control. We then developed, optimized, and validated an MFSA that simultaneously measures the secretion of combinations of different cytokines on a single-CAR T cell level. We identified IFNg/TNFa/Granzyme B as the most relevant combination of cytokines and we used our novel multicolor ELISPOT assay to functionally and numerically characterize two clinical-grade CAR T cell products.

Conclusions: We have developed a novel multicolor fluorescent spot assay (MFSA) for the quantitative and functional assessment of CAR T cell products. The clinical value of our novel assay will be assessed in clinical studies correlating the pre-infusion assessment of CAR T cell products with the patients' outcome.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare.

3 - CAR-based Cellular Therapy – Preclinical

P118

PROCESSING AND CRYOPRESERVATION OF PERIPHERAL BLOOD LEUKAPHERESIS FOR DLI ADMINISTRATION OR CAR-T MANUFACTURING

Serena Urbani[1], Julien Camisani[2], Oliver Link[2], Rita Antonini[1], Lucia Bianchi[1], Valeria Calossi[1], Carmela De Sanzo[1], Francesca Felicioni[1], Valentina Fulgido[1], Gaetano Mobilio[1], Michela Santosuosso[1], Irene Sodi[1], Riccardo Saccardi[1]

[1]Cell Therapy and Transfusion Medicine Unit, Careggi University Hospital, Firenze, Italy, [2]Cytiva, Eysins, Switzerland

Background: Autologous Mononuclear cells from Apheresis [MNC (A)] products contain mononuclear cells (MNC) collected from peripheral blood by an apheresis procedure and are intended for clinical use other than Hematopoietic Stem Cells Transplantation (HSCT), such as Donor Lymphocytes Infusions (DLIs) or Genetically modified Immune Effector Cells (IECs).

We carried out a validation of MNC (A) automated processing by Cytiva, aimed to cryopreservation, storage and thawing/ washing for subsequent manipulation. The following processes were assessed:

1. Cryopreservation
2. Thawing
3. Washing
4. Density-Gradient-Based Separation (DGBS).

Methods: Peripheral Blood Leukapheresis were cryopreserved by a standardized controlled temperature freezing technique and stored in freezing bags in liquid nitrogen. The bags were thawed using a SmartMax device (CellThaw Protocol) and washed using SmartWash Protocol v314 on Sepax 2 S-100.

Finally, the washed product was stratified on a density gradient in order to increase the MNC purity, using NeatCell Protocol v319.

A sample was drawn after any step to evaluate WBC, GRC, RBC, MNC, $CD3^+$ cells content and viability by flow-cytometer analysis.

Results: Characterization and yields of TNC, MNC, and $CD3^+$ cells of the thawed units, after density gradient separation (NeatCell output), and comparison with waste fraction of density gradient separation, are reported here: the product composition in terms of MNC components is very similar between the fraction obtained after NeatCell and its waste fraction; NeatCell allows a 36% yield of WBC and 24,7% of CD3 of the thawed product, while depleting unwanted GRC and RBC cells to provide a purer cellular product. Viability of all fractions is >97%.

Process performance (from washed product):	NeatCell output	NeatCell waste
MNC %	96,1	96,9
MNC yield %	36,4	62,3
WBC yield %	36,2	61,5
CD3 yield %	24,7	77
GRC depletion %	64,6	
RBC depletion %	75,4	
Overall process performance (from fresh product):	**Without NeatCell**	**With NeatCell**
MNC yield %	93,1	33,8
CD3+ yield %	76,3	18,9
GRC depletion %	78,7	93,5
RBC depletion %	43,9	86,1

Conclusions: Sepax technology allows a highly automated processing of Autologous MNC in a closed system. High Lymphocytes yield and viability after thawing/washing process were shown, therefore allowing further manipulation such as CAR-T manufacturing.

DGBS, carried out after the washing procedure, resulted in a loss of both WBC and Lymphocytes, but allows a purer cellular product by further depleting undesirable GRC and RBC cells.

DGBS shall be avoided if the primary goal is to increase MNC recoveries and shall be considered if the primary goal is to maximize cellular product purity.

Disclosure: Nothing to declare.

5 - Cellular Therapies other than CARs

P119

SARS-COV-2 T-CELLS FOR ADOPTIVE CELL THERAPY IN IMMUNOCOMPROMISED CANCER PATIENTS

Rafet Basar[1], David Marin[2], Nadima uprety[2], May Daher[2], Ye Ii[2], Christina Ganesh[2], Kimberly Klein[2], Mayra Shanley[2], Fernando Martinez[2], Fleur Aung[2], Ana Karen Nunez Cortes[2], Sunil Acharya[2], Pinaki Banerjee[2], Indreshpal Kaur[2], Mariam Ammari[2], Sheetal Rao[2], Richard Champlin[2], Elizabeth J. Shpall[2], Katayoun Rezvani[2]

[1]MD Anderson Cancer Center, Hosuton, United States, [2]MD Anderson Cancer Center, Houston, United States

Background: SARS-CoV-2 causes serious infections in immuno-compromised cancer patients with reported mortality up to 20%. Furthermore, a proportion of immunocompromised patients with

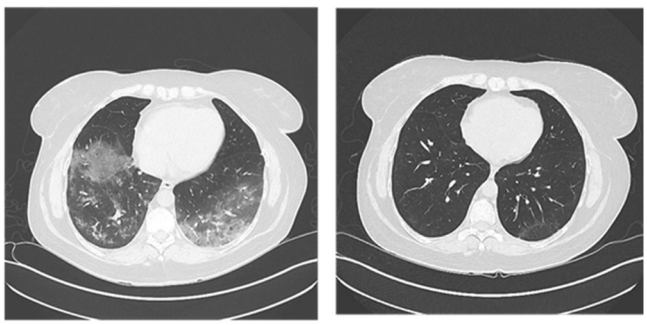
COVID19 develop persistent or recurrent infection in spite of receiving novel antiviral therapies. Adoptive cell therapy with off-the-shelf, partially HLA matched, allogeneic cytotoxic T-lymphocytes (CTLs) has been successfully used to treat immunosuppressed patients with other severe viral infections such as adenovirus, cytomegalovirus and BK virus.

Methods: We manufactured 11 SARS-CoV-2 specific CTL cell lines (COVID-CTLs) from the peripheral blood of 11 healthy donors who had recovered from COVID19. Briefly, cells were cultured with a combination of peptide libraries spanning the entire sequence of the SARS-CoV-2 in the presence of IL-2/4/7 for 14 days, cryopreserved and banked. For each cell line, SARS-CoV-2 reactive T-cells were enumerated. The trial opened in December 2020 and 26 patients have been enrolled so far. Table-1 shows the patients characteristics. Cell lines was selected based on the degree of HLA matching between the line and the patient. Consideration for the frequency of SARS-CoV-2 reactive T-cells was also given. Patients received one infusion of 2x105 cell/kg. Infusions could be repeated at 2 weeks intervals if the patient failed to respond. Patients could not receive steroid treatment immediately prior or after infusion of the CTLs. Responses were defined as improvement by at least one category in the WHO COVID severity scale within 28 days of the infusion. In vivo CTL expansion was assessed using an HLA-based flow cytometry chimerism assay.

Table 1. Patients' characteristics

Variable	n (%)
Age median (range)	54.5 (23-82)
Sex	
female	8 (30.8)
male	18 (69.2)
Recipient of allogeneic SCT	
no	12 (46.2)
yes	14 (53.8)
Underlaying disease	
AML/MDS	8(30.8)
CML/MF	4 (15.4)
ALL	2 (7.7)
NHL	9 (34.6)
Clinical characteristics	
Requiring Oxygen	5 (19.2)
Multifocal pneumonia	26 (100)
Number of CTL infusions	
1	24 (92.3)
2	2 (7.7)

Figure 1, Chest CT showing pneumonia resolution in patient number 4



Patient 4 baseline

Patient 4, 2 weeks after infusion

Results: We did not observe any toxicity (any grade) attributable to the CTLs, including cytokine release syndrome (CRS) or graft vs host disease (GVHD). Twenty-six out of the 26 patients treated (100%) responded. The median time to response was 17 days (range 5-28 days). No patient had a recurrence of the COVID19 infection during the follow-up. We confirmed in vivo expansion of donor-derived COVID-CTLs in the peripheral blood of patients, with the peak expansion observed 7-14 days post-infusion.

Conclusions: COVID-CTLs are safe. Although the design of the study is not adequate to assess the efficacy of the CTLs, the fact that 25/26 severely immunocompromised patients improved, none requiring mechanical ventilation or ICU admission, gives a strong signal in favor of the efficacy of the CTLs. The trial is being amended to include contemporaneous matched controls.

Clinical Trial Registry: 2020-0759,https://clinicaltrials.gov/ct2/show/NCT04742595

Disclosure: • Rafet Basar and The University of Texas MD Anderson Cancer Center have an institutional financial conflict of interest with Takeda Pharmaceutical for the licensing of the CAR-NK cell technology

• Rafet Basar and The University of Texas MD Anderson Cancer Center have an institutional financial conflict of interest with Affimed Pharmaceutical.

5 - Cellular Therapies other than CARs

P120

PRECISION-ENGINEERED CELL THERAPY ORCA-T DEMONSTRATES HIGH RELAPSE-FREE SURVIVAL AT 1 YEAR WHILE REDUCING GRAFT-VERSUS-HOST DISEASE AND TOXICITY

Caspian Oliai[1], Rasmus Hoeg[2], Anna Pavlova[3], Arpita Gandhi[4], Lori Muffly[3], Rohtesh Mehta[5], Samer Srour[5], Edmund Waller[6], Robert Lowsky[3], Sagar Patel[7], Bhagirathbhai Dholaria[8], Jeremy Pantin[9], Amandeep Salhotra[10], Nathaniel Fernhoff[11], J. Scott McClellan[11], Mehrdad Abedi[2], Robert Negrin[3], Everett Meyer[3]

[1]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, United States, [2]University of California, Davis, Sacramento, United States, [3]Stanford University, Stanford, United States, [4]Oregon Health and Science University, Portland, United States, [5]MD Anderson Cancer Center, Houston, United States, [6]Emory University, Atlanta, United States, [7]University of Utah, Salt Lake City, United States, [8]Vanderbilt University Medical Center, Nashville, United States, [9]Sarah Cannon Center for Blood Cancer at TriStar Centennial Medical Center, Nashville, United States, [10]City of Hope National Medical Center, Duarte, United States, [11]Orca Bio, Menlo Park, United States

Background: Allogeneic hematopoietic stem cell transplants (alloHSCT) remain the only curative treatment for many hematologic malignancies; however, they are associated with significant toxicity. Strategies to maintain the graft-vs-tumor and graft-vs-infection effects while eliminating GvHD have long been a key goal in the field.

Orca-T is a high-precision cell therapy consisting of stem and immune cells, derived from allogeneic donors, that leverages highly purified, polyclonal donor regulatory T cells to control alloreactive immune responses.

Methods: As of 25 Oct 2022, 151 patients had received Orca-T and had ≥ 100 days of follow-up (f/u). These patients had a diagnosis of acute leukemia in CR [AML (44%), ALL (31%), MPAL (3%), CML w/prior blast crisis (5%), or high-risk MDS (15%). Patients received Orca-T as part of a single-center Phase 2 study (n = 34) or a multi-center Phase 1b study (n = 117). Median f/u

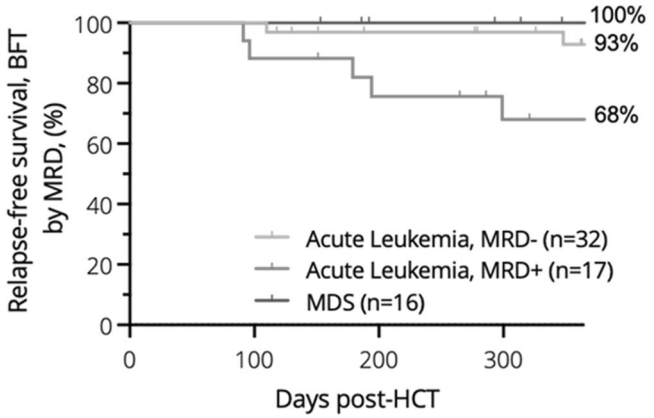
was 15 months (range 3-43); 146 pts had > 1 year and 86 had >18 months of f/u. Patients were aged 19-71 (median 48) and 57% male. Donors were HLA-matched related (52%) or unrelated (48%). Patients received investigator's choice of myeloablative conditioning (MAC) regimens (busulfan-based (77%); TBI-based (23%)) prior to Orca-T, followed by single-agent GvHD prophylaxis with either tacrolimus (n = 148) or sirolimus (n = 3). For comparison, an independent CIBMTR-based cohort was identified which consisted of patients with AML, ALL, or MDS who received MAC alloHSCT with a PBSC source between 2016-2018 followed by tacrolimus/methotrexate prophylaxis.

Results: Orca-T was successfully manufactured in a single, centralized GMP manufacturing facility, distributed, and infused throughout the U.S.

Orca-T outperformed standard of care alloHSCT. GVHD and relapse-free survival (GRFS) and overall survival was 70% and 88% at 1 year in the overall Orca-T study population compared to 21% and 68% at 1 year in the CIBMTR comparator cohort, respectively. Non-relapse mortality (NRM) was lower with Orca-T at 4% at 1 year compared to 10% at 1 year in the CIBMTR cohort.

Median times to neutrophil and platelet engraftment for all Orca-T recipients were 13 and 16 days, respectively; graft failure was 1.6%.

Clinical outcomes with Orca-T appeared to be enhanced with a conditioning regimen of busulfan, fludarabine, and thiotepa ("BFT", n = 71 patients, median f/u 14 months). Relapse free survival (RFS) was 87% at 1 year in this group, 93% among MRD- patients and 68% among MRD+ (Figure). NRM was 0% at 1 yr. Severe infections (Grade 3 + MOP infections per the BMT-CTN grading scale) occurred in 9% of these patients. Grade ≥ 3 aGvHD and moderate to severe cGvHD rates were low in this group at 1.5% and 5%, respectively. Additionally, GRFS was 81% and overall survival was 94% at one year.



Conclusions: At more than 1 year of median f/u, outcomes with Orca-T demonstrate robust graft-vs-tumor and graft-vs-infection effects while markedly reducing GvHD and NRM despite MAC. These outcomes were accomplished with reliable cell manufacturing and distribution of Orca-T nationally. A multi-center randomized controlled phase 3 trial comparing Orca-T to SOC is currently enrolling across the US (NCT05316701).

Clinical Trial Registry: https://clinicaltrials.gov/ct2/show/NCT05316701

Disclosure: Caspian Oliai | Research Funding: Pfizer, Jazz Pharmaceuticals, Orca Bio, Arog, Seagen

Rasmus Hoeg | Research Funding: Orca Bio

Anna Pavlova | Current Employment/Equity: Orca Bio

Arpita Gandhi | Research Funding: Orca Bio; Consultancy: Care Dx; Honoraria: Gamida

Lori Muffly | Consultancy: Amgen, Pfizer, Kite, Medexus, CTI Biopharma, Astellas, UpToDate; Research Funding: Kite, Astellas, Jasper, Adaptive, BMS, Novartis, Orca Bio; Honoraria: Adaptive, UpToDate

Rohtesh Mehta | Research Funding: Syndax, Orca Bio

Samer Srour | Research Funding: Orca Bio

Edmund Waller | Research Funding: Verastem Oncology, Orca Bio; Consultancy, BoD or Advisory Committee: Verastem Oncology

Robert Lowsky | Research Funding: Orca Bio

Sagar Patel | Honoraria: Kite, Medexus Pharma, CareDx; Research Funding: Orca Bio

Bhagirathbhai Dholaria | Research Funding: Poseida, Takeda, Pfizer, Janssen, Wugen, Molecular Templates, Orca Bio, Angiocrine, BMS, MEI Pharma; Consultancy: BEAM Therapeutics, Gamida Cell, Arivan, Jazz Pharmaceuticals; Honoraria: MJH Biosciences

Jeremy Pantin | Consultancy: NKARTA, Omeros; Speakers Bureau: Omeros; Honoraria: Cardinal Health; Research Funding: Orca Bio

Amandeep Salhotra | Advisory Board: Kadmon; Research Funding: BMS

Nathaniel Fernhoff | Current Employment/Equity: Orca Bio

J. Scott McClellan | Current Employment/Equity: Orca Bio

Mehrdad Abedi | Speakers Bureau: BMS, AbbVie, Kite, Celgene; Consultancy: Celgene; Equity Holder: CytoDyn; Research Funding: Orca Bio

Robert Negrin | Consultancy: Garuda, Kuur, Amgen, Novartis, Magenta; Equity Holder: Magenta, CoImmune, BioEclipse Therapeutics; Honoraria: UpToDate

Everett Meyer | BoD/Advisor: indee labs; Co-founder & Scientific Advisor: GigaGen, Triursus Therapeutics; Research Funding: Orca Bio

This study was sponsored by Orca Bio

5 - Cellular Therapies other than CARs

P121

MULTISTATE MODEL ANALYSIS OF PROPHYLACTIC/PRE-EMPTIVE DONOR LYMPHOCYTE INFUSION FOR HIGH-RISK ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROME IN COMPLETE HEMATOLOGIC REMISSION AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

Giuliano Filippini Velázquez[1], Jan Frederic Weller[2], Anna Rubeck[3], Tobias Arndt[3], Stefan Schiele[3], Markus Mezger[2], Gernot Müller[3], Claudia Lengerke[2], Martin Trepel[1], Maximilian Christopeit[2], Christoph Schmid[1]

[1]Augsburg University, Augsburg, Germany, [2]Tübingen University Hospital, Tübingen, Germany, [3]Augsburg University, Institute of Mathematics, Computational Statistics and Data Analysis, Augsburg, Germany

Background: Donor lymphocyte infusion (DLI) is given in complete hematologic remission (CHR) after allogeneic stem cell transplantation (alloSCT) to prevent relapse in AML/MDS, either as prophylaxis in high-risk patients without evidence of imminent relapse (proDLI), or pre-emptively in patients with incomplete chimerism (preDLI-IC) or minimal residual disease (preDLI-MRD). The antileukemic efficacy is counterbalanced by the risk of DLI-induced Graft-versus-Host disease (GvHD) and its potentially associated morbidity/mortality.

Methods: We retrospectively analysed clinical outcomes and GvHD-incidence in all consecutive patients with AML/MDS receiving unmodified (CD3 +) proDLI/preDLI in two German centres between 2007 and 2021 according to institutional standards. No ex-vivo T cell depletion had been used for SCT. For inclusion, minimal follow-up after first DLI had to be 100 days to assure the detection of post-DLI acute GvHD. Criteria for DLI

were: CHR, no immunosuppression for ≥4 weeks, no active GvHD, no history of GvHD ≥III, and no active infection. As per institutional protocol, proDLI/preDLI was to be given in 4-6 weeks' intervals at escalating doses, which differed according to donor type and time since alloSCT. Beyond standard outcome analysis, a multistate model (allowing for non-absorbable states) was fitted to evaluate the probability of final treatment success, i.e., being alive and in remission without or with ongoing low dose immunosuppression (IS) for DLI-induced GvHD. Further, an exploratory analysis correlating cytogenetics at diagnosis and long-term survival after DLI1 was performed.

Results: Eighty-three patients (AML/MDS, n = 75/8, **Table 1**) were identified, representing a high-risk cohort with high-risk ELN/IPSS (58%), TP53mut/del (10%), SCT in active disease (59%) and second alloSCT (10%). ProDLI/preDLI-IC/preDLI-MRD was given in 43%/33%/24%. Median number of DLI/patient was 3 (1-5).

Following DLI1, median follow-up of survivors was 41 months. Response to preDLI (n = 47) was 83% (preDLI-IC: 22/27, preDLI-MRD: 17/20). Two-year overall/leukemia-free survival (OS/LFS) from DLI1 was 82%/70% for proDLI, 81%/74% for preDLI-IC and 61%/48% for preDLI-MRD. Two-year cumulative incidence (CI) of aGvHD I-IV/III-IV was 51%/18%. Two-year CI of cGvHD/extensive cGvHD was 46%/7%. Two-year non-relapse mortality/relapse incidence/leukemia-associated death (NRM/RI/LAD) were 8%/28%/17%. Two-year GvHD-relapse-free survival (GRFS) was 63%. Using the multistate model, probability of final treatment success was 63% (alive/in remission/without IS, n = 45; alive/in remission/with low dose IS, n = 7). 34/52 patients transiently requiring IS could discontinue the drugs later. In univariate analysis, the following cytogenetic/molecular abnormalities were associated with long term survival: DNMT3A (6/6, of which preDLI=5), FLT3-TKD (4/4; preDLI=2), Trisomy 8 (8/9, preDLI=3), del7 (7/8, preDLI=3), TP53mut/del (6/8, preDLI=5).

Conclusions: High rates of long-term survival were observed in this high-risk cohort receiving pro/pre DLI in CHR after alloSCT. Rates of DLI-induced GvHD were considerable, however, severe grades were rare, and most patients requiring IS could discontinue it over time. Hence, as shown in the multistate model, final treatment success was achieved in >60%, with 54% being alive/in remission/without IS by end of study. The data provide an improved estimate of risks and benefits of pro/preDLI. Beyond, exploratory analysis identified genetic subtypes associated with favourable outcome after SCT + DLI.

Table 1. Patients' characteristics

		Total (%)
Diagnose	AML	75 (90%)
	MDS	8 (10%)
Risk group		
AML, according to ELN	low	6 (7%)
	intermediate	29 (35%)
	high*	40 (48%)
	high*	8 (10%)
MDS, according to IPSS		
Number of allo-SCT	First alloSCT	75 (90%)
	Second alloSCT	8 (10%)
Stage at this alloSCT	CR	34 (41%)
	Active disease	49 (59%)
Donor type	MSD	20 (24%)
	MUD 10/10	47 (57%)
	MUD 9/10	10 (12%)
	Haploidentical	6 (7%)
Conditioning intensity (TCI) according to Spyridonidis et al, BMT 2020	low	8 (10%)
	intermediate	25 (30%)
	high	50 (60%)
Extramedullary disease before alloSCT	yes	5 (6%)
	no	78 (94%)
Type of DLI	proDLI	36 (43%)
	preDLI-IC	27 (33%)
	preDLI-MRD	20 (24%)
Interval from alloSCT to first DLI in median (range)	all patients	182 (73-1306) days
	proDLI	203 (118-498) days
	preDLI-IC	173 (121-470) days
	preDLI-MRD	184 (73-1306) days
Initial cell dose in median (range)	MSD	1 (0.5-10) x 10^6 /Kg CD3+
	MUD 10/10	0.2 (0.1-10) x 10^6 /Kg CD3+
	MUD 9/10	0.2 (0.2-1) x 10^6 /Kg CD3+
	Haploidentical	0.2 (0.2-1) x 10^6 /Kg CD3+
Number of DLI/patient	1	24 (29%)
	2	16 (19%)
	3	31 (37%)
	4	8 (10%)
	5	4 (5%)

ELN European Leukemia Network, *DLI* donor lymphocyte infusion, *proDLI* prophylactic DLI, *preDLI* preemptive DLI, *IC* incomplete chimerism, *MRD* minimal residual disease, *alloSCT* allogeneic stem cell transplantation, *CR* complete remission, *MSD* matched sibling donor, *MUD* matched unrelated donor, 9/10 and 10/10 refers to HLA-match, TCI: transplant conditioning intensity

*Totally 8 patients (10%) with TP53 mutation/deletion

Disclosure: Nothing to declare

5 - Cellular Therapies other than CARs

P122

T-ALLO10 INFUSION AFTER ABDEPLETED-HSCT IN CHILDREN AND YOUNG ADULTS WITH HEMATOLOGIC MALIGNANCIES: IMPROVED IMMUNE RECONSTITUTION IN THE ABSENCE OF SEVERE GVHD

Alice Bertaina[1,2], Rosa Bacchetta[1,2], David Shyr[1,2], Gopin Saini[1], Jennifer Lee[1], Karen Kristovich[1,2], Rajni Agarwal-Hashmi[1,2], Orly Klein[1,2], Kathryn Melsop[1], Keri Tate[1], Giulia Barbarito[1], Linda Oppizzi[1], Pauline Chen[1], Alma-Martina Cepika[1], Maria Grazia Roncarolo[1,2]

[1]Stanford University School of Medicine, Stanford, United States, [2]Lucile Packard Children's Hospital, Palo Alto, United States

Background: The use of allogeneic hematopoietic stem cell transplantation (HSCT) for treating pediatric patients with acute

Table 1. Patients and Transplants Characteristics

	Cohort 1					Cohort 2				Cohort 3
Subject	**367-01-01**	**367-01-02**	**367-01-03**	**367-01-04**	**367-01-05**	**367-02-01**	**367-02-02**	**367-02-03**	**367-02-04**	**367-03-01**
Age	20 years	24 years	10 years	1.7 years	5 years	23 years	5 years	10 years	13 years	20 years
Disease Diagnosis	AML	B cell ALL	AML	AML	B cell ALL	B cell ALL	B cell ALL	MDS with Monosomy 7	MDS with Monosomy 7	ALL
Disease status at time of transplant	CR2	CR2+ (2nd transplant)	CR2 (2nd transplant)	CR2	CR2+ (2nd transplant)	CR2	CR2+	High risk disease	High risk disease	CR2
Day of IP Infusion	D + 40	D + 35	D + 61	D + 40	D + 41	D + 33	D + 39	D + 42	D + 36	N/A
T-allo10 dose	1 x 10^5 cells/ kg	1 x 10^5 cells/ kg	1 x 10^5 cells/ kg	1 x 10^5 cells/ kg	1 x 10^5 cells/ kg	3 x 10^5 cells/kg	3 x 10^5 cells/kg	3 x 10^5 cells/kg	3 x 10^5 cells/kg	1x10^6 cells/Kg
Acute GvHD	Yes D + 30 (prior to T-allo10)	Yes D + 68	Yes D + 68	No	No	No	No	Yes D + 35 (prior to T-allo10)	No	N/A
Acute GvHD Grading (Max grade)	Skin: Stage 1 Overall: Grade 1	GI: Stage 1 Overall: Grade 2	Skin: Stage 3 Overall: Grade 2	N/A	N/A	N/A	N/A	Skin: Stage 2 Overall: Grade 1	N/A	N/A
Chronic GVHD	No	No	Skin and Lung	No	No	No	No	No	N/A	N/A
$CD4^+$ T cell Immune Reconstitution by D + 60 (± 10 days) post HSCT	N/A	No	N/A	Yes	No	Yes	Yes	N/A	Yes	N/A
Infections	CMV, BK virus	CMV, HHV6, Adenovirus, BK virus	CMV, Adenovirus, Norovirus	C. diff, CMV	Adenovirus, HHV6	Sars-CoV-2	Adenovirus, HHV6	HHV6	HHV6	N/A
Relapse	No	No	No	Yes, D + 307	Yes, D + 90	No	No	No	No	N/A
Last follow-up	D + 365	D + 365	D + 365	D + 307	D + 90	D + 270	D + 180	D + 120	D + 75	D 0

leukemia has been limited by the availability of HLA-matched donors. $TCR\alpha\beta^+$ T-cell and $CD19^+$ B-cell depletion (αβdepleted) of the graft has significantly broadened the use of HLA-mismatched related and unrelated donors. However, the incidence of viral reactivations (~50%) and leukemic relapse (25-30%) after αβdepleted-HSCT remains significant, mostly because of the suboptimal immune reconstitution (IR) due to the extensive ex vivo $TCR\alpha\beta^+$ T-cell depletion and the use of pre-HSCT serotherapy.

Methods: We have developed an innovative T-cell immunotherapy, the T-allo10 drug product. T-allo10 product is generated in vitro from donor $CD4^+$ T cells and is enriched in type 1 regulatory T (Tr1) cells, which are host alloantigens specific and therefore suppress host-reactive $TCR\alpha\beta^+$ T cells causing GvHD. It also contains polyclonal naive and memory $TCR\alpha\beta^+$ T cells able to respond to pathogens and tumor antigens. We hypothesized that the infusion of T-allo10 after αβdepleted-HSCT will a) expedite IR by providing a source of $TCR\alpha\beta^+$ T cells, which support immune responses and facilitate the generation of donor-derived naive T cells, and b) modulate anti-host immune responses thanks to the function of alloantigen specific Tr1 cells. The improved IR will reduce the risk of infections and leukemic relapse, without increasing the risk of GvHD.

Results: We report the preliminary results of a single center, non-randomized, non-controlled open-label Phase I/Ib trial in children and young adults with hematologic malignancies receiving αβdepleted-HSCT (NCT 04640987).

At present, we enrolled 10 patients (Table 1) with high-risk disease (i.e., 3 patients received a 2nd HSCT) in the Phase I portion of the study: 9/10 received the T-allo10 infusion. No DLT (grade IV acute GvHD, grade 3 or 4 treatment-related adverse events) have been observed. Two patients developed grade II acute GvHD (22%), and 1 of these 2 patients developed chronic GvHD (11%). Four out of the 6 evaluable patients (66%) achieved the IR efficacy endpoint (Figure 1), reaching the threshold of 50 $CD3^+CD4^+$ T cells/mcl by Day +60 post αβdepleted-HSCT. These data compare favorably to our historical control Cohort in which only 31% of patients achieved this endpoint (Figure 1). Interestingly, $TCR\alpha\beta^+$ $CD3^+CD4^+$ T cells with a memory phenotype increase following the T-allo10 infusion. In all patients, Tr1 cells are detected in the peripheral blood shortly after T-allo10 infusion (within the first 7 days). In Cohort 2 patients, the % of Tr1 cells reached 19.9%, 11.5%, and 5.2% of the memory $CD4^+$ T cell population, with the highest value observed at day +7 post-T-allo10 infusion. $CD4^+CD25^{hi}CD127^{lo}$ Treg cells were also detected in Cohort 2 patients, at high frequencies early after T-allo10 cell infusion, reaching 8-17% of the $CD4^+$ T cell subset 1 to 7 days post-T-allo10 infusion.

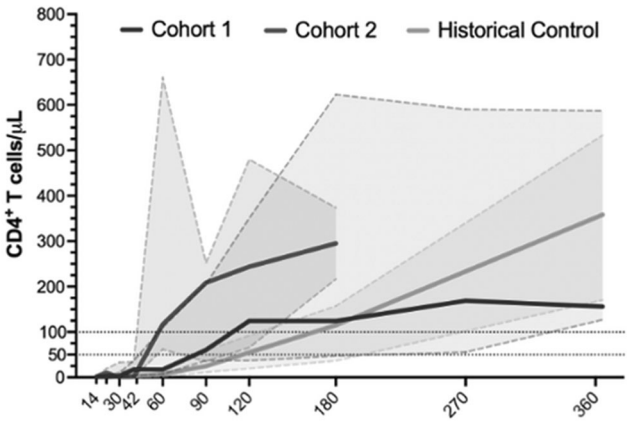


Fig1: CD4 IR improved in T-allo10 compared to controls group and it is dose dependent
Longitudinal analysis of CD4 IR in T-allo10 cohort 1, cohort 2 and historical controls. The data shows median values of CD4 cells/ul at different time points post-HSCT (lines) with interquartile range (shaded area).

Conclusions: These early results support our hypothesis that the adoptive transfer of T-allo10 cells boosts T-cell immune

reconstitution without increasing the risk of GvHD and show that Tr1 cells and $CD4^{+}CD25^{hi}CD127^{lo}$ Treg cells are detected in the peripheral blood of T-allo10 infused patients.

Clinical Trial Registry: NCT04640987, https://clinicaltrials.gov/ct2/show/NCT04640987

Disclosure: Nothing to declare.

5 - Cellular Therapies other than CARs

P123

FIRST-IN-HUMAN STUDY OF MDG1011, A TCR-T CELL THERAPY DIRECTED AGAINST HLA-A*02:01-RESTRICTED PRAME, FOR HIGH-RISK MYELOID AND LYMPHOID NEOPLASMS (CD-TCR-001)

Simone Thomas[1], Martin Wermke[2], Vladan Vucinic[3], Eva Wagner-Drouet[4], Andreas Mackensen[5], Robert Zeiser[6], Gesine Bug[7], Michael Schmitt[8], Petra Prinz[9], Dolores Schendel[9], Kai Pinkernell[9,10], René Goedkoop[9]

[1]University Hospital Regensburg, Regensburg, Germany, [2]University Hospital Carl Gustav Carus Dresden, Dresden, Germany, [3]University Hospital Leipzig, Leipzig, Germany, [4]University Medical Center Mainz, Mainz, Germany, [5]University of Erlangen-Nuernberg, Erlangen, Germany, [6]University of Freiburg Medical Center, Freiburg, Germany, [7]Goethe University Frankfurt, University Hospital Frankfurt, Frankfurt, Germany, [8]University Hospital Heidelberg, Heidelberg, Germany, [9]Medigene AG, Martinsried, Martinsried, Germany, [10]Glycostem, Oss, Netherlands

Background: Preferentially expressed antigen in melanoma (PRAME) is a cancer-testis antigen present in several solid and hematological malignancies. This multicenter Phase I study (NCT03503968) evaluated the safety and feasibility of escalating doses of MDG1011 in patients with refractory/relapsed (r/r) AML, MDS or multiple myeloma (MM).

Methods: Treatment was conducted with MDG1011 after lymphodepletion with fludarabine (25 mg/m² x 3d) and cyclophosphamide (300 mg/m² x 3d) in patients with HLA-A*02:01- and PRAME-positive r/r disease. Dose escalation included 3 dose levels (DL), $0.1x10^6$ (DL1), $1x10^6$ (DL2) and $5x10^6$ (DL3) TCR-T cells/kg BW, respectively. The primary objectives were to assess safety and tolerability of MDG1011 and establish maximum tolerated dose and/or recommended Phase II dose. Secondary objectives were to evaluate efficacy and correlation with PRAME expression through immune monitoring (quantification of PRAME mRNA levels in bone marrow (BM) and/or peripheral blood (PB) and monitoring of TCR-T persistence in PB).

Results: 13 patients with advanced, myeloid and lymphoid neoplasms, and a median age of 65 years were enrolled and underwent leukapheresis (n = 10 with AML, n = 1 with MDS/MPN and n = 2 with MM). MDG1011 manufacturing feasibility was high with release criteria met for 12/13 patients (92.3%).

9 patients were treated with MDG1011 at the three escalating DLs (n = 3, 4 and 2 patients, respectively); 4 patients succumbed to their disease before TCR-T infusion. All 13 patients experienced adverse events (AEs), of which 54/124 AEs were ≥ grade 3 toxicities (NCI CTCAE v4.01), 31/124 AEs related to lymphodepletion and 21/124 AEs related to MDG1011. 12 SAEs were reported in 7/9 treated patients. Grade 1 cytokine release syndrome (CRS) occurred in 1 patient at DL2, grade 2 CRS in 1 patient at DL3 that was manageable with tocilizumab. Neurotoxicity (ICANS) or dose-limiting toxicity were not reported.

In patients receiving MDG1011, 4 died from their disease (none in DL3, none considered related to MDG1011) and 4 experienced disease progression. 1 patient with AML with extramedullary disease (DL1) experienced complete remission at week 4 but had progressed by month 3. In addition, 1 patient with multilineage MDS/MPN (DL3) remained without progression to secondary AML through month 12. In this patient, TCR-T cells were detected in PB at week 4 through month 12, whereas PB PRAME levels were no longer detected at week 4 but gradually increased thereafter while remaining clearly below the baseline level. In concordance, blast counts both in PB and/or BM remained well below baseline.

TCR-T cells were present in 6 of 8 patients within 4 weeks. PRAME (BM) decreased in 4 patients (3 AML, 1 MM) while a slight increase occurred in 1 patient (MM). PRAME (PB) decreased at week 4 for 2 patients treated at the highest dose but increased thereafter.

Conclusions: In heavily pre-treated patients with advanced myeloid and lymphoid neoplasms, treatment with MDG1011 was generally safe and well tolerated up to $5x10^6$ PRAME-specific TCR-T cells/kg. Clinical observations were corroborated by persistence of MDG1011 cells in PB and reductions in PRAME mRNA levels in PB and/or BM.

Clinical Trial Registry: https://clinicaltrials.gov/ct2/show/NCT03503968

Disclosure: Simone Thomas, Medigene is the Sponsor of the clinical trial

Martin Wermke, Nothing to declare

Vladan Vucinic, Nothing to declare

Eva Wagner-Drouet, Travel grant: MSD,Janssen, Medac; advisory board: Kite Gilead, Novartis, BMS

Andreas Mackensen, Honoraria by Gilead/KITE, BMS/Celgene, Novartis, Miltenyi Biomedicine

Robert Zeiser, Honoraria by Novartis, Sanofi, Incyte and MNK

Gesine Bug, Honoraria by Novartis, Pfizer, Eurocept, Kite/Gilead, BMS/Celgene and Jazz

Michael Schmitt, Apogenix: Funding for collaborative research; BMS: Financial support of educational activities and conference, travel grants. Co-PI of clinical trials on CAR-T cells; Hexal: Financial support for research on biosimilars, travel grants; Kite/Gilead: Financial support of educational activities and conference, travel grants. Co-PI of clinical trials on CAR-T cells; MSD: Ad board member, PI of clinical trials on letermovir; Novartis: Collaborative research grant. Co-PI of clinical trials on CAR-T cells; TolerogenixX, Heidelberg: Co-Founder and shareholder.

Petra Prinz, Medigene is the Sponsor of the clinical trial

Dolores Schendel, Medigene is the Sponsor of the clinical trial

Kai Pinkernell, Medigene is the Sponsor of the clinical trial

René Goedkoop, Medigene is the Sponsor of the clinical trial.

5 - Cellular Therapies other than CARs

P124

HIGH-THROUGHPUT ASSESSMENT OF T CELL RECEPTOR SEQUENCES WITH SPECIFICITY TO THE MOST COMMON PATHOGENS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Chrysoula Pantazi[1,2,3], Elisavet Vlachonikola[2,3], Anna Vardi[1], Eleni Zotou[1,3], Kyriakos Koukoulias[1], Ioanna Vallianou[1], Maria Giannaki[1], Zoe Boussiou[1], George Karavalakis[1], Apostolia Papalexandri[1], Minas Yiangou[3], Ioanna Sakellari[1], Anastasia Chatzidimitriou[2,4], Anastasia Papadopoulou[1], Evangelia Yannaki[1,5]

[1]Gene and Cell Therapy Center, "George Papanikolaou" Hospital, Thessaloniki, Greece, [2]Institute of Applied Biosciences (INAB), Centre for Research and Technology Hellas (CERTH), Thessaloniki, Greece,

[3]School of Biology, Development and Molecular Biology, Aristotle University of Thessaloniki, Thessaloniki, Greece, Karolinska Institute, Stockholm, Sweden, [5]Hematology, University of Washington, Seattle, United States

Background: Adoptive immunotherapy with pathogen-specific T cells (pSTs) recognizing a broad range of pathogen-derived peptides through their native T-cell receptor (TR) has successfully emerged as an alternative treatment of opportunistic infections post allogeneic hematopoietic cell transplantation. However, the TR repertoire of ex vivo generated pSTs for immunotherapy has not yet been fully elucidated.

Methods: Herein, we analysed the TR beta-chain gene repertoire by next-generation sequencing (NGS) of two distinct immunotherapy products, i) tri-virus specific T cells (*tri-VSTs*) targeting cytomegalovirus (CMV), Epstein Barr virus (EBV) and BK virus (BKV) and ii) pentavalent-specific T cells (*penta-STs*) additionally targeting adenovirus (ADV) and the fungus *Aspergillus fumigatus* (AF), which are under evaluation in phase I/II clinical trials (EudraCT: 2014-004817-98/2020-004725-23, respectively). GMP-grade tri-VSTs and penta-STs were manufactured after exposure of peripheral blood mononuclear cells (PBMCs) from immunocompetent donors to CMV, EBV, BKV ± AdV and AF overlapping peptides and a 10-day culture. Specificity of donor-derived cell products and patient-derived PBMCs was assessed by IFN-γ Elispot. TCRB sequencing was performed in the whole T cell products (tri-VSTs $n = 2$, penta-STs $n = 4$), their corresponding pathogen-specific cell subsets ($n = 26$) post immunomagnetic IFN-γ enrichment and in patient PBMCs ($n = 26$). Immunogenetic analysis was performed by RT-PCR amplification of TRBV-TRBD-TRBJ rearrangements according to the BIOMED-2 protocol and paired-end NGS (Miseq/NextSeq). The NGS sequences after length and quality filtering were submitted to IMGT/HighVQUEST for annotation. Metadata analysis and clonotype computation (TRB rearrangements using the same TRBV gene and identical CDR3 amino acid sequence) were based on a validated purpose-built bioinformatics platform (*tripr*).

Results: Tri-VSTs and penta-STs provided a diverse TR repertoire consisting of 6,580-33,863 unique clonotypes/sample (median: 22,530) and demonstrated high clonality levels with the median frequency of the major clonotype being 6.48% (range: 2.23%-20.7%). The clonotypes identified in the enriched subpopulations were subjected to strict filtering: i) ≥10 read counts, ii) higher frequency in the enriched subpopulations over the unselected product as defined by the greater frequency (fold increase) of each post-enrichment clonotype than the median fold increase of all enriched clonotypes. The applied criteria resulted in 9,799 clonotypes, of which 8,749 were present in a single specific-cell fraction, arguably suggesting that they are pathogen-specific (CMV-specific: 2,768, EBV-specific: 1,763, BKV-specific: 2,003, ADV-specific: 1,363, Asp-specific: 852). Indeed, several of those identified virus-specific clonotypes could be tracked in vivo in two patient-derived PBMCs up to 15 weeks post tri-VST infusion with ranging frequencies 0.002%-12.7% (Pt1: 32 CMV-specific, 25 EBV-specific and 29 BKV-specific & Pt2: 20 CMV-specific, 31 EBV-specific and 31 BKV-specific clonotypes). Importantly, their presence in vivo was correlated with a decrease in the corresponding viral load, an increase in the frequency of circulating virus-specific T cells and ultimately, clinical response.

Conclusions: Overall, our findings elucidate the diverse immunogenetic profile of ex vivo generated pSTs, identify potential pathogen-specific clonotypes conferring protection against infections and provide a novel method to track in vivo the pSTs. Prospectively, the identification of optimal TRs that mediate clinical responses may serve as a stratification tool for patients at risk for suboptimal responses and help to select the best candidates for adoptive immunotherapy.

Clinical Trial Registry: EudraCT: 2014-004817-98, 2020-004725-23

Disclosure: Funding for this project was provided by Research, Technology Development and Innovation (RTDI) State Aid Action "RESEARCH - CREATE - INNOVATE" (T2EΔK-02437).

5 - Cellular Therapies other than CARs

P125

A CLINICAL TRIAL OF ADOPTIVE IMMUNOTHERAPY OF STEROID-REFRACTORY CHRONIC GVHD WITH MULTIPLE INFUSIONS OF CRYOPRESERVED DONOR-DERIVED REGULATORY T (TREG) CELLS

Mario Arpinati[1], Gabriella Chirumbolo[2], Martina Barone[2], Simonetta Rizzi[1], Barbara Sinigaglia[1], Tiziana Montemurro[3], Cristiana Lavazza[3], Emanuela Sergio[4], Marie-Laure Yaspo[5], Francesco Barbato[1], Michele Dicataldo[1], Enrico Maffini[1], Michele Cavo[1,2], Francesca Bonifazi[1]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [2]Università di Bologna, Bologna, Italy, [3]IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, [4]AUSL Bologna, Bologna, Italy, [5]Max Planck Institute for Molecular Genetics, Berlin, Germany

Background: Steroid refractory chronic GVHD has a poor prognosis, with only about 10-20% patients stopping immunosuppressive within 4 years. Chronic GVHD has been associated with selectively delayed Treg cell recovery, leading to the hypothesis that the infusion of healthy Treg cells may improve their recovery and possibly ameliorate chronic GVHD symptoms.

Methods: In the current trial (NCT02749084) we treated patients with steroid refractory chronic GVHD with multiple infusions of cryopreserved GMP-purified Treg cells. Each patient received three infusions of Treg cells each one month apart. The study had a dose escalating 3 + 3 design, with three dose levels (0.5, 1 and 2x10e6/kg total dose, respectively) with safety as the primary end point. Treg cells were isolated in a two-step procedure by immunomagnetic depletion of CD8+ and CD19+ cells followed by enrichment of CD25+ cells.

Results: Eleven Treg products have been prepared. Median purity was 94% (IQ 93-96%), 90% (IQ 90-94%) and 71% (IQ 66-77%) as based on identification of CD4 + CD25 +, CD4 + CD25 + CD127- and CD4 + CD25 + CD127-foxp3+ cells, respectively. No contamination (percentage <0.1%) was observed by CD19 +, CD8+ and CD56+ cells. Median contamination by effector T cells (defined as CD4 + CD25 + CD127+ cells) and by Th17 cells (defined as CD161 + CD196 +) was 11% and 1.6%, respectively, resulting in the infusion of 2.8x10e4/kg effector T cells and 3.9x10e3/kg Th17 cells. Nine out of 11 products have received at least one infusion of purified T regs, 3 at the first dose level (0,5x10e5 Treg/kg total dose), and 6 at the second dose level (10e6 Treg/kg total dose). No infusion related events were observed. One patient developed a DLT (CMV pneumonia) one month after the last infusion. 5 more SAEs were observed during the 12 months predetermined observation period but were considered unrelated to the infusion. Importantly, no acute GVHD or early flares of chronic GVHD were observed. Disease responses observed in the 8 evaluable patients who received all three Treg infusions are reported in Table 1. Interestingly, 5 out patients were able to reduce the dose of prednisone at the 12 month time point, with two patients being able to stop prednisone. While Treg numbers and percentages did not change significantly during the study, NGS analysis of TCR sequences confirmed the persistence of the infused Treg clones for up to 12 months after treatment.

Table 1: NIH-based evaluation of response in the 8 patients who received three T reg infusions.

3 months				
	CR	**PR**	**SD**	**Prog**
Global	0	7 (87%)	1 (13%)	0
Skin	0	2 (33%)	4 (67%)	0
Mouth	0	2 (33%)	4 (67%)	0
Eyes	0	2 (33%)	3 (67%)	0
Lung	0	0	6 (100%)	0
12 months[a]				
	CR	PR	SD	Prog
Global	0	5 (71%)	0	2 (29%)
Skin	0	3 (50%)	3 (50%)	0
Mouth	1 (25%)	2 (50%)	2 (25%)	0
Eyes	1 (15%)	1 (15%)	5 (70%)	0
Lung	0	0	4 (71%)	2 (29%)

[a]one of the eight patients missed the 12 month follow up visit due to worsening clinical conditions
abbreviations: CR: complete response; PR: partial response; SD: stable disease; Prog: progression.

Conclusions: Treatment of patients with steroid-refractory chronic GVHD with purified cryopreserved donor T regs appears feasible and safe and may improve disease severity in some patients.

Clinical Trial Registry: NCT02749084

Disclosure: The study has received funding from the European Union H2020 research and innovation programme under grant agreement No 643776 ("Tregeneration")

The authors have no conflict of interest related to the present work.

5 - Cellular Therapies other than CARs

P126

CLINICAL APPLICATION OF DIRECTLY SORTED HAPLOIDENTICAL T REGULATORY AND MEMORY T CELLS IN PATIENTS WITH REFRACTORY GVHD AND VIRAL INFECTIONS

Viktoria Vedmedskia[1], Dmitry Pershin[1], Mariya Fadeeva[1], Elena Kulakovskaya[1], Tatiana Sozonova[1], Anna Vasilieva[1], Maria Klimentova[1], Svetlana Radygina[1], Maria Dunaikina[1], Larisa Shelikhova[2], Dmitry Balashov[1], Michael Maschan[1]

[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation, [2]Dmitry Rogachev National Medical Research Center Of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: The most significant non-relapse cause of morbidity and mortality after HSCT are graft-versus-host disease (GvHD) and viral infections, commonly associated with prolonged pharmacological immune suppression (IST). Direct sorting of donor Treg cells and memory T cells for adoptive transfer is being developed as a cell therapy approach to treat patients with GVHD, refractory to IST and concomitant viral infections. Combination of immunomagnetic and flow-based sorting can be used to create highly pure populations with defined composition. We report here on the first compassionate use of this approach.

Methods: Six patients after allogenic HSCT (TCRab/CD19 depletion) with IST-refractory chronic GvHD received infusions of Treg cells. Five of them had ongoing viral infections and received Infusions of memory T cells.

Cells products were obtained from haploidentical donors according to good manufacturing practice standard. Sorting of Treg cells was performed by MACSQuant® Tyto® Cell Sorter after pre-enrichment of CD25+ cells with the CliniMACS Prodigy from the apheresis product. Treg cell was defined by CD4 + CD25 + CD127- markers. Sorting of memory T cells (all CD4 + /CD8+ cells except CD45RA + CD197+ population) was performed from PBMC obtained with BD Vacutainer® CPT™ Mononuclear Cell Preparation Tube. Infusion dose information and composition of cells products are given in the table. The median time after HSCT to the moment of infusion was 9 month (min 120 days, max 1 year). Viremia was monitored by PCR. Detection and monitoring of virus-specific donor T cells was performed by IFNγ ELISpot assay. CD4+FoxP3+-cells persistence in the blood was monitored every week by FACS. Additionally, expression of CTLA-4 and heterogeneity within the memory Treg compartment (CD197/CD45RA) were assessed. Before the infusion IST was withdrawn and one infusion of cyclophosphamide at 400 mg/m^2 was given.

Results: Clinical response to the treatment was observed in all 6 patients. One patient succumbed to septic event four weeks after the infusion of Treg/Tmemory. No adverse effects and decline of clinical condition because of the alloreactive lymphocytes infusion were observed in 5 patients. FoxP3+cells appearance was detected in 4 patients on day 7 and maximum level of FoxP3+cells (7-32 cells/mkl) was achieved on the 21st day after infusion in all patients. The Treg population was represented mainly by highly proliferating T effector memory phenotype (CD197-CD45RA-). Distinguishing feature of Treg cells persistence was stable high levels of FoxP3 expression (MFI median in patients was 6903 (4503–9318), MFI median in healthy controls was 2797 (2051–4139), $p < 0.0001$) and CTLA-4 expression (MFI median in patients was 2740 (1677-16033), MFI median in healthy controls was 1275 (810-2213), $p = 0.0022$).

Clinical and laboratory indicators are presented in the Table:

Conclusions: Our first experience confirms the feasibility of direct sorting in the GMP-grade conditions of highly pure populations of regulatory and memory T cells by means of immunomagnetic and flow-based approach. Infusions were associated with clear increment of Treg cells in the blood and meaningful clinical responses. Reduction of GVHD manifestations were correlated with stable Treg cells persistence and high level of FoxP3 expression throughout the period of monitoring.

Disclosure: M.Maschan recieved lecturer's fee from Miltenyi Biotec.

5 - Cellular Therapies other than CARs

P127

PATIENT-TAILORED ADOPTIVE IMMUNOTHERAPY WITH EBV-SPECIFIC T CELLS FROM STEM CELL AND THIRD PARTY DONORS

Britta Maecker-Kolhoff[1], Agnes Bonifacius[1], Britta Lamottke[1], Sabine Tischer-Zimmermann[1], Rebecca Schultze-Florey[1], Lilia Goudeva[1], Hans-Gert Heuft[1], Lubomir Arseniev[1], Rita Beier[1], Gernot Beutel[1], Gunnar Cario[2], Birgit Fröhlich[3], Johann Greil[4], Leo Hansmann[5], Justin Hasenkamp[6], Michaela Höfs[7], Patrick Hundsdoerfer[5], Edgar Jost[8], Kinan Kafa[9], Oliver Kriege[10], Nicolaus Kröger[11], Stephan Mathas[5], Roland Meisel[12], Michaela Nathrath[13,14], Mervi Putkonen[15], Sarina Ravens[1], Hans Christian

Pt	Age at therapy	Indication for HSCT	Time after HSCT	f-up after cell therapy, days	GVHD	Viral infection	clinical effects	T reg dose /kg	% FoxP3	T memory dose /kg	expansion T reg, # *fold (+28 vs. day before)*	max Fox P3, % of CD4
P1	8 years	Aplastic anemia	4 m	120	cGvHD	yes	+++	5,00E + 05	91	1,00E + 05	x8	11
P2	3 years	APDS with PIK3D mutation	1 year	90	cGvHD	yes	++	5,00E + 05	94.9	1,00E + 05	x24	21
P3	4 years	AML	4 m	90	cGvHD	no	+++	5,00E + 05	95.9	-	x7	3
P4	13 years	ALL, B-I	1 year	60	cGvHD	yes	+/- Septic event	2.50E + 05	93.9	1,00E + 05	x2	16
P5	4 years	SCID with ADA deficiency	5 m	28	cGvHD	yes	++	5,00E + 05	94.8	1,00E + 05	x8	56
P6	7 years	neuroblastoma	1 year	28	cGvHD	yes	++	5,00E + 05	95.8	1,00E + 05	x4	16

Reinhardt[7], Elisa Sala[16], Martin Sauer[1], Clemens Schmitt[5], Roland Schroers[17], Nina K. Steckel[7], Ralf Ulrich Trappe[18], Mareike Verbeek[14], Daniel Wolff[19], Rainer Blasczcyk[1], Britta Eiz-Vesper[1]

[1]Hannover Medical School, Hannover, Germany, [2]University Hospital Schleswig-Holstein, Kiel, Germany, [3]University Children's Hospital Muenster, Muenster, Germany, [4]University Children's Hospital Heidelberg, Heidelberg, Germany, [5]Charité - Universitätsmedizin Berlin, Berlin, Germany, [6]University Medicine Göttingen, Göttingen, Germany, [7]University Hospital of Essen, Essen, Germany, [8]University Medical Center RWTH Aachen, Aachen, Germany, [9]Martin Luther University Halle-Wittenberg, Halle, Germany, [10]Johannes Gutenberg-University Medical Centre, Mainz, Germany, [11]University Medical Center Hamburg Eppendorf, Hamburg, Germany, [12]Heinrich Heine University, Düsseldorf, Germany, [13]Klinikum Kassel, Kassel, Germany, [14]Technical University Munich, Munich, Germany, [15]Turku University Hospital, Turku, Finland, [16]University Hospital of Ulm, Ulm, Germany, [17]Knappschaftskrankenhaus University Hospital, Bochum, Germany, [18]Ev. Diakonie-Krankenhaus, Bremen, Germany, [19]University Hospital of Regensburg, Regensburg, Germany

Background: Immunosuppressed patients are at risk of virus-induced complications, among which EBV-associated lymphoproliferative disorders represent the most frequent malignant complication. Adoptive transfer of EBV-specific T cells can restore specific immunity, leads to control of EBV replication and regression of EBV-associated lymphoproliferation. Here, we provide data of consecutive runs of a personalized T-cell manufacturing program evaluating donor, patient, T-cell product and outcome data.

Methods: Patient-tailored clinical-grade EBV-specific cytotoxic T-lymphocyte (EBV-CTL) products from stem cell donors (SCD), related third party donors (TPD) or unrelated TPD from the allogeneic T-cell donor registry (alloCELL) established at Hannover Medical School were manufactured by immunomagnetic selection using CliniMACS Plus or Prodigy and EBV PepTivators EBNA-1 and Select. Consecutive manufacturing processes were evaluated from quality control data and patient outcome and side effects were retrieved by retrospective chart analysis. EBV load was quantified by whole blood qPCR analysis according to local standards. EBV-specific T cells in patient blood were measured by interferon-γ ELISpot analysis.

Results: Forty clinical-grade EBV-CTL products from SCDs, related TPDs or unrelated TPDs were generated for 37 patients with and without transplantation history within a median time-frame of 5 days from donor identification to product manufacturing. Regarding quality of T-cell product no significant differences were observed between SCD and TPD products regarding cell number, product composition, and cell purity. 34 patients received 1-14 EBV-CTL products (fresh and cryopreserved) with a median cell number of 2.5x10e4 CD3+ cells/kg body weight. EBV-CTL transfer led to complete response in 19 of 30 patients who were evaluated for clinical response. In HSCT patients, complete response (CR) rate was slightly higher in patients receiving EBV-CTL from SCD (9/10 CR) than from TPD (5/11 CR). The majority of patients showed a decline in EBV load after transfer. No infusion-related toxicity was reported. Three of 10 patients with SCD-derived CTLs developed de novo GvHD after transfer, two of which in context with unmanipulated donor lymphocyte infusion (n = 1) and forced reduction of immunosuppression (n = 1). No de novo GvHD occurred in the TPD CTL group. EBV-specific T cells in patients' blood were detectable in 16/18 monitored patients (89%) after transfer and detection correlated with clinical response.

Conclusions: In conclusion, personalized clinical-grade manufacturing of EBV-CTL products from SCD, related TPDs or unrelated TPD is feasible and their adoptive transfer is effective and safe in the majority of patients. While SCD-derived CTL appeared to be slightly more effective in inducing CR, TPD CTL exhibited no de novo GvHD development. Prospective clinical trials are needed to further explore the potential of SCD and TPD derived EBV-CTL adoptive therapy.

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to declare.

5 - Cellular Therapies other than CARs

P128

COMBINED CAR-NK AND CAR-GD T CELLS AS A THERAPEUTIC TOOL POST ALLO-SCT

Nassim Salem[1,2,3], Anne-Sophie Chretien[1,2,4], Marie-Sarah Rouviere[1,2], Amira Ben Amara[1], Alexandrine Faivre[1], Anne-Charlotte Le Floch[1,2,4], Laurent Gorvel[1], Armelle Goubard[1], Rémy Castellano[1,2], Geoffrey Guittard[1], Yves Collette[1,2], Jacques Nunès[1], Daniel Olive[1,2,4], Raynier Devillier[1,2,4]

[1]Centre de Recherche en Cancerologie de Marseille, Marseille, France, [2]Institut Paoli Calmettes, Marseille, France, [3]Faculté de Pharmacie, Marseille, France, [4]Faculté de Médecine, Marseille, France

Background: Allogeneic hematopoietic stem cell transplantation (Allo-SCT) is the main curative treatments for Acute Myeloid Leukemia (AML). While procedure related mortality related has significantly decreased over the 2 past decades, relapse of AML remains the major challenge, occurring in 20-50% according to disease risk. While T cells have a major role in the (graft versus leukemia) effect, post allo-SCT T cell-based immunomodulation is appealing to decrease relapse. However, T cells are also highly involved in graft-versus host disease (GVHD), limiting the clinical use of such strategies. As an alternative source for post allo-SCT immunomodulation, NK cells and Tγδ lymphocytes (γδT) are

appealing because they can mediate a GVL effect without triggering GVHD. We propose here an expansion process, to generate a clinically compatible cell therapy product composed of both NK cell and gd T cells for future application after allo-SCT as well as CAR generation.

Methods: From healthy donor peripheral blood mononucleate cells, NK cells and γδT are expanded during 14 days using feeder cell support. The phenotypic changes between are assessed using mass cytometry. Following a co-culture with leukemic blasts, cytotoxicity, degranulation and cytokine production were measured by flow cytometry. As for the in vivo study a luciferase-expressing leukemic cell line was injected to NSG mice, and a bioluminescence and clinical follow-up was performed. Lentiviral transduction was used to generate CAR-NK/CAR-γδT.

Results: The process allowed us to achieve a 1000-fold expansion for both NK cells and γδT within 14 days. Conventional ab T cells represented systematically less than 5%. Both NK cells and γδT acquired a hyperactivated phenotype especially, with an increased expression of NKG2D and BCL-2 in both cell types and NKp30 in NK cells, which led to major degranulation and cytokine production abilities toward leukemic blaststogether with a significant cytotoxicity leading up to 80% of apoptotic blasts in 1h in vitro. In vivo, we showed a tumor charge decrease together with less circulating blasts (29 vs 5 blasts/µL of blood). Also, mice receiving combined NK and γδT cells displayed a significant prolonged survival compared with untreated controls, without developing GVHD.

Moreover, the genetic editing led to a combined αCD19 CAR-NK and CAR-γδTproduct with enhanced degranulation capacities against $CD19^{pos}$ targets.

Conclusions: We set up a cellular immunotherapy product with highly activated NK and γδT cells in large amount, possibly compatible with future clinical application in the context of allo-SCT, by inducing a high anti leukemic effect without triggering GVHD. Moreover, this expansion process is compatible with genetic manipulation, opening perspectives of future improvement of the cell product.

Disclosure: D.O. is a cofounder and shareholder of Imcheck Therapeutics, Alderaan Biotechnology, Emergence Therapeutics, and Stealth IO.

5 - Cellular Therapies other than CARs

P129

FIRST IN HUMAN CLINICAL RESPONSES AND PERSISTENCE DATA ON TEG001: A NEXT GENERATION OF ENGINEERED ALPHA/BETA T-CELLS TARGETING AML AND MM WITH A GAMMA9DELTA2 TCR

Moniek de Witte[1], Jojanneke Scheepstra[1], Naomi Weertman[1], Annet Daudeij[1], Lotte van der Wagen[1], Rimke Oostvogels[1], Colin de Haar[1], Henk-Jan Prins[1], Carli Bartels-Wilmer[1], Willem Dohmen[1], Inez Johanna[1], Zsolt Sebestyen[1], Jurgen Kuball[1], Trudy Straetemans[1]

[1]University Medical Center Utrecht, Utrecht, Netherlands

Background: γδT cells target malignant cells by sensing cancer mediated metabolic changes via their γδTCR. We have developed the TEG001 cell product, which are αβ T cells expressing the high affinity Vγ9Vδ2 TCR clone 5. TEG001 showed tumor reactivity towards a range of hematological malignancies. Here we present the results of dose level 1 and 2, addressing the safety and tolerability of TEG001 in patients with acute myeloid leukemia (AML) or multiple myeloma (MM).

Methods: The TEG001 study is a single center, investigator-initiated study, with a standard 3 + 3 dose escalation design. Cohorts receive a single infusion of $1x10^6$ TEG001 cells/kg (dose level 1), $3x10^6$ TEG001 cells/kg (dose level 2) and $1x10^7$ TEG001 cells/kg (dose level 3). Relapsed/refractory AML/high risk MDS and MM patients were eligible. AML patients with > 30% blasts or circulating blasts required bridging therapy. TEG001 cells were produced as previously described (doi: 10.3389/fimmu.2018.01062). Conditioning consisted of fludarabine i.v. 25 mg/m^2 (day -4 to -2) and cyclophosphamide i.v. 900 mg/m^2 (day -2). Pamidronate (PAM) (30 mg i.v.) was administered on day 0 and 28 to propagate TEG001 activity. TEG001 cells were measured in peripheral blood by flowcytometry. The primary endpoint was the development of dose-limiting toxicities (DLTs) to determine the maximum tolerated dose. Main criteria for reaching DLTs were TEG001 related adverse events (AEs) requiring ventilator support and grade 4 AEs not related to the underlying disease. AEs contributable to cytokine release syndrome (CRS) and/or immune effector cell-associated neurotoxicity syndrome (iCANS) grade 3 responding to tocilizumab and/or steroids were not defined as DLT.

Results: Fourteen patients were included. Eight patients were not evaluable for the primary endpoint (insufficient response to bridging therapy (N = 3); abrogated TEG001 production (N = 2); TEG001 product not meeting the target dose (N = 2); COVID-19 hospital restrictions (N = 1)). In the six patients infused in dose level 1 and 2 (AML N = 5; MM N = 1), no DLTs were observed. No AEs ≥ grade 3 related to TEG001 were observed. Patient 16 (dose level 2), who received PAM according to the protocol on day 0 and 28, developed seizures at day 29 and 30. The seizure responded well to levetiracetam and no other neurological signs associated with iCANS were observed. No infections or abnormalities in the spinal fluid or brain imaging were identified and connection of the seizure to TEG001 remained inconclusive. In all patients TEG001 cells were detectable in peripheral blood. In dose level 1, patient 7 had stable disease (SD, duration 3M). In dose level 2, patient 9 had SD (duration 12M) and patient 16, who had 28% bone marrow blasts prior to TEG001 infusion showed full hematological recovery and achieved a complete remission (CR, duration 6M).

Conclusions: TEG001 cells are well-tolerated at the first 2 dose levels tested. TEG001 cells show persistence up to day 56. In the 5 AML patients, we observed 1 complete remission and 2 patients with stable disease. The TEG001 study is recruiting patients for dose level 3.

Clinical Trial Registry: NL6357

Disclosure: Research Grants 2019 KWF 12586 to MdW, JK, TS; KWF 13493 to MdW, JK.

JK is inventor on multiple patents dealing with gdTCRs, ligands, isolation strategies of engineered immune cells. JK is cofounder and shareholder of Gadeta (www.gadeta.nl). JK received research support from Gadeta.

5 - Cellular Therapies other than CARs

P130

DONOR-DERIVED ANTI-LEUKEMIA CTLS FOR THE CONTROL OF LEUKEMIA RELAPSE IN HIGH-RISK PEDIATRIC PATIENTS GIVEN HAPLOIDENTICAL HSCT

Matteo Tanzi[1], Enrica Montini[1], Agnese Rumolo[1,2], Patrizia Comoli[1], Antonia Moretta[1], Giovanna Giorgiani[1], Santina Recupero[1], Tommaso Mina[1], Gloria Acquafredda[1], Jessica Rotella[1], Stella Boghen[1], Marco Zecca[1], Daniela Montagna[1,2]

[1]Foundation IRCCS Policlinico San Matteo, Pavia, Italy, [2]University of Pavia, Pavia, Italy

Background: Adoptive cell therapy based on the infusion of donor-derived cytotoxic T lymphocytes (CTLs) able to recognize patients' leukemia blasts (LB) is a promising approach to prevent or control leukemia relapse after allogeneic hematopoietic stem cell transplantation (HSCT). The success of this approach mainly depends on the ability to ex vivo generate high quality donor-derived anti-leukemia CTLs in compliance with Good Manufacturing Practice.

Methods: We have developed a procedure for generating large numbers of donor-derived CTLs directed against LB, through stimulation of CD8-enriched T lymphocytes with IFN-Dendritic Cells (DC) pulsed with apoptotic LB in the presence of IL-12, IL-7, IL-15 and IFN alfa2b during priming phase. After priming phase, CTLs underwent one or two rounds rapid antigen independent expansion in the presence of IL-2, IL-15, OKT3 and irradiated allogeneic feeder cells. Using this approach, 47 batches of PMTC were produced, in the Cell Factory of Fondazione IRCCS Policlinico San Matteo, for 20 pediatric patients given haploidentical HSCT for high-risk acute leukemia. The quality of each batch was evaluated in terms of microbiological safety and immunological efficacy.

Results: Variable numbers of CTLs were produced, depending from patients' weight and numbers of infusions they have received. Expansion rate was very homogeneous and there were no significant differences between CTLs obtained after the first rapid expansion round (105 ± 21 fold the number of cells seeded at the beginning of the culture) or after the second round (118 ± 15 fold). Microbiological quality controls (CQ) demonstrated that all batches were sterile, were free of mycoplasma and adventitious viruses, and conformed to acceptable endotoxin levels. Biological CQ, including cell viability, identity, phenotype and potency were in compliance with the defined cut off. Fresh anti-leukemia CTLs displayed high percentages of cell viability (mean: 89% ± 6%), that were maintained after thawing (mean 80% ± 5%). The majority of effector cells were CD3 + /CD8+ (mean 73%, ± 5%), and functional evaluation demonstrated that all batches of CTLs were able to lyse patients' LB (range 19-74% of specific lysis at effector:target ratio of 25:1), while the lysis against patients' derived normal cells was lower (range 9-28% of specific lysis at the same ratio). Anti-leukemia CTLs were also able to secrete sizeable amounts of IFN gamma and TNF alfa in response to patients' LB. So far, six patients received CTLs, on a compassionate base, for the treatment of post-HSCT molecular or hematological relapse, while six patients were enrolled in a phase I/II trial based on infusion of escalating dose of CTLs (starting from 5x10e4/kg up to 8x10e6/kg) every three weeks, for the prevention of leukemia recurrence. No severe adverse reactions, and no grade 2-4 toxicities, including occurrence of severe GVHD were recorded during follow-up. Preliminary results demonstrated that anti-leukemia CTLs might have a role in both prevention and treatment of post-haplo-HSCT recurrence, leading to long-term remission.

Conclusions: These results demonstrated that our protocol is highly reproducible and allows the generation of large numbers of safe and functional donor-derived anti-leukemia CTLs for the prevention/treatment of leukemia recurrence in high-risk pediatric patients.

Disclosure: Nothing to declare.

5 - Cellular Therapies other than CARs

P131

A SIX-YEAR RETROSPECTIVE ANALYSIS OF THE USE OF DONOR LYMPHOCYTE INFUSION IN A NATIONAL ALLOGENEIC TRANSPLANT CENTRE

Conor Browne[1], Christopher Armstrong[1], Fiona Lynott[1], Greg Lee[1], Nicola Gardiner[1], Carmel Waldron[1], Robert Henderson[1], Larry Bacon[1], Elizabeth Vandenberghe[1], Nina Orfali[1], Catherine M. Flynn[1], Eibhlin Conneally[1], Patrick J. Hayden[1]

[1]St James' Hospital, Dublin, Ireland

Background: Donor lymphocyte infusion (DLI) can be given prophylactically (Pro-DLI) in the setting of complete donor chimerism (DC) to prevent relapse, pre-emptively (Pre-DLI) for mixed chimerism (MC) or positive minimal residual disease (MRD), or therapeutically (T-DLI) as treatment for relapsed disease post allogeneic stem cell transplant (AlloSCT).

Methods: The records of consecutive AlloSCT recipients who received DLI between 1/1/2015 and 31/12/2020 were retrieved from the St. James's Hospital transplant database. Responses to DLI, rates of graft versus host disease (GVHD), disease free survival (DFS) and overall survival (OS) were assessed. Statistical analysis was performed using SPSS version 28 and STATA.

Results: 472 AlloSCT's occurred and 106 (22%) patients subsequently received DLI. Clinical details are shown in Table 1. Of these 106 patients, 16 (15%) received Pro-DLI; 8 for high risk disease with complete DC and 8 as part of the FLAMSA transplant protocol, 57 (54%) received Pre-DLI; 55 for MC and 2 for positive MRD assays and 33 (31%) received T-DLI. 204 DLI doses were infused. The median follow-up (FU) from first DLI was 29 months. Patients received a median of 2 (1-8) doses. The median interval from AlloSCT to the first DLI dose was 222 days. The median first dose of DLI was 0.32 (0.1-0.59) x10^7 CD3+ cells/kg. The median overall dose of DLI was 0.5 (0.1-5.16) x10^7 CD3 cells/kg. The median interval between DLI doses was 73 days.

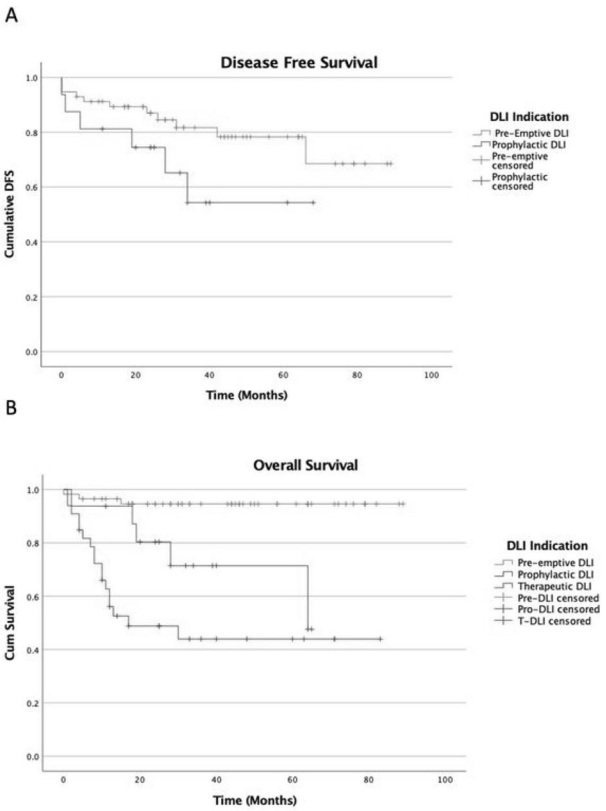


Table 1.

Patient Characteristics	N=106	Transplant Characteristics	N=106
Gender no. (%)		**Conditioning Regimen no (%)**	
Male	61 (58)	Flu/Bu/ATG	46 (43)
Female	45 (42)	Flu/Mel/Alemtuzumab	19 (18)
Median Age at DLI 1 years (range)	57 (22-70)	BEAM Alemtuzumab	14 (13)

48 (45%) DLI recipients developed GVHD following DLI. 41 (39%) patients developed acute GVHD (aGVHD); 12 (11%) Grade I and 29 (27%) Grade II-IV aGVHD. The median time to onset of aGVHD post-first DLI was 56 days. 22 (21%) developed chronic GVHD.

In the Pro-DLI cohort (n = 16), 5 (33%) patients relapsed post DLI at a median FU of 29 months.

In the Pre-DLI cohort (n = 57), DC rose in 51 (89%) patients. The median DC prior to DLI was 60% and 48 (84%) achieved complete DC post-DLI. 10 (18%) patients relapsed after Pre-DLI. The median time to relapse in both the Pro-DLI and the Pre-DLI cohorts was 13 months. In the T-DLI cohort (n = 33), 22 (67%) responded to DLI (complete remission (CR), partial remission or complete DC) of which 16 (48%) achieved CR. Of DLI responders, 11 (50%) relapsed at a median of 9 months.

DFS in the Pro-DLI and the Pre-DLI cohorts (Graph 1(A)) is estimated at 87.6% at 2 years and didn't differ significantly between these groups (p = 0.09). OS in all 106 DLI recipients was estimated at 76.8% at 2 years (Graph 1(B)), survival being poorest at 44% in T-DLI at 30 months (p < 0.001).

In a univariate Cox regression analysis, response to DLI was a positive predictor for OS (p < 0.001), relapsed disease a negative predictor (p < 0.001) and aGVHD was not significantly associated with OS (p = 0.434).

Table 1. Patient Characteristics

	N = 106	Transplant Characteristics	N = 106
Gender no. (%)		**Conditioning Regimen no (%)**	
Male	61 (58)	Flu/Bu/ATG	46 (43)
Female	45 (42)	Flu/Mel/Alemtuzumab	19 (18)
		BEAM Alemtuzumab	14 (13)
Median Age at DLI 1 years (range)	57 (22-70)	Bu/Cy	9 (9)
Disease Group: no. (%)		Cy/TBI	3 (3)
AML	41 (39)	FLAMSA-Bu	14 (13)
MDS/MPD	26 (25)	Other	5 (5)
ALL			
NHL	4 (4)		
HL	28 (26)		
CLL	6 (6)	**Disease Status at Transplant no. (%)**	
	1 (1)	CR 1/2	62 (58)
		CR 3/4	6 (6)
		Partial Remission	22 (21)
Co-Morbidity Index no. (%)		Relapse/Refractory	4 (4)
HCT-CI 0-1	65 (61)	Unknown	12 (11)
HCT-CI > / = 2	41 (39)		
Associated Treatment with DLI		**GVHD Prophylaxis no. (%)**	
Pro/Pre-DLI no. (% of N = 73)	7 (10)	Ciclosporin	78 (74)
T-DLI no. (% of N = 33)	31 (94)	Tacrolimus	28 (26)

Conclusions: Pro-DLI and Pre-DLI resulted in complete DC in >80% of patients and a DFS estimate of 87.6% at 2 years. T-DLI, in combination with other agents, resulted in CR in 48% and an OS estimate of 44% at 2.5 years.

Disclosure: Nothing to Declare.

5 - Cellular Therapies other than CARs

P132

VIRUS SPECIFIC T-CELLS AGAINST ADV, EBV AND CMV IN INFECTED MULTI-TREATED POST-HSCT PATIENTS

Esther Hazane Leroyer[1], Danièle Bensoussan[1], Maud D'Aveni[1], Jean Hugues Dalle[2], Nadine Petitpain[1]

[1]CHRU Nancy, Vandoeuvre Les Nancy, France, [2]Hôpital Robert Debré APHP, Paris, France

Background: Post-transplant viral (adenovirus-ADV, cytomegalovirus-CMV or Epstein Barr virus-EBV) replication/disease remains a major cause of mortality in the context of allogeneic stem cell transplantation (allo-SCT). Despite the adequate use of antiviral drugs, Virus Specific T cells (VST) still represent a promising efficient immunotherapy.

Methods: Since 2016, we obtained the advanced-therapy medical products (ATMP) authorization to treat 29 recipients of allo-SCT in France with polyclonal ADV-VST (n = 13), CMV-VST (n = 7), EBV-VST (n = 8) and both ADV-VST and CMV-VST (n = 1). VSTs were generated in Nancy, by a 6-hour ex vivo stimulation with an appropriate peptide pool (PepT-ADV5 Hexon, -CMV pp65, -EBV Select, Miltenyi Biotec), and isolated by a CliniMACS immunomagnetic selection using the IFN-γ capture system (Miltenyi Biotec). Infused VST derived from the original stem cell donor (n = 13) or a third party with a haploidentical donor (n = 16). The clinical and biological follow-up was collected with frequent questionnaires addressed to physicians. The efficacy at 1-month has been evaluated. We defined complete response (CR) as complete clearance of the virus and partial response (PR) as viral load decrease ≥1log. We compared recipient outcomes with Student t, Mann-Whitney or Chi^2 tests where appropriated.

Results: From May 2016 to January 2022, we report 33 VST infusions for 29 patients (4 patients received 2 infusions). Median patients'age was 14 years old (range 0,3 to 68). The mean number of previous therapeutic lines was 2, 3 and 1 for ADV, CMV and EBV patients, respectively. The median CD3-IFN-γ T-cells (10^e4/kg) infused was 0,25 (range 0,086 to 1,052) for ADV-VST, 1,01 (range 0,482 to 5,059) for CMV-VST and 0.79 (range 0,268 to 1,63) for EBV-VST (no significant difference). Four patients died within the first month. Responders (PR and CR) at 1 month represented 64% of the 25 patients still alive (*p < 0.001*). The mean viral load at the day of VST infusion (D0) and the median CD3 + T cells were not significantly different between CR/PR and non-responders (NR) patients. Interestingly, 61% responders benefited from haploidentical donor's VSTs, different from the original stem cell donor. In vivo expansion data were available for 11 patients with 8 of them experiencing specific immune reconstitution. Six de novo cases of GVHD (23%) were reported during or after the first month post infusion and up to 3 months. Overall survival was 54% and 35% at 3 and 12 months post-infusion, respectively, and was significantly higher when D0 viral load was ≤3.75 log (*p < 0.05*). The first cause of death in the 3 months following VST infusion was the initial virus related replication/disease (n = 8). After 3 months, causes of death were HSCT toxicity related mortality (n = 4), septic shock (n = 2), mixed hepatopathy (ADV replication and hepatic GVHD) (n = 1), and relapse from initial disease (n = 2).

Conclusions: In this retrospective single-production-center cohort, almost 2/3 of patients responded to the last resort treatment, VST infusion. Adoptive transfer of VST cells seems to be a rapidly efficient and safe therapeutic option. Our results question its place in the early therapeutic lines, when viral load is low and expansion time greater.

Disclosure: Danièle Bensoussan, startup Seminov.

5 - Cellular Therapies other than CARs

P133

DONOR LYMPHOCYTE INFUSIONS (DLI) IN MYELOFIBROSIS: TREATMENT PATTERNS, EFFICACY AND SAFETY. A EUROPEAN MULTICENTRE RETROSPECTIVE REAL-WORLD STUDY

Alex Rampotas[1], Katja Sockel[2], Catrin Theuser[2], Martin Bornhaeuser[2], Rafa Hernani[3], Juan Carlos Hernandez Boluda[3], Albert Esquirol Sanfeliu[4], Daniele Avenoso[5], Panagiotis Tsirigotis[6], Marie Robin[7], Tomasz Czerw[8], Grzegorz Helbig[9], Claire Roddie[1], Jonathan Lambert[1], Fotios Panitsas[10], Donal McLornan[1]

[1]University College London Hospital NHS Foundation Trust, London, United Kingdom, [2]University Hospital Dresden, Dresden, Germany, [3]Hospital Clínico Universitario de Valencia, Valencia, Spain, [4]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [5]King's College Hospital NHS Foundation Trust, London, United Kingdom, [6]Attikon University Hospital, Athens, Greece, [7]Hôpital Saint-Louis, Paris, France, [8]National Institute of Oncology, Gliwice, Poland, [9]Medical University of Silesia, Katowice, Poland, [10]Laikon University Hospital, Athens, Greece

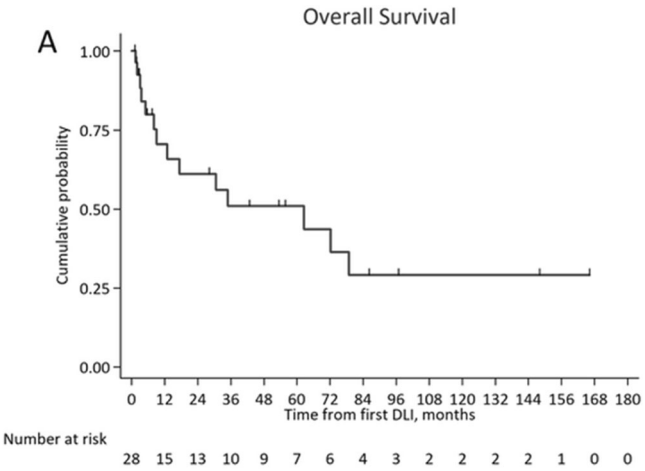
Background: Allogeneic haematopoietic cell transplantation (allo-HCT) remains the only curative option for Myelofibrosis (MF). Relapse remains a significant problem in up to 20-30% of cases. Approaches to relapse prevention and management vary greatly including use of Donor Lymphocyte Infusions (DLI) representing one of the most effective strategies. Utilisation of DLI post allo-HCT is predominantly either an escalating dose regimen (EDR) or 'bulk salvage' therapy. Optimal timing and regimen choice remains undetermined. We hereby report on a multicentre MF allo-HCT cohort who received DLI.

Methods: Patient selection included MF allo-HCT patients from 8 European transplant centres who received DLI between 2005-2022. Response was assessed by IWG-MRT defined response (albeit this is unvalidated post-transplant). Kaplan-Meier estimator and log-rank test were used to estimate survival endpoints.

Results: Patient, disease and transplant characteristics are shown in **Table 1**. Median age was 58 years (IQR:53 – 62.5) and 19 (68%) were male. Karnofsky performance status was >80 in all patients and the majority had DIPPS+ Int-2 or High-risk disease at time of allo-HCT. Median time from diagnosis to allo-HCT was 23.4 months (IQR:8-44**)**. Driver mutation status was JAK2; n = 18(64.3%), CALR; n = 2(7.1%), 'Triple Neg' n = 2(7.1%) and unknown n = 6(21.4%); 57.1% received a JAK inhibitor prior to allo-HCT. T cell depletion was utilised in 20(71.2%) regimens. Regarding donor type, 14 (50%) had a Matched Sibling Donor and 14(50%) an Unrelated Donor. The majority received PBSC (n = 26;92.9%), 11 patients had a history of acute and 8 patients had chronic GVHD, respectively.

Indication for DLI was a decrease in recipient chimerism (n = 13) or clinician defined relapse (n = 15; haematological (n = 11) and molecular relapse (n = 4). For the entire cohort, median time to DLI administration was 10.4 months (IQR:5.5-23.6 months). Median DLI doses administered was 2 (range, 1-5) with a median 1st dose of 1x10^6/kg (range 0.5 – 10). Of 16 patients receiving >1 dose of DLI, 12 were part of an EDR. Median follow up from 1st DLI was 55.4 months (IQR:27.7-96.5). Regarding response 15/28(54%) patients had a IWG-MRT defined response (unvalidated post-transplant); CR (n = 5), PR (n = 1) and clinical improvement (n = 9). Stable disease was reported in 6 patients with and no response or progression in 7. Chimerism levels improved in 16 patients. Where DLI was administered for falling chimerism, it was increased in 9/13 after a median of 2 infusions (range 1-4). 5 patients remained in remission with a median follow up 55 months. For clinical relapse, 9/15 patients had a response and remained in remission (median follow up: 42 months). DLI induced aGVHD was reported in 11 cases, grade 3/4 (n = 7).

Median OS from time of 1st DLI, censored at time of 2nd allo-HCT(N = 4), was 62.6 months (IQR:10- NR). Cumulative incidence of relapse/ progression after 1st DLI (death as competing) was 30.8% (95% CI 14.4-48.9%) at 6-months. Regarding cause of death, this was due to progressive disease (n = 8/14) or infectious complications (n = 3/14).



Conclusions: Albeit a heterogeneous cohort, clear efficacy of DLI is evident in this challenging cohort of relapsed MF patients post allo-HCT. More prospective studies are warranted to identify the optimal DLI regimen and timing.

Disclosure: AR: Conference fees (Gilead).

5 - Cellular Therapies other than CARs

P134

INB-100: RELAPSE PROPHYLAXIS POST-HAPLOIDENTICAL BONE MARROW TRANSPLANTATION AND CYCLOPHOSPHAMIDE (HAPLO/CY) BY INFUSION OF DONOR-DERIVED EXPANDED/ACTIVATED GAMMA-DELTA (ΓΔ) T CELLS: A PHASE I TRIAL

Joseph McGuirk[1], Sunil Abhyankar[2], Trishna Goswami[3], Rupal Soder[4], Mariska ter Haak[3], Tyce Bruns[5], Samantha Langford-Youngblood[3], Lawrence Lamb[3]

[1]University of Kansas, Westwood, United States, [2]University of Kansas Cancer Center, Westwood, United States, [3]In8bio, Inc, New York, United States, [4]Midwest Stem Cell Therapy Center, Kansas City, United States, [5]University of Kansas Medical Center, Fairway, United States

Background: Effector gd T cells, are nature's anti-cancer cell that can recognize and directly kill malignant cells in a non-MHC restricted manner. Relapse post Haplo/Cy bone marrow transplantation (BMT) occurs in ~51% of patients within 1 year and may be mitigated by infusing expanded, activated donor-derived haploidentical gd T cells (EAGD) post-transplant. Additionally, data suggest post-transplant Cy may lead to poor immune reconstitution and higher risk of infections. We report data on the first two dose levels (DL) of a Phase 1 trial assessing the safety and efficacy of allogeneic EAGD cells. Increasing doses of EAGD are administered to patients undergoing haploidentical transplants

Baseline Characteristics	***N = 28***	**Haematopoietic Transplant Characteristics**	***N = 28***	**DLI indication and specifics**	***N = 28***
Age	58 IQR: 52.5 – 62.75	**Type of transplant**		***Rationale for use***	
		Sibling	14/28 (50%)	*Falling Chimerism*	13/28 (46.4%)
		Matched unrelated 10/10	13/28 (46.5%)	*Clinical Relapse*	3/28 (10.7%)
		Matched unrelated 9/10	1/28 (3.5%)	*Relapse*	12/28 (42.9%)
Sex (Male)	19/28 (67.9%)	**T-cell depletion**		***GvHD post DLI***	
		Yes	20/28 (71.4%)	*Yes*	11/28 (39.3%)
		No	5/28 (17.8%)	*No*	17/28 (60.7%)
		Not known	3/28 (10.7%)		
DIPSS +	(*Not Known 1/28)	**Source of HSCs**		***Worst GvHD grade***	(*Not Known 1/11)
Low	0/28	PBHSC	26/28 (92.9%)	*1*	4/11
Int-1	6/28 (21.4%)	Bone marrow	2/28 (7.1%)	*2*	1/11
Int-2	16/28 (57.1%)			*3*	2/11
High Risk	5/28 (17.8%)			*4*	3/11
Disease Status	(*Not known 3/28)	**Donor's sex**		***Doses used***	
Complete remission	0/28	Male	18/28 (64.3%)	*1*	12/28 (42.9%)
Partial Remission	3/28 (10.7%)	Female	10/28 (35.7%)	*2*	6/28 (21.4%)
Clinical Improvement	4/28 (14.2%)			*3*	4/28 (14.2%)
Stable Disease	8/28 (28.6%)			*≥4*	6/28 (21.4%)
Progressive Disease	10/28 (35.7%)				
Splenomegaly		**Donor's age (median)**	42.5 IQR 27 -54.75	***Time to first DLI (days, median)***	317 IQR: 162.5 – 775.25
Yes	16/28 (57.1%)				
No	6/28 (21.4%)				
NK	6/28 (21.4%)				
Disease Driving Mutation		**CMV status**			
JAK2	18/28 (64.3%)	Donor(-)/Recipient(-)	10/28 (35.7%)		
Calreticulin	2/28 (7.1%)	Donor(+)/Recipient(-)	2/28 (7.1%)		
MPL	0/28	Donor(-)/Recipient(+)	5/28 (17.8%)		
Triple Negative & other	3/28 (10.7%)	Donor(+)/Recipient(+)	11/28 (39.3%)		
NK	5/28 (17.8%)			***Outcomes***	**N = 28**
High Risk Mutations		**ABO group matching**		*No response or Progressive Disease*	7/28 (25%)
ASXL1	3/28 (10.7%)	Matched	15/28 (53.5%)	*Stable Disease*	6/28 (21.4%)
Monosomy 7	1/28 (3.5%)	Minor incompatibility	7/28 (25%)	*Clinical Improvement or increased chimerism*	9/28 (32.1%)
		Major Incompatibility	6/28 (21.5%)	*Partial Remission*	
		Bidirectional	0/28	*Complete Remission*	1/28 (3.5%)
					5/28 (17.8%)
Specific Comorbidity Index	(*Not known 2/28)	**Engraftment**		**Chimerism Improvement**	
0	13/28 (46.4%)	Yes	28/28 (100%)	Yes	16/28 (57.1%)
1	3/28 (10.7%)	No	0/28	No	12/28 (42.9%)
2	4 (14.2%)				
≥3	8 (28.6%)				
Karnofsky Performance Scale		**Time to engraftment** (median, days)	20 IQR 15-21	**Toxicity (other than GvHD)**	
100	8			Yes	3/28 (10.7%)
90	9			No	25/28 (89.3%)

Baseline Characteristics	N = 28	Haematopoietic Transplant Characteristics	N = 28	DLI indication and specifics	N = 28
80	10				
NK	1/28 (3.5%)				
Prior exposure to JAK inhibitors		**Acute GvHD**		**Death**	
Yes	16/28 (57.1%)	Yes	11/28 (39.3%)	Yes	14/28 (50%)
No	12/28 (42.9%)	No	17/28 (60.7%)	No	14/28 (50%)
		Chronic GvHD		**Cause of Death**	
		Yes	8/28 (28.6%)	Progressive Disease	8/14 (57.1%)
		No	20/28 (71.4%)	Infection	3/14 (21.4%)
				Graft failure	1/14 (7.1%)
				Secondary malignancy	1/14 (7.1%)
				Not Known	1/14 (7.1%)

for underlying hematologic malignancies to prevent relapse, with corresponding preliminary clinical and biologic correlative findings.

Methods: Adult patients with newly diagnosed or relapsed ALL, CML, AML undergoing consolidative haploidentical transplant with reduced-intensity flu/cy/TBI conditioning received EAGD intravenously within 7 days of neutrophil engraftment. Peripheral blood was collected at EAGD infusion and monthly thereafter through day +90, with additional collections every 6 months through 1 year. Primary endpoints include dose-limiting toxicities (DLT), grade 3-4 adverse events including graft-versus-host disease (GvHD) while secondary endpoints include relapse and overall survival. Biologic parameters included multiparameter flow cytometric immunophenotyping and single-cell cytokine analysis of the EAGD graft. Peripheral blood analysis includes leukocyte count and differential, immunophenotyping, and serum Th1/Th2/Th17 cytokine analysis.

Results: 10 patients have been enrolled with four treated at DL1 of 1 x 10^6 EAGD/kg and two additional patients treated at DL2 (3 x 10^6 EAGD/kg). One screen failure, one manufacturing failure, one patient died prior to dosing, and one received an out of study specification product. All four patients in DL1 remain in morphologic complete remission (CR) at 32.2, 29.8, 18.1 and 3.8 months post-BMT at data cut-off of 18Dec2022. One patient received intermittent hypomethylating therapy for occurrence of recipient chimerism. Majority of toxicities related to EAGD cells were grade (Gr) 1-2 skin and Gr2 GI acute GvHD. Other toxicities include constipation, CMV reactivation, emesis, fatigue, and hypomagnesaemia. One patient sustained chronic mild GvHD of her oral surface. No DLTs, treatment-related ≥ Gr3 adverse events, neurotoxicity or cytokine release syndrome were reported. Significant peripheral lymphodepletion persisted through the first 100 days post-BMT followed by slow recovery of CD3 + CD4 +, CD3 + CD8+ and gd T cells. Interestingly, B cell counts recovered in the first 30 days and NK cells remained within the low normal range throughout. T cells transitioned from a CD45 + CD27- effector phenotype to CD45RA CD27 central to effector memory phenotype as recovery progressed. CD3, CD4, CD25, and FoxP3 Treg cells remained <3% of circulating T cells. Preliminary serum cytokine and chemokine analysis revealed predominant expression of IFNγ, IL-12p70, IP-10, RANTES and TNFα.

Conclusions: The preliminary results of this Phase 1 study of donor-derived, EAGD cells has demonstrated the therapy to have a robust safety profile, with no infusional toxicity, treatment associated SAEs, or grade 3-4 acute or extensive chronic GVHD. The absence of relapse suggest the possibility that this therapy will be an effective measure in mitigating relapse after HaploBMT.

Clinical Trial Registry: NCT03533816
Disclosure: Nothing to declare.

5 - Cellular Therapies other than CARs

P135

ROLE OF HISTOCOMPATIBILITY, ACCESSORY CELLS AND FREEZE-THAWING FOR IMMUNOSUPPRESSION BY PLACENTA-DERIVED DECIDUA STROMAL CELLS

Olle Ringden[1], Myrese Witkamp[1], Dominik Schefberger[1], Anna Arbmann[1], Behnam Sadeghi[1]

[1]Karolinska Institutet, Huddinge, Sweden

Background: Mesenchymal stromal cells (MSCS) are very rare precursor cells (< 1;10000nucleated cells) in all tissues of the body. MSCs from all tissues, even fibroblasts are immunosuppressive. We introduced bone marrow derived (BM)-MSCs for treatment of severe acute GVHD. Some, but not all patients responded. The fetus is protected from the mothers HLA haploidentical immune system by the placenta. Fetal membrane derived so called decidua stromal cells (DSCs) gave a stronger immunosuppression in vitro in Mixed Lymphocyte Culture (MLC) and responses in acute GVHD than BM-MSCs or other sources of MSCs. DSCs differ in many ways from BM-MSCs, they are half the size and do not differentiate well to bone and fat. DSCs inhibit MLC by direct contact and not mainly by soluble factors as do BM-MSCs. Blocking experiments suggest that interferon-gamma, prostaglandin E-2, IDO and PD-L1 are involved in the immunosuppressive mechanism. DSCs have a stronger effect on coagulation and hemostasis compared to BM-MSCs. DSCs have been successfully used to treat acute GVHD, hemorrhagic cystitis, ARDS and radiculomyelopathy.

Methods: Placentas were obtained from caesarean sections. DSCs were isolated and expanded from the fetal membranes in a GMP-lab. Mouse(m)- MSCs were obtained from femur and tibia. In MLC, m-splenocytes or human(h) PBL were used as responder cells. Stimulatory cells were m-splenocytes or h- PBL pooled from five donors. Con A was also used for stimulation. In trans-well experiments, DSCs were seeded in the upper chamber. CD3 + T-cells, CD14+monocytes and CD56 + NK cells were isolated by positive selection. Cells were stored frozen in liquid nitrogen. Viability was measured in room temperature.

Results: When 10% m-MSCs were added to MLCs, being autologous, allogeneic, or haploidentical (F1), > 95% inhibition was seen. Using h-DSCs(xeno), inhibition was median 68%. Using h-PBL as stimulators of m-solenocytes-hDSCs showed a median inhibition of 88%. Trans-well experiments indicated that h-DSCs needed direct contact for inhibition to occur. CD14+cells reduced the immunosuppressive effect by DSCs. NK cell activation by IL-2 was increased by a median of 58% when DSCs were added. Fresh or frozen-thawed DSCs had the same viability and similar immunomodulatory effects.

Conclusions: Histocompatibility, direct contact and CD14+cells had impact on DSCs immunomodulation, but freeze-thawing did not.

Disclosure: No conflict of interest.

5 - Cellular Therapies other than CARs

P136

RAPID IMMUNE RECONSTITUTION AND ELEVATED REGULATORY T CELL FREQUENCIES IN PATIENTS TREATED WITH ORCA-T

Arpita Gandhi[1], M. Scott Killian[2], Anna Pavlova[3], Cameron Bader[3], Sean Summers[2], Fernando Teque[2], J. Scott McClellan[2], Nathaniel Fernhoff[2], Everett Meyer[3]

[1]Oregon Health and Science University, Portland, United States, [2]Orca Bio, Menlo Park, United States, [3]Stanford University, Stanford, United States

Background: Immune reconstitution following myeloablative allogeneic hematopoietic stem cell transplant (MA-alloHSCT) is significantly delayed for T cell depleted allografts when compared to T-cell replete allografts, a feature that has been implicated in higher rates and grades of infection, less GVT, and worse overall survival. Orca-T is a high precision cell therapy currently being investigated for the treatment of certain hematological malignancies otherwise treated with MA-alloHSCT. The cellular drug products of Orca-T (HSPCs, Tregs, and Tcons) are administered at high purity, in controlled doses, and on an established schedule with the intent to reconstitute the blood and immune system while controlling GVHD. Here, we present data on the immune reconstitution in 100 adult patients who received Orca-T.

Methods: In the context of an ongoing multicenter Phase Ib clinical trial of Orca-T in recipients with hematologic malignancies (NCT04013685), we performed longitudinal measurements (days -28, 28, 56, 100, 180, and 365 post-transplant) of immune reconstitution in the first 100 consecutive patients. With fresh whole blood, clinical 5-part leukocyte differentials were performed at clinical sites, and lymphocyte subset frequencies were measured by flow cytometry in a central lab. Principal component analysis (PCA) was performed to investigate potential associations with recipient sex (male vs. female) and donor relation (related vs. unrelated).

Results: T cell and B cell counts were readily observed at days 28 and 56 respectively, and increased with each subsequent time point. Median NK cell levels were observed to be in the normal range at all post-transplant time points. CD4 + T cell and Treg cell counts exhibited similar post-transplant patterns with both being appreciably present at d28 and increasing with each subsequent time point. Strikingly, relative to the level measured in 75 corresponding PBSC donors, the Treg frequency among CD4 + T cells was significantly elevated at all time points post-transplant. Median CD8 + T cell counts increased for the first 6 months post-transplant and then plateaued in the normal range. Upon PCA, very few significant differences were observed in 2-group comparisons of recipient sex and donor relation.

Conclusions: Orca-T patients exhibit early immune reconstitution of each of the major leukocyte and lymphocyte subsets hypothesized to control relapse and infection. Concomitantly, elevated Treg frequencies were also observed. This feature of immune reconstitution profiles of Orca-T recipients may be correlated to the reduced occurrence and severity of acute and chronic GVHD in these patients (Oliai et al., ASH 2022). Similar immune reconstitution profiles were observed in patients of disparate sex and regardless of donor relation. Prospective comparisons of immune reconstitution between Orca-T and standard-of-care patients will be performed in our ongoing phase 3 clinical trial (NCT05316701).

Clinical Trial Registry: https://clinicaltrials.gov/ct2/show/NCT04013685

Disclosure: Arpita Gandhi | Consultancy: Care Dx; Honoraria: Gamida; Research Funding: Orca Bio
M. Scott Killian | Current Employment/Equity: Orca Bio
Anna Pavlova | Current Employment/Equity: Orca Bio
Cameron Bader | Nothing to declare
Sean Summers | Current Employment/Equity: Orca Bio
Fernando Teque | Current Employment/Equity: Orca Bio
J. Scott McClellan | Current Employment/Equity: Orca Bio
Nathaniel Fernhoff | Current Employment/Equity: Orca Bio
Everett Meyer | BoD/Advisor: indee labs; Co-founder & Scientific Advisor: GigaGen, Triursus Therapeutics; Research Funding: Orca Bio
This study was sponsored by Orca Bio.

5 - Cellular Therapies other than CARs

P137

MESENCHYMAL STROMAL CELLS FOR THE TREATMENT STEROID REFRACTORY GRAFT-VERSUS-HOST DISEASE IN CHILDREN

Krzysztof Czyzewski[1,2], Robert Debski[1,2], Monika Richert-Przygonska[1,2], Agnieszka Majk[2], Kamila Jaremek[2], Oliwia Grochowska[2], Joanna Stankiewicz[1,2], Lukasz Ledzinski[3], Sylwia Koltan[1,2], Jan Styczynski[1,2]

Medicum, Nicolaus Copernicus University in Torun, Bydgoszcz, Poland, Antoni Jurasz University Hospital No 1, Bydgoszcz, Poland, [3]Central Pharmacy, Antoni Jurasz University Hospital No 1, Bydgoszcz, Poland

Background: Mesenchymal stromal (MSC) cells are multipotent non-hematopoietic stem cells, that can differentiate into other cells. MSC have immunoregulatory and immunosuppressive activity by secretion of chemokines, cytokines and extracellular vesicles. The first-line treatment of acute and chronic graft versus host disease (GVHD) are corticosteroids. However 50% of acute GVHD cases are resistant to high doses of corticosteroids and 50-60% moderate/severe chronic GVHD require "steroid-sparing" treatment. MSC is an option for next lines treatment of steroid refractory (SR) GVHD.

The objective of the study was the analysis of safety and efficacy of MSC use in pediatric patients with SR GVHD in single center experience.

Methods: We retrospectively analyzed the use of cryopreserved commercially available third-party donor Wharton's jelly derived mesenchymal stromal cells in patients with SR GVHD after allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Results: Fifteen children (11 boys, 4 girls) with median age 4 years (age range 8,5 months-16,5 years), diagnosed for ALL (n = 5), primary immunodeficiencies (n = 5), AML (n = 3), SAA (n = 2) recipients of allo-HSCT (9 MUD-PB, 4 MUD-BM, 2 MSD-PB) were included into the

study. In all patients SR GVHD was diagnosed (12 acute GVHD, grade 2-4: 4-skin+gastro-intestinal,3- skin, 2-gastro-intestinal, 1-skin+lungs, 1-hepatic+gastro-intestinal, 1-skin+hepatic+gastro-intestinal; 3 chronic GVHD, grade moderate-severe: 1-skin, 1-sclerodermatous, 1-skin+eye). The total number of 45 MSC intravenous infusions were performed (median: 2, range: 1-8). The median number of infused MSCs was $1.39x10^6$/kg b.w. (range 0.85-2.99) in 1-4 weeks intervals. In 14/15 patients before MSC administration combined therapy with corticosteroids was performed including 1-3 agent/therapy (ciclosporine, tacrolimus, mycophenolate mofetil, vedolizumab, ruxolitinib, basiliximab, extracorporeal photopheresies). The median time from GVHD diagnosis to first infusion of MSC was 105 days (range 15-305 days); 73% (11/15) achieved a response (53% complete response, 20% partial response), while 27% (4/15, all acute GVHD) did not respond to MSC therapy. Overall, 91% (10/11) of patients with complete/partial response are alive (1 patient died due to leukemic relapse). Among 4 non-respond patients, 2 died due to GVHD progression, 1 due to infection and 1 due to toxic encephalopathy. No adverse event related to MSC administration was observed in all patients.

Conclusions: Administration of MSC is a safe and effective therapeutic option in our experience in pediatric patients with steroid refractory acute or chronic GVHD. Further studies concerning optimal dose, interval between doses and number of doses are needed.

Disclosure: Nothing to declare.

5 - Cellular Therapies other than CARs

P138

FAMILIAL CD45RA$^-$ CELLS CONTAINING PATHOGEN-SPECIFIC MEMORY T-CELLS AS COMPLEMENTARY STRATEGY TO TREAT SEVERE REFRACTORY INFECTIONS AND EBV

Carlos Echecopar Parente[1], Karima Al-Akioui Sanz[2], Maria Dolores Corral Sánchez[1], Luisa Sisinni[1], David Bueno Sánchez[1], Cristina Ferreras[2], Raquel De Paz[3], Antonio Balas[4], Eduardo López-Granados[5], Berta González Martínez[1], Víctor Galán Gómez[1], Pilar Guerra García[1], Sonsoles San Román Pacheco[1], Isabel Martínez Romera[1], Antonio Pérez Martínez[1,2,6]

[1]Pediatric Hemato-Oncology, University Hospital La Paz, Madrid, Spain, [2]University Hospital La Paz Research Institute (IdiPAZ), Madrid, Spain, University Hospital La Paz, Madrid, Spain, [4]Histocompatibility Unit, Centro de Transfusión Comunidad de Madrid, Madrid, Spain, [5]Immunology Unit, University Hospital La Paz, Madrid, Spain, Universidad Autónoma de Madrid, Madrid, Spain

Background: Immunocompromised patients are susceptible to high-risk opportunistic infections and malignant diseases. Most antiviral and antifungal drugs are quite toxic, relatively ineffective, and induce resistance in the long term. The adoptive passive transfer of pathogen-specific cytotoxic T-cells has shown a minimal toxicity profile and effectiveness in treating several infections, but this therapy have the main limitations of regulatory issues, high cost, and absence of public cell banks. However, CD45RA$^-$ cells containing pathogen-specific memory T-cells involve a less complex manufacturing and regulatory process and are cheaper, feasible, safe, and potentially effective.

Methods: We present preliminary data from six immunocompromised patients: four who had severe infectious diseases and two who had EBV lymphoproliferative disease. All of them underwent multiple safe familial CD45RA$^-$ T-cell infusions as adoptive passive cell therapy, containing pathogen-specific memory T-cells.

Patients	Sex	Age (years)	Primary disease	Immuno-suppression therapy	Lympho-cytes at time of infection	Infectious disease	Viral copies or GMN at diagnosis (copies/μL)	Standard therapy and duration	Virsl copies or GMN after standard therapy (copies/μL)
1	F	37	Kidney transplantation	Prednisone Everolimus Tacrolimus	670/μL	BKV nephritis	5.6×10^5	IS minimization, leflunomide and IGs. (4 months	7.5×10^3
2	M	19	Chronic granuloma-tous disease and MUD HSCT	Methylprednisolone (0.5 mg/kg/d) Cyclosporin	50/μL	CMV encephalitis	3.69×10^7 in LCR 4.97×10^3 in serum	Foscarnet (7 days), ganciclovir and specific CMV IGs (parenteral and intrathecal) (2 months)	2.3×10^3
3	M	7	Multivisceral transplantation	Methylprednisolone (2 mg/kg/d) Sirolimus	1.310/μL	CMV systemic infection	1.14×10^3	Ganciclovir (2 months) Foscarnet (1 month) and weekly IGs (2,5 months)	<1.000
4	F	15	CTLA4 haploinsufficiency and MUD HSCT	Abatacept	870/μL	Lung aspergillosis	2,99	Surgical resection (x2) Voriconazole and amphotericin B. (2 years)	0.52
5	F	12	Multivis-ceral transplantation	Methylprednisolone 0.3 mg/kg/d Tacrolimus Everolimus	230/μL	Liver EBV PTLD	1.2×10^5	IS minimiza-tion, Rituximab and chemotherapy (2,5 years)	1.07×10^5
6	F	9	Primary Immunode-fficiency	None	340/μL	EBV DLBCL	4.09×10^5	Rituximab and chemotherapy (8 months)	0

Results: The infusions were safe, there was no case of graft-versus host disease and they showed a clear clinical benefit. The patients treated for BK virus nephritis, Cytomegalovirus encephalitis, Cytomegalovirus reactivation, and pulmonary aspergillosis experienced pathogen clearance, complete resolution of symptoms in 4-6 weeks and a lymphocyte increase in 3 of 4 cases after 3–4 months. Donor T cell transient microchimerism was detected in one patient. The two patients treated for EBV lymphoproliferative disease underwent chemotherapy and $CD45RA^-$ memory T-cells containing EBV cytotoxic lymphocytes. Donor T-cell microchimerism was observed in both patients. The viremia cleared in one of the patients, and in the other, despite the viremia not clearing, hepatic lymphoproliferative disease remained stable and was ultimately cured with EBV-specific cytotoxic T Lymphocytes.

Conclusions: The use of familial $CD45RA^-$ T cells containing specific cytotoxic T-lymphocytes could be a feasible, safe and potential effective approach for treating severe pathogen infections in immunocompromised patients through a third party donor. Furthermore, this approach might be of universal use with fewer institutional and regulatory barriers.

Disclosure: Nothing to declare.

5 - Cellular Therapies other than CARs

P139

ADD-BACK NK CELLS FOLLOWING HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANT IN PEDIATRIC HIGH-RISK B CELLS ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL)

Daniela D'Angelo[1], Fabiana Cacace[2], Emanuela Rossitti[1], Valeria Caprioli[2], Maria Rosaria D'Amico[2], Giuseppina De Simone[2], Mario Toriello[2], Maisto Giovanna[2], Donato Madalese[2], Alessandra Cianflone[2], Peppino Mirabelli[2], Roberta Penta de Vera d'Aragona[2], Francesco Paolo Tambaro[2]

[1]University of Naples "Federico II", Napoli, Italy, [2]AORN Santobono Pausilipon, Napoli, Italy

Background: Natural killer lymphocytes (NKs) are cells of innate immunity that protect against tumor and infections, and recognize self and non-self HLA class I ligands. Killer-cell Immunoglobulin-like Receptors (KIRs) are inhibitory molecules expressed on NK surface. They act "educating" NKs in effective defense against unhealthy self/non-self cells and tolerance towards healthy self cells. NKs play a key role in preventing early relapse of hematologic malignancies, virus infection with no graft versus host disease (GvHD) after haploidentical hematopoietic stem cell transplantation (haplo-HSCT).

In B-/T-cell alpha/beta depleted haplo-HSCT, donor-versus-recipient alloreactive NKs exert an efficient graft versus leukemia (GvL) effect, mediated by inhibitory KIRs where the HLA ligand is missing on recipient cells.

NKs after haplo-HSCT are immature, $CD56^{bright}$, derived from $CD34^+$ stem cells. They are not effective as the mature NKs with a $CD56^{dim}$ phenotype, characterized by CD16, CD57 and KIRs in late stages.

We evaluated the alloreactive effect of donor-derived NKs in 3 pediatric high-risk B-ALL who underwent B-/T-cell alpha/beta depleted haplo-HSCT followed by donor NK infusion.

Methods: Patients' characteristics are summarized in the Table. Median follow-up was 180 days after transplantation. All 3 patients were male; median age was 13 months. Patients 1 and 2 had infant ALL, patient 3 had refractory-relapsed (r/r) ALL. All patients received a median of 3 lines chemotherapy. Patient 1 received a prior allo-HSCT. Two patients received chemo-based conditioning regimens. Patient 3 received Total Body Irradiation (TBI)-based conditioning regiment plus chemotherapy. All patients received rituximab and letermovir for EBV and CMV prophylaxis, respectively. Mother was Donor for all patients. Median $CD34^+$, $CD19^+$, $CD3^+$-alpha/beta cell dose was 8.8, 0.05, 0.41 x 10^6/kg, respectively. NKs alloreactivity was tested by evaluating KIR genotyping and KIR/KIR-ligand mismatch in graft-versus-host direction. All three patients present KIR/KIR-ligand mismatch. NK reconstitution was analyzed in all three transplanted patients.

Results: Engraftment was day +13, +14 and +19 for ANC, and +14, +18 and +17 for PLT, for patients 1, 2 and 3, respectively. All three patients showed a fast reconstitution of NKs at day +14. Patients received NKs infusion at median day +36. No infusion reactions were observed. Median NK infused were 256x10^6/kg. None of the patients developed EBV reactivation. Patient 1 developed CMV and ADV reactivation at day +19 and +288, respectively, without needing to treat. Patient 2 developed Grade 2 acute GvHD (skin) at day +48, treated by steroid, and Score 3 chronic GvHD (skin) 5 months after transplantation, resolved with cyclosporin treatment. No Grade GvHD 3-4 was observed. Currently all patients are in CR with full donor chimerism.

Conclusions: Alloreactive NKs add-back infusion after B-/T-cell alpha/beta depleted haplo-HSCT could represent an effective option to improve transplant outcome. NKs may improve efficacy by enhancing GvL and contribute to maintain "disease control" through immunologic surveillance in high-risk ALL. Infusion of phenotypic mature donor NKs could be more useful to maintain the immunologic control of MRD and virus reactivation, without increase aGvHD incidence. Our preliminary observations should be confirmed in clinical trial of a larger number of patients and extended to other haplo-HSCT platforms.

Disclosure: Nothing to declare.

5 - Cellular Therapies other than CARs

P140

EVALUATION OF THE SINGLE NEEDLE/DOUBLE NEEDLE AMICUS EXTRACORPOREAL PHOTOPHERESIS (ECP) SYSTEM WITH SOFTWARE VERSION 6.1 IN HEALTHY HUMAN SUBJECTS

Axel G. Stover[1], Danielle Badgley[1], Cheryl Huber[1], Adrienne Karpiel[1], Gregory Coultas[1], Carrie Pineda[1], Zahra Ali[1], Jennifer Weitgenant[1], Barbara Brantigan[1], Divya Srivastava[1], Thomas Gniadek[1]

[1]Fresenius Kabi USA, LLC, Lake Zurich, United States

Background: The Amicus Blue Separator System for ECP (Fresenius Kabi), performs on-line photoactivation and reinfusion of mononuclear cells (MNCs). This study evaluated safety and performance of a new disposable kit enabling single- (SN) or double-needle (DN) vascular access and new device software (SW).

Methods: This Institutional Review Board approved study enrolled healthy adults who met safety guidelines for whole blood and apheresis donations. MNCs were collected with the Amicus Separator (SW 6.1), sampled from the Amicus return line during the collection as well as before (untreated) and after addition of 8-MOP/photoactivation (treated) with the Phelix device (SW 2.1); for this study, treated cells were not reinfused to the donors. Whole-blood-to-process was set at 500, 2000 or 5000 mL. Conversions (SN-to-DN or DN-to-SN) were also

performed. Testing included cell counts (KX-21, Sysmex), complement activation (C3a, C5a immunoassays, Quidel), plasma free hemoglobin (modified Harboe method), Factor VIII activity (ACL Elite, Werfen), and lymphocyte proliferation (phytohemagglutinin culture/carboxyfluorescein succinimidyl ester labeling). Apoptosis was assessed from cultured cells based on phosphatidylserine expression by Annex V/CD2/CD19/7AAD labeling and flow cytometry.

Results: 22 subjects enrolled (16 male/6 female, mean age 52.0 [range 22-74] years) for 20 evaluable procedures. Two procedures could not be completed: one due to vein infiltration and another pre-procedure hemoglobin below the cutoff for volunteer blood donation (a study-specific requirement). No device errors or alarms prevented procedure completion. Mean procedure time was 88.1 minutes (SD 32.27). Lymphocyte apoptosis after 72-hour culture was 83.59% (SD 7.124%) for treated vs. 10.48% (SD 2.881%) for untreated cells, $p = 0.0002$. Lymphocyte proliferation over 72 hours post-treatment was 0.90% (SD 0.532%) for treated cells vs. 73.14% (SD 11.003%) for untreated cells, $p < 0.0001$. Free hemoglobin measured in the return line as well as treated cells was below safety limits and activated complement was not significantly different between treated cells and return line samples. Mean Factor VIII activity was lower in the treated samples vs. the return line: 46.1% (SD 15.88%) vs. 126.6% (SD 59.61%), $p < 0.0001$. Subject Factor VIII activity did not differ significantly pre vs. post collection procedure (146.9%, SD 53.77 vs. 135.5%, SD 48.38). All parameters met the acceptance criteria. Overall, MNC collection efficiency (CE1) was equivalent between DN (75.31%, SD 9.702%) and SN procedures (79.24%, SD 7.576%), $p = 0.5321$; as well as between DN and conversion procedures (78.93%, SD 6.996%), $p = 0.4902$.

Parameter Procedure type	N	Mean (SD)	Lower 95% confidence limit of the mean	Lower bound, tolerance interval (95% confidence, 90% population capture)
Lymphocyte proliferation inhibition (%)				
All procedures	20	98.77	98.66	97.75
Single needle	8	98.84	98.68	97.81
Double needle	6	98.53	98.31	97.22
Conversion	6	98.91	98.74	97.96
Lymphocyte apoptosis (%				
All procedures	20	83.59	80.26	69.87
Single needle	8	80.80	74.43	61.13
Double needle	6	87.38	81.19	69.66
Conversion	6	83.52	76.31	62.88
ParameterProcedure type	**N**	**Mean (SD)**	**Median**	**Min, Max**
MNC collection efficiency (CE1, %)				
All procedures	20	77.96 (7.873)	80.32	62.0, 87.8
500 mL	7	84.89 (2.980)	85.91	80.5, 87.8
2,000 mL	7	76.61 (6.853)	78.78	64.2, 83.5
5,000 mL	6	71.46 (6.928)	70.59	62.0, 81.6

Conclusions: This study evaluated 20 simulated ECP procedures with the Amicus ECP system (SN, DN and conversion). Only one subject experienced an adverse event (vein infiltration). Overall, the MNC collection efficiency was satisfactory and comparable to published reports. Photoactivation consistently reduced lymphocyte proliferation and induced apoptosis over the course of 72 hours. Pre- and post-procedure subject laboratory evaluation indicated no clinically significant abnormalities. Taken together, this study does not suggest any new procedural risks or hazards while demonstrating the safety and performance of this new option for single-needle vascular access as well as updated device software.

Clinical Trial Registry: n/a

Disclosure: All authors are employed by the device manufacturer.

29 - Chronic Leukaemia and Other Myeloproliferative Disorders

P141

TKI IN RELAPSE PROPHILAXIS AFTER ALLOGENEIC TRANSPLANTATION IN CML/ADVANCED PHASES

Antonella Gozzini[1], Riccardo Boncompagni[1], Chiara Nozzoli[1], Ilaria Cutini[1], Scappini Barbara[1], Riccardo Saccardi[1]

[1]AUO Careggi, Florence, Italy

Background: The revolutionary clinical activity of tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia (CML) has transformed patient outcome. Consequently, allogeneic stem cell transplantation (allo-SCT) is no longer the only treatment modality with the ability to deliver long-term survival. In contrast to the central position it held in the treatment algorithm 20 years ago, allografting is now largely reserved for patients with either chronic-phase disease resistant to TKI therapy or advanced-phase disease. The major causes of transplant failure in patients allografted for CML are transplant toxicity and disease relapse. The role of TKIs in relapse preventing after allo-SCT is still to be defined.

Methods: Between 2016 and 2022, 11 patients affected by CML advanced phases received allo-SCT. 10/11 were blast crisis, one was a chronic phase, primary cytogenetic resistant to second and third generation TKis. We report the main clinical characteristics of patients at time to transplant in Table 1. All 10 CB patients treated with TKis obtained CP2, no t315I mutation or compound mutations were identified. The transcript level was <1% for 9/11 patients at the transplant. 8/11 patients received myloablative conditioning regimen. 6/11 patients received TKIs prophylaxis with Ponatinib 15 mg/die: the therapy started within 60 days after SCT for 2 years, if well tolerated.

AGE (at HCT)	**median (c.i.)**	**44,8 (27 - 63)**	
TKI pre transplant	Imatinib	2	18%
	Dasatinib	6	54%
	Ponatinib	4	36%
Status at transplant	CP2	10	90%
	CP1	1	10%
Conditioning regimen	TBF MAC	8	72%
	TBI Cy	1	6%
	TBIFlu200	1	6%
	TBF RIC	1	6%
HCT-CI	low	7	63%
	intermediate	3	27%
	high	1	10%
MATCH HLA	ID sibling	3	28%

AGE (at HCT)	**median (c.i.)**	**44,8 (27 - 63)**	
	haploidentical	4	36%
	MUD	4	36%
TKI post SCT	Ponatinib	6	55%

Results: NRM was 27%. 1 patient died because of relapse, 1 patient died for infectious event and one for acuteGVHD. No patients had molecular relapse and no patients received DLI infusion. With a median follow up of 796 days, 72% (8/11) of patients are alive in deep molecular response with fully donor chimerism. Acute GVHD incidence was 45%; chronic GVHD (only grade 1-2) developed in 30% of patients.

Conclusions: Thirty to 70% relapse are reported after Allo-SCT for CML. Several factors determine the risk of disease recurrence after a transplant, including AP disease at SCT and the use of a RIC regimen. DLI remains the most effective salvage therapy in patients relapsing after allograft, even though the most of data originated from patients allografted in first CP.

Post-transplant administration of TKIs has the potential to reduce disease relapse, but selection of drug and administration scheduling is still to be clarified.

Disclosure: Nothing to declare.

29 - Chronic Leukaemia and Other Myeloproliferative Disorders

P142

FEASIBILITY OF EARLY DOSE REDUCTION OF FRONTLINE DASATINIB IN CHRONIC MYELOID LEUKEMIA PATIENTS: A 3-YEAR FOLLOW UP RESULTS OF DAS-CHANGE STUDY

Dong-Yeop Shin[1], Sung-Eun Lee[2], Jee Hyun Kong[3], Sukjoong Oh[4], Hawk Kim[5], Sung Hyun Kim[6], Young Rok Do[7], Won Sik Lee[8], Jae-Yong Kwak[9], Dae Young Zang[10], Seong Nam Im[11], Dong-Wook Kim[12]

[1]Seoul National University hospital, Seoul, Korea, Republic of, [2]Seoul St. Mary's Hospital, The Catholic University, Seoul, Korea, Republic of, [3]Wonju College of Medicine, Yonsei University, Wonju, Korea, Republic of, [4]Hanyang University College of Medicine, Seoul, Korea, Republic of, [5]Gachon University Gil Hospital, Incheon, Korea, Republic of, [6]Dong-A University College of Medicine, Busan, Korea, Republic of, [7]School of Medicine, Keimyung University, Daegu, Korea, Republic of, [8]Inje University College of Medicine, Inje University Busan Paik Hospital, Busan, Korea, Republic of, [9]Jeonbuk National University medical School, Jeonju, Korea, Republic of, [10]Hallym University College of Medicine, Anyang, Korea, Republic of, [11]Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea, Republic of, [12]Uijeongbu Eulji Medical Center, Eulji University, Uijeongbu, Korea, Republic of

Background: Dasatinib is a potent second generation tyrosine kinase inhibitor (TKI) used for a first line treatment option for patients with chronic myeloid leukemia (CML). Dasatinib has high rates of deep molecular responses (MRs) compared to the first generation TKI imatinib. However, dose reduction due to adverse events (AEs) including cytopenia and pleural effusion is common in patients treated with dasatinib.

Methods: We performed a prospective clinical trial which enrolled patients with newly diagnosed chronic phase CML who had initiated dasatinib as the frontline treatment, experienced dasatinib-related AEs within 12 weeks from the start of dasatinib treatment, and CHANGEd their treatment with reduced dose of 80mg daily were enrolled (DAS-CHANGE study, NCT04150471). For efficacy evaluation, BCR-ABL1/ABL1 levels were measured at screening and every 3 months during treatment by internationally standardized real-time quantitative polymerase chain reaction assay in a central laboratory. The primary endpoint was to evaluate MMR at 12 months. Data of molecular response rates and AEs were collected during a 3 year follow-up period.

Results: A total of 90 patients were screened, and 81 patients were enrolled into the study. Eight patients failed screening because BCR-ABL1 transcript was not decreased below 10% at 3 months and 1 patient withdrew consent. Median age was 52 years, and male genders were 54.3%. Every patient has Korean ethnicity. 18.5% of patients had high Sokal risk score. BCR-ABL1/ABL1 was dropped to a median 0.032% by international scale (IS) at 12 months. Although patients who experienced dose reduction due to AEs within 3 months were enrolled in this study, most patients (96.3%) were able to complete 12 cycles of dasatinib treatment, which suggested that early dose reduction strategy in patients treated with dasatinib could improve the tolerability of continuous dasatinib treatment. Cumulative major molecular response (MMR) rates were 71% at 12 months, and reached up to 85% and 94% at 24 and 36 months, respectively. MR4.0 (BCR-ABL1/ABL1 ratio ≤ 0.01% by IS) and MR4.5 (BCR-ABL1/ABL1 ratio ≤ 0.0032% by IS) were 24% and 11% at 12 months, 46% and 23% at 24 months, 65% and 44% at 36 months, respectively. Most common grade 3/4 AEs were thrombocytopenia (27.2%), and neutropenia was followed by (11.1%). Pleural effusion was occurred in 35.8% of patients, grades were 1 or 2 in most cases. Only one patient (1.2%) experienced grade 3 pleural effusion in our study.

Conclusions: Our results suggests that early dose reduction of dasatinib due to adverse events is safe and feasible. Early dose reduction does not compromise efficacy in patients with newly diagnosed CML. A proactive reduction of dasatinib in the early period in newly diagnosed CML could improve the tolerability of dasatinib without compromising the efficacy.

Clinical Trial Registry: NCT04150471

Disclosure: Nothing to declare.

29 - Chronic Leukaemia and Other Myeloproliferative Disorders

P143

THE CLINICAL VALUE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO AT THE DIAGNOSIS OF MYELOPROLIFERATIVE NEOPLASM

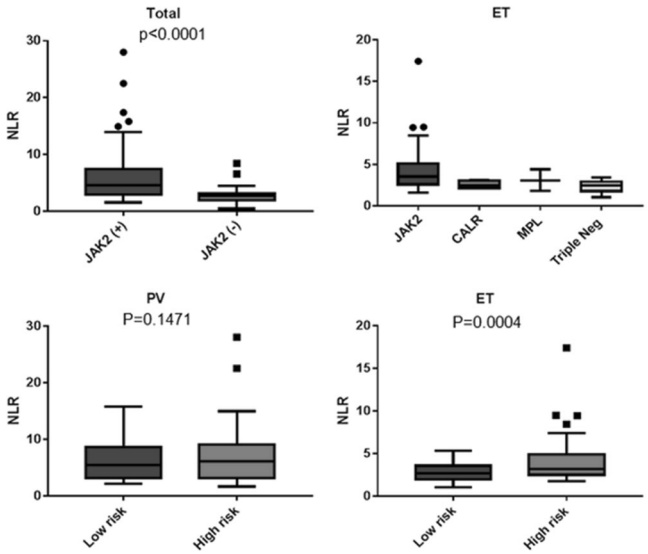
Jong-Ho Won[1], Seug Yun Yoon[1], Min-Young Lee[1], Kyoung Ha Kim[1], Namsu Lee[1]

[1]Soonchunhyang University Seoul Hospital, Seoul, Korea, Republic of

Background: Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), along with polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are clonal disorders of hematopoietic stem cells. MPNs are cancers in which malignant clones trigger cytokines that sustain inflammatory drive. Neutrophile-to-lymphocyte ratio (NLR), calculated as the ratio of absolute neutrophil count to absolute lymphocyte count, is a fast and simple method in assessing inflammatory status and has been reported to be associated with various diseases. In a previous study, we confirmed that NLR in patients with MPN was higher than that in the normal population. We also suggested that NLR would be more beneficial than EPO in diagnosing PV. In this study, we aimed to investigate clinical significance of NLR at the time of MPN diagnosis.

Methods: We retrospectively analyzed electronic medical records of patients who visited Soonchunhyang University Hospital Seoul or Soonchunhyang University Hospital Bucheon. Patients with PV, ET, and MF who met the 2016 WHO criteria were included.

Results:



Among 186 MPN patients, the most common diagnosis was ET (40.9%, 76/186), followed by PV (39.2%, 73/186) and MF (19.9%, 37/186). The median NLR was higher in PV group (6 ± 2.92) than in ET group (2.97 ± 1.22) and MF group (4.47 ± 2.29). The median NLR in the *JAK2* positive group was significantly higher than that in the *JAK2* negative group (5.79 vs. 2.85, respectively, $p < 0.001$). Most patients with PV were proven to be *JAK2* positive, and the NLR was high. In patients with PV, there was no change in NLR according to risk. In patients with ET, the NLR was also higher in the *JAK2*-positive group compared to the other group. In addition, it was established that the NLR was greater in ET patients at high risk compared to those at low risk (4.001 ± 0.34 vs 2.752 ± 0.26, $p = 0.0004$). (Figure) As the disease advanced in patients with MF, the amount of peripheral blood cells other than neutrophils and lymphocytes increased, diminishing the clinical significance of NLR.

Conclusions: NLR was shown to be elevated in *JAK2*-positive MPN patients. This can help in the diagnostic suspicion of PV/ET in patients.

Disclosure: The authors have no conflicts of interest to declare.

16 - Conditioning Regimens

P144

FLUDARABINE EXPOSURE IMPACTS OUTCOMES OF LARGE B-CELL LYMPHOMA PATIENTS RECEIVING TREATMENT WITH CHIMERIC ANTIGEN RECEPTOR T-CELLS

Mario Andres Sanchez-Salinas[1,2], Javier Varela[3], Victor Navarro[4], Cecilia Carpio[1,2], Norberto Nuñez[5], Carla Alonso-Martinez[3], Maria Jose Carreras[3], Iñaki F. Troconiz[6], Anna Farriols[3], Maria Guerra[3], Lucas Rivera[3], Carol Valdivia[3], Francesc Bosch[1,2], Gloria Iacoboni[1,2], Marta Miarons[3], Pere Barba[1,2]

[1]Deparment of Hematology, Vall D'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall D'Hebron., Barcelona, Spain, Universitat Autonoma de Barcelona, Barcelona, Spain, [3]Pharmacy Service, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Oncology Data Science Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain, [5]Vall d'Hebron Institut de Reserca, Barcelona, Spain, [6]Pharmacometrics and Systems Pharmacology Research Unit, School of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain

Background: Lymphodepleting chemotherapy (LDC) has a key role in the treatment success of chimeric antigen receptor (CAR) T-cell therapy. Pharmacokinetic (PK) parameters of fludarabine in the context of LDC have been associated with outcomes in patients with acute lymphoblastic leukaemia but there is scarce data on large B-cell lymphoma (LBCL) patients. Thus, we aimed to study the impact of fludarabine PK on outcomes in this population.

Methods: We conducted a prospective study including adult patients with relapsed/refractory LBCL receiving CAR-T therapy with commercially available axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) at our institution, between March 2021 and September 2022. All patients received LDC with fludarabine and cyclophosphamide (planned fludarabine total dose of 90mg/m² for axi-cel and 75mg/m² for tisa-cel). In total, seven blood samples were taken on days -5, -4, -3 and 30 minutes before CAR-T infusion for each patient to determine fludarabine levels through liquid chromatography MS/MS. We calculated fludarabine exposure as area under the curve (AUC, mg×h/L) applying a population PK model (Langenhorst. ClinPharmacokinetic2019), implemented in NONMEMv7.4. Patients were divided according to 3 exposure threshold levels based on Scordo.ASH22[O657]. We aimed to identify the impact of AUC and pre-infusion fludarabine levels on efficacy and safety outcomes after CAR T-cell therapy.

Results: Fifty-four consecutive patients were included. Baseline characteristics are summarized in Table1. Complete (CR) and overall (ORR) response rates were 63% and 81%, respectively. Median PFS and OS were 14.6 months (CI95% 6.21–not reached [NR]) and NR (CI95% 13-NR), respectively. Incidence of grade ≥3 CRS and ICANS were 14.8% and 9.2%, respectively. Median number of samples analyzed per patient were 7 (IQR = 6-7), 90% (n = 339/378) of the planned samples. Despite patients treated with axi-cel received a higher fludarabine dose than tisa-cel recipients, median exposure was similar in both groups (AUC 25.3 and 25.2). Median fludarabine levels before CAR-T infusion were 5.3ng/mL, also similar in both groups (5 vs 6.7 ng/mL). Patient distribution according to AUC was: <18 (n = 18), 18-25 (n = 27), >25 (n = 9). CR and ORR were higher in patients with intermediate fludarabine exposure (53% vs. 78% vs. 50% and 71% vs. 100% vs. 75%, respectively). Median PFS (5.4, 14.6 and 5 months,p = 0.012) and OS (13 vs. NR vs. 5 months, p = 0.04) were longer in the intermediate group as well. Also, patients with high fludarabine levels at time of CAR-T infusion (> 12ng/mL) had a shorter median PFS (2.6 months vs. NR) and OS (5.1 months vs. NR). Pre-infusion fludarabine levels assessed as a continuous variable were associated with a shorter PFS (HR 1.05 (95%CI 1-1.11, p = 0.03) and OS (HR 1.14 (95%CI 1.06-1.24, p = 0.001). Finally, fludarabine exposure and pre-infusion levels were not associated with a higher risk of CRS or ICANS.

Conclusions: To our knowledge this is the first study evaluating the impact of fludarabine PK on outcomes in patients with LBCL receiving CAR-T cell therapy. Over- and underexposure, as well as high fludarabine levels before CAR T-cell infusion, were associated with worse efficacy outcomes. Dose modulation strategies could potentially improve efficacy results of this promising therapy.

Disclosure: Pere Barba: declares having received honoraria from Allogene, Amgen, BMS, Kit/Gilead, Incyte, Jazz Pharmaceuticals, Miltenyi Biomedicine, Nektar Novartis and Pierre Fabre.

Gloria Iacoboni: Consultancy and Honoraria: Novartis, Roche, Kite/Gilead, Bristol-Myers Squibb, Abbvie, Janssen, Sandoz, Miltenyi, AstraZeneca.

The rest of the authors declare no conflict of interest related to this study.

16 - Conditioning Regimens

P145

AGE IMPACTS RISK OF MIXED CHIMERISM FOLLOWING RIC HCT FOR NON-SCID INBORN ERRORS OF IMMUNITY

Taylor Fitch[1,2], Adam Lane[1,2], John McDonnell[1,2], Jack Bleesing[1,2], Michael Jordan[1,2], Ashish Kumar[1,2], Pooja Khandelwal[1,2], Ruby Khoury[1,2], Rebecca Marsh[1,2], Sharat Chandra[1,2]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, United States, [2]University of Cincinnati College of Medicine, Cincinnati, United States

Background: Alemtuzumab, fludarabine and melphalan containing reduced intensity conditioning (RIC) was commonly used in patients undergoing allogeneic hematopoietic cell transplantation (HCT) for definitive treatment of high-risk inborn errors of immunity (IEI). Although survival is favorable, there is increased risk of mixed chimerism leading to secondary graft failure and subsequently secondary interventions (donor lymphocyte infusion (DLI), CD34+ stem cell boost or second HCT). Our aim was to evaluate if patient age impacts the risk of developing mixed chimerism with this regimen.

Methods: We retrospectively reviewed records of patients who underwent HCT for non-SCID IEIs with an uniform RIC regimen that included intermediate schedule alemtuzumab (1 mg/kg divided over days -14 to - 10), fludarabine (150 mg/m2 or 5 mg/kg if weight <10 kg divided over days -9 to -4), and melphalan (140 mg/m2 or 4.7 mg/kg if weight <10 kg on day-3) between 2010 and 2020 at our institution. Mixed chimerism was defined as <95% donor on 2 or more consecutive occasions on whole blood.

Results: Median age was 3.6 years (range, 0.35-27.2 years). Patients were categorized into 3 age groups <1, 1-5, and > 5 years of age. Forty-nine patients (52.7%) developed mixed chimerism at a median of 34 days post HCT (range, 10-1396 days). Mixed chimerism developed in 88.9 % (n = 16/18) for <1 years of age, 57.1% (n = 20/35) for years 1-5, and 35% (n = 14/40) for patients >5 years. Patients <5 years of age were significantly more likely to develop mixed chimerism (X^2 (3, $N = 93$) = 14.8, $p = 0.001$). Analysis of the cumulative incidence function demonstrated significantly increased incidence of developing mixed chimerism if <1, p = 0.0002. Twenty-seven patients (29.0%) required one or more secondary intervention(s).

Ninety-three patients underwent HCT as shown in table 1.

Number of Patients	Number of patients	93
Age at HCT, years	< 1	18, (19.4%)
	1-5	35, (37.6%)
	> 5	40, (43.0%)
Diagnosis	HLH	49, (52.6%)
	Other	44, (47.3%)
HLA Match	Matched Related Donor (MRD)	21, (22.6%)
	Matched Unrelated Donor (MUD)	44, (47.3%)
	Mismatched Unrelated Donor	28, (30.1%)
Graft Source	Bone Marrow	78, (83.9%)
	PBSC-No manipulation	6, (6.4%)
	PBSC-CD34 selected or alpha/beta depleted	9, (9.7%)
Mixed Chimerism	**Mixed chimerism**	49, (52.7%)
GVHD	All acute GVHD	31, (33.3%)
	Grade II-IV GVHD	21, (22.6%)
	Chronic GVHD	6, (6.5%)
Secondary Interventions	**Total number of patients requiring Secondary Interventions**	27, (29.0%)
	DLI	18, (19.4%)
	CD34 Boost	14, (15.1%)
	Second HCT	9, (9.7%)

Patients <1 years with mixed chimerism were significantly more likely to require secondary intervention than patients > 5 years of age (X^2 (3, $N = 93$) = 15.46, $p = 0.004$). Competing risk regression analysis to estimate the odds of development of mixed chimerism as a function of age category, estimated an increase in odds of development of mixed chimerism for ages <1 (OR 3.72, $p = 0.006$, 95% CI 1.46-19.46) and 1-5 years (OR 2.18, $p = 0.022$, 95% CI 1.12-4.24) compared to age >5 years. There was no significant association between mixed chimerism and graft source, graft type, CD34 /CD3 dose, underlying disease (HLH vs non-HLH), or if the patient developed GVHD.

Conclusions: Our study demonstrates that young age (< 5 years), especially age <1 year is associated with increased risk of developing mixed chimerism in patients undergoing RIC-HCT with intermediate schedule alemtuzumab, fludarabine and melphalan for non-SCID IEIs. In addition, children < 1 year of age required more secondary interventions. Our data suggests to tailor regimen intensity based on age to reduce incidence of mixed chimerism. Children <5 years, particularly those <1 year of age, would benefit from increasing the intensity of RIC regimen. Possible strategies include adding thiotepa to the RIC regimen or using a busulfan based reduced toxicity regimen.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P146

INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION AFTER HIGH-DOSE THIOTEPA AND CONCURRENT PHENYTOIN

Maria Assunta Limongiello[1], Elisabetta Metafuni[1], Sabrina Giammarco[1], Federica Sorà[1], Francesco Autore[1], Idanna Innocenti[1], Alberto Fresa[2], Eugenio Galli[1], Andrea Bacigalupo[2], Patrizia Chiusolo[1,2], Simona Sica[1,2]

[1]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica e Ematologia, Rome, Italy, [2]Università Cattolica del Sacro Cuore, Rome, Italy

Background: Thiotepa is an alkylating compound with immunosuppressive properties which holds favourable characteristics as the capability of penetrating the blood-brain barrier combined with reduced non-haematologic toxicity. This feature led to a widespread

use of this compound within transplant preparative regimens. In 1999, our centre described a first report of inappropriate secretion of antidiuretic hormone syndrome (SIADH) in a patient with primary central nervous system lymphoma who underwent high-dose thiotepa as conditioning for autologous stem cell transplantation (ASCT). The conditioning protocol consisting of thiotepa, busulfan and fludarabine (TBF), initially designed for cord blood transplant, is actually widely used as standard myeloablative conditioning regimen for allogeneic stem cell transplantation (HSCT).

Methods: This is a monocentric analysis on 259 patients who underwent HSCT after TBF conditioning regimen between May 2018 and November 2022.

Results: During this period, 18 patients developed SIADH with an incidence of 7%. Baseline patients' characteristics are listed in Table 1. Sex was male in 8 cases (44 %) and female in 10 cases (56 %). Median age was 59 years (range 30 – 70). Seven patients had acute myeloid leukemia (AML) (38 %), 8 patients had myelofibrosis (MFI) (44%), 1 patient had mixed phenotype acute leukemia (MPAL) (6%), 1 patient had lymphoplasmacytic lymphoma (LPL) (6 %), 1 patient had systemic mastocytosis (SM) (6 %). Five patients (28%) underwent standard TBF, 9 patients (50%) TBF2 (busulfan for 2 days), 4 patients (22 %) TBF1 (1 day busulfan). Hyponatremia was detected at 48 hours from thiotepa infusion in 8 patients (44 %), at 72 hours in 8 patients (44 %), and at 96 hours in 2 patients (12 %). Laboratory tests showed the following median values: sodium (Na) 121.5 mmol/l (range 112-130), cortisol 136.5 ng/ml (range 121-175), antidiuretic hormone (ADH) 2 pg/ml (range 0.6-72.7), plasma osmolarity 259.5 mOsm/l (range 250-282), urine osmolarity 371.5 mOsm/kg (range 341-378), urinary sodium 103 mmol/l (range 53-147). Clinically, 13 patients (72 %) had nausea and among them, 9 had also vomiting, 2 had also profuse sweating and confusion, 1 had also nystagmus and subjective vertigo. One patient (6 %) had headache only, 1 (6 %) had disorientation and tremors. Three patients (16 %) had no symptoms.

Table 1. Patients' characteristics

Total patients number	18
Gender n (%)	Male 8 (44 %)
	Female 10 (56 %)
Median age at transplant	
Years (range)	59 years (30-70)
Hematological disease n (%)	
AML	7 (38%)
MFI	8 (44 %)
MPAL	1 (6 %)
LPL	1 (6 %)
SM	1 (6%)
Conditioning n (%)	
TBF	5 (28 %)
TBF2	9 (50 %)
TBF1	4 (22 %)
Median sodium value (range, mmol/l)	121.5 (112-130) (NV 135-145)
Median cortisol value (range, ng/l)	136.5 (121-175) (NV 60-220)
Median ADH value (range, pg/ml)	2 (0.6-72.7) (NV < 8)
Median plasma osmolarity value (range, mOsm/l)	259.5 (250-282) (NV 280-295)
Median urine osmolarity value (range, mOsm/kg)	371.5 (341-378) (NV 50-1200)
Median urinary sodium value (range, mmol/24h)	103 (53-147) (NV 40-220)
Symptoms n (%)	
Headache	1 (6%)
Disorientation and tremors	1 (6%)
Nausea and vomiting	13 (72%)
No symptoms	3 (16%)

Conclusions: Despite the limits of a retrospective study, our real-life analysis shows that the presence of hyponatremia with corresponding serum hypo-osmolality and continuing urinary sodium excretion are suggestive of SIADH diagnosis in the presence of normovolemia. Administration of normal saline, diuretics and fluid restriction was followed by a rapid normalization of the hyponatremia in all patients together with normalization of the neurological condition. Moreover, hyponatremia and neurological symptoms developed 48-72 hours after thiotepa infusion while on phenytoin prophylaxis for busulfan. The role of phenytoin as a potential inhibitor of ADH secretion seems also relevant, as shown in a recent Swedish study. In conclusion, strict monitoring of fluid balance and electrolytes should be undertaken during conditioning in order to promptly detect SIADH onset, allowing immediate treatment of patients receiving concomitant thiotepa and phenytoin.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P147

CHIMERISM ANALYSIS POST-HSCT WITH A TREOSULFAN-BASED CONDITIONING REGIMEN FOR PEDIATRIC NONMALIGNANT DISEASES

Ehud Even-Or[1,2], Ziv Cohen[2], Irina Zaidman[1,2], Yael Dinur Schejter[1,2], Adeeb Naser Eddin[1,2], Polina Stepensky[1,2]

[1]Hadassah Medical Center, Jerusalem, Israel, [2]The Hebrew University, Jerusalem, Israel

Background: Allogeneic Hematopoietic stem cell transplantation (HSCT) offers cures for a wide variety of pediatric nonmalignant diseases by providing healthy stem cells, which may produce the missing enzymes or replace malfunctioning cells. Unlike HSCT for malignant diseases, in transplants for nonmalignant diseases, full-donor chimerism (FD) is not necessarily required and a state of stable mixed donor-recipient chimerism (MC) may suffice for a cure. The clinical significance of MC and the factors affecting the evolvement of this condition are poorly understood. In recent years, the use of treosulfan-based conditioning regimens for HSCT in nonmalignant diseases became popular due to the myeloablative quality and low toxicity profile of these regimens. Rates of MC with treosulfan-based regiments are relatively high. In this study, we aimed to shed light on the phenomenon of MC by analyzing clinical data and post-HSCT chimerism results of pediatric patients who received a treosulfan-based conditioning regimen in our center.

Methods: In this retrospective study, we collected and analyzed clinical and transplant data from medical charts of pediatric patients who underwent HSCT for nonmalignant diseases with a treosulfan-based conditioning regimen at Hadassah Medical Center. The collected clinical data included patient demographics, primary disease, post-HSCT clinical course, and outcomes. Transplant data included donor and graft parameters, time to engraftment, and chimerism at several time points post-HSCT.

Results: Out of the 92 patients who were included in the study, 27 (29.3%) developed MC, and 65 (70.7%) achieved full-donor chimerism. Survival rates were similar between the two groups (88.9% vs 90.8% overall survival in the MC and FD groups respectively, $p = 0.882$). Acute GvHD rate was significantly lower in the MC group (14.8% vs 41.3% GvHD rate in the MC and FD groups respectively, $p = 0.016$). Graft cellularity in the MC group was higher than in the FD group (mean TNC $5.3x10^8$ vs $4.1x10^8$ in the MC and FD groups respectively, $p = 0.047$). No correlation was found between engraftment time and the development of mixed chimerism. Patient age at transplant was significantly lower in the MC group (mean age 1.41 years vs 4.14 years in the MC and FD groups respectively, $p < 0.001$). Looking at primary disease, patients with SCID developed significantly more MC (9 out of 18 SCID patients, 50%) than patients with other diseases ($p = 0.033$). Other factors associated with donor match such as family vs unrelated donors, degree of HLA match, blood type, donor and recipient pre-HSCT CMV status, were not found to be correlated to the development of MC in our cohort.

Conclusions: Stable MC is a common condition in post-HSCT pediatric nonmalignant patients treated with a treosulfan-based conditioning regimen. In our cohort, acute GvHD rate was significantly lower in the MC group, suggesting that a state of MC may pose as an advantage in nonmalignant diseases where FD chimerism is not mandatory. Younger age was associated with developing MC, possibly due to differences in chemotherapy bioavailability and metabolism in younger patients. Larger studies are required to better understand the factors associated with the development of MC and its possible advantages.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P148

FLUDARABINE, BUSULFAN AND MELPHALAN BASED CONDITIONING REDUCED RELAPSE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ADULT PATIENTS WITH MYELOID MALIGNANCIES: A MULTICENTER RETROSPECTIVE ANALYSIS

Jieling Jiang[1], Sanbin Wang[2], Xiaojin Wu[3], Xiaolin Yin[4], Xiaofan Li[5], Dong Wu[6], Quanyi Lu[7], Kourong Miao[8], Houcai Wang[9], Jiong Hu[10]

[1]Ruijin Hospital affiliated to Shanghai JiaoTong university School of Medicine, Shanghai, China, [2]The 920th Hospital of Joint Logistics Support Force of People's Liberation Army of China, Kunming, China, [3]The First Affiliated Hospital of Soochow University, Soohow, China, [4]The 923th Hospital of Joint Logistics Support Force of People's Liberation Army of China, Nanning, China, [5]Fujian Medical University Union Hospital, Fuzhou, China, [6]Shanghai JiaoTong University Affiliated sixth People's Hospital, Shanghai, China, [7]Zhongshan Hospital Affialted to Xiamen University, Xiamen, China, [8]The First Affilated Hospital of Nanjing Medical University, Nanjing, China, [9]Shanghai Tenth People's Hospital, Shanghai, China, [10]Ruijin Hospital Affiliated to Shanghai JiaoTong university School of medicine, Shanghai, China

Background: Fludarabine in combination with full dose of busulfan has become the most popular myeloablative conditioning regimen for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients with myeloid malignancies, while relapse was till the main obstacle for cure. We observed a particular low incidence of relapse in patients prepared with double alkylating agents of busulfan and melphalan in our previous single center phase II study (NCT04269811). To further evaluate the efficacy of the regimen, we designed a multicenter retrospective study and tried to verify our previous results in large samples.

Methods: The inclusion criteria were : 1) Adult patients (16 to 70 years old) with myeloid malignancies including AML, MDS-EB-1, MDS-EB-2 and CMML; 2) Patients received first allo-HSCT from HLA matched sibling donors(MSDs), matched unrelated donor(MUDs), related haplo-identical donor(HIDs) or cord blood(CB) during Jan.2020 to Mar. 2022; 3) Conditioning regimen included busulfan (≥ 3.2mg/kg) and melphalan(≥ 100mg/m2); fludarabine, cladribine, cytarabine, etopodide or cyclophosphamide could be used in combination, while venetoclax, thiotepa and total body irradiation(TBI) were excluded. Clinical data were collected and the data for patients who were alive were censored at last follow-up on May 31, 2022. The statistics was performed by SPSS and R software. The overall survival(OS) and disease free survival (DFS) were calculated using the Kaplan-Meier method and compared by log-rank tests. The cumulative incidence of relapse(CIR) and non-relapse mortality(NRM) were calculated using a competing-risk setting.

Results:

Characteristics	Values/n	Characteristics	Values/n
All eligible patients	202	Donor type	
Age, median (range) years	45 (16 ~ 67)	MSD (1 homogeneic)	45 (22.3%)
Sex		MUD	10 (4.9%)
Male	116 (57.4%)	HID	143 (70.8%)
Female	86 (42.6%)	CB	4(2.0%)
Diagnosis		GVHD prophylaxis	
AML	153 (75.7%)	No prophylaxis	1(0.5%)
MDS	43(21.3%)	PTCy based	167 (82.7%)
CMML	6(3.0%)	ATG based	34 (16.8%)

A total of 202 patients from nine HSCT centers were enrolled in this study. Most patients(193/202) received conditioning only consisted of different dose of fludarabine, busulfan and melphalan. Post transplantation cyclophosphamide (PTCy) based graft-versus-host disease (GVHD) prophylaxis strategy was used in 167 out of all patients. The median follow-up time was 314 days (range, 8~841days) for the whole cohort and the baseline data were summarized in Table-1. Three patients developed primary engraft failure. The median time for neutrophil and platelet recovery were 13 days (range, 9 ~ 22 days) and 14 days (range, 9 ~ 121 days), respectively. The 100-day cumulative incidence of grade II-IV acute GVHD was 11.4 ± 2.2% and the 2-year cumulative incidence of moderate/severe chronic GVHD was 6.4 ± 1.7%. At last follow-up, eighteen patients died of non-relapse reasons and sixteen patients relapsed including eight patients were still alive. The 1-year and 2-year NRM were both 10.3% ± 2.4% and the CIR at 1-year was 6.9% ± 2.2%, while the CIR at 2-year was 17.8% ± 1.7%. The 1-year OS and DFS were 86.7% ± 2.7% and 83.4% ± 3.0%, while the 2-year OS and DFS were 79.9% ± 4.3% and 72.4% ± 5.5%, respectively. Subgroup analysis showed no significance in OS and DFS when grouping by sex, age(<50y vs. ≥50y), diagnosis (AML vs. MDS), disease risk index (DRI, low risk vs. intermediate risk vs high/very high risk) and transplantation conditioning intensity(TCI, low vs. intermediate vs. intensive).

Conclusions: These results identified with our previous study and supported that busulfan and melphalan based conditioning was associated with low relapse rate and acceptable NRM in adult patients with myeloid malignancies. Randomized controlled clinical trial should be warranted to evaluate this regimen further.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P149

REDUCED INTENSITY ALLOGENEIC TRANSPLANTATION COMBINED WITH STRATEGIC DONOR LYMPHOCYTE INFUSION USE OFFERS AN EFFECTIVE AND TOLERABLE CURATIVE THERAPY FOR OLDER PATIENTS WITH MYELOID DISEASE

Chris Armstrong[1], Eibhlin Conneally[1], Catherine Flynn[1], Nicola Gardiner[1], Hayley Foy-Stones[1], Mairead Ní Chongháile[1], Nina Orfali[1]

[1]St. James' Hospital, Dublin, Ireland

Background: Reduced-intensity conditioning (RIC) regimens offer potentially curative transplants to older patients with aggressive myeloid disease including AML, MDS and MPN, but are associated with an increased incidence of relapse compared to myeloablative regimens. Donor lymphocyte infusions (DLIs) administered strategically in high-risk patients (prophylactic) or in cases of mixed donor chimerism (pre-emptive) can attenuate this increased relapse risk in those who have not experienced de novo GVHD. Increasingly DLI is also used as an adjunct to salvage treatment after relapse (therapeutic). We here examine the effectiveness and potential burden of this approach in older patients.

Methods: We performed a national retrospective review of 174 patients with myeloid disease who received peripheral blood stem cell grafts between 2015 and 2022, following reduced intensity Flu-Bu-ATG conditioning (Fludarabine 30/m^2 D-9 to D-4, Busulfan 3.2mg/kg D-5 to D-4, ATG Grafalon® 10mg(SIB)/20mg(MUD)/kg D-3 to D-1). Patients received CNI/MTX as GVHD prophylaxis. Statistical analysis was performed using *STATA*.

Results: The median age of our cohort was 60yrs (range 27-74) (*Table 1*). 162 had intermediate or high-risk CIBMTR DRI scores. The median age-adjusted HCT-CI was 2. Neutrophil engraftment was universal and platelet engraftment was 97.1% at a median of 20 and 22 days respectively. The cumulative incidence (CI) of acute GVHD at 1- and 2-years was 28.2% and 55.4% respectively. The CI of chronic GVHD at 1- and 2-years was 16% and 24%.

Overall survival (OS) at 1 and 2 years was estimated at 80.7% and 71.1%, and similar across disease groups ($p = 0.45$) and age groups ($p = 0.38$). The cumulative incidence of NRM at 2 years was 12.5% and was not affected by age ($p = 0.63$). The cumulative incidence of relapse at 1 and 2 years was 21.7% and 31.4%, occurring at an overall median of 197 days (64.8% in year 1). Reduced relapse was seen in aGVHD and cGVHD ($p = 0.02$, $p = 0.04$) but increased in those with a high DRI ($p = 0.04$) or recipients of a cryopreserved graft ($p = 0.01$).

At a median follow up of 610 days, 61 patients had received a DLI. Median time to first infusion was 183 days. 44 patients received DLIs in remission. 3 received prophylactic infusions due to high-riskdisease despite full donor chimerism and subsequently remained in remission. Mixed chimerism was detected at D90 in 113 patients, of whom 41 received a pre-emptive DLI. Subsequent relapse rates were 19.5% vs. 37.7% in those with mixed chimerism who did not receive a pre-emptive DLI ($p = 0.05$). Therapeutic DLIs were administered to 17 patients with confirmed relapse after D90. Median survival in this group was 600 days, compared to 351 days in patients who relapsed beyond D90 but did not receive a therapeutic DLI ($n = 27$). Survival in those receiving a DLI for any indication was significantly greater than non-recipients ($p = 0.004$).

Table 1: Demographics

Sex	
Male	106 (60.9%)
Female	68 (39.1%)
Age	Median: 60 Range: 27-74
Disease	
AML	91 (52%)
MDS	43 (25%)
MPN	40 (23%)
CIBMTR Disease Risk Index	
Low	12 (7%)
Intermediate	108 (62%)
High	54 (31%)
Age-adjusted HCT-CI	Median: 2 Range: 1-8
Donor	
Sibling	77 (44%)
Unrelated	97 (56%)
GVHD	
Acute	103/173 (59%)
Chronic	25/164 (15%)
Cryopreservation of graft pre-infusion	20 (11%)
Mortality	
Non-relapse	19
Relapse	30
Donor Lymphocyte Infusion	
Prophylactic	3/44 Full donor chimerism
Pre-emptive	41/113 Mixed chimerism
Therapeutic	17/44 Relapsed

Conclusions: We validate the high clinical efficacy and tolerability of RIC HSCT in older patients with myeloid disease and confirm the potent immunomodulatory role of DLI to help safely abrogate the inherent increased relapse risk.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P150

TOTAL BODY IRRADIATION PROCEDURES IN THE FORUM TRIAL

Bianca Hoeben[1,2], Chiara Julita[3], Valeria Tremolada[3], Peter Bader[4], Jochen Buechner[5], Jean-Hugues Dalle[6], Marianne Ifversen[7], Franco Locatelli[8], Petr Sedláček[9], Jerry Stein[10], Ulrike Pötschger[11], Karin Dieckmann[12], Detlef Imhoff[4], Rudolf Schwarz[13], Alexandra Jensen[14,15], Valentine Martin[16], Sylvie Helfre[17], Claire Charra-Brunaud[18], Elisa Meldolesi[19], Eugenio

Vinés[20], Hans Theodor Eich[21], Natalia Pinto[22], Michaela Jirkovska[9], Örs Ferenczi[23], Agnieszka Dybko[24], Mogens Bernsdorf[7], Claudia Linsenmeier[25], Charalampos Zampatis[26], Alexander Fosså[5], Monika Sandorova[27], Jordi Giralt[28], Christina Peters[29,11], Adriana Balduzzi[30]

[1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, [3]ASST Monza, Ospedale San Gerardo, Monza, Italy, [4]Goethe-University Frankfurt, Frankfurt, Germany, [5]Oslo University Hospital, Oslo, Norway, [6]Robert Debré Hospital, GHU APHP Nord Université Paris Cité, Paris, France, [7]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [8]IRCCS Bambino Gesù Children's Hospital, Rome, Italy, [9]Teaching Hospital Motol, 2nd Medical School, Charles University Motol, Prague, Czech Republic, [10]Schneider Children's Medical Center, Tel Aviv, Israel, [11]Children's Cancer Research Institute, Vienna, Austria, [12]Medical University Vienna, Vienna, Austria, [13]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [14]University Hospitals Gießen and Marburg (UKGM), University Hospitals Gießen and Marburg (UKGM), Germany, [15]Philipps University, Marburg, Germany, [16]Gustave Roussy, Paris, France, [17]Institut Curie, Paris, France, [18]Institut de Cancérologie de Lorraine Alexis Vautrin, Nancy, France, [19]IRCCS Fondazione Policlinico Universitario 'A.Gemelli', Rome, Italy, [20]School of Medicine, Pontificia Universidad Católica de Chile, Red de Salud UC-Christus, Santiago, Chile, [21]University Hospital Muenster, Muenster, Germany, [22]Hospital de Pediatría 'Prof. Dr. Juan P. Garrahan', Buenos Aires, Argentina, [23]National Institute of Oncology, Budapest, Hungary, [24]Lower Silesian Oncology, Pulmonology and Hematology Center, Wroclaw, Poland, [25]University Hospital Zürich, Zürich, Switzerland, [26]St. Savvas Anticancer Hospital, Athens, Greece, [27]Oncological Institute of St. Elizabeth, Bratislava, Slovakia, [28]Vall d'Hebron University Hospital, Barcelona, Spain, [29]St. Anna Children's Hospital, Vienna, Austria, [30]Università degli Studi di Milano Bicocca, Fondazione MBBM / Ospedale San Gerardo, Monza, Italy

Background: In the ALL SCTped FORUM study (NCT01949129, 2013-2019), TBI during conditioning for HSCT in children with high-risk ALL was performed in many international radiotherapy centers. We aimed to evaluate the variability of the TBI procedures.

Methods: An electronic survey investigating TBI delivery technique characteristics was distributed among the FORUM Principal Investigators and forwarded to their respective radiation oncologists.

Results: Responses were collected from 54 radiotherapy centers in 25 countries, serving 53 of the 88 FORUM centers. Thirty-nine radiotherapy centers treated ≤10 patients annually. Forty-three had treated ≤10 patients with TBI within the FORUM trial, and few 26-30 (n = 3) or >40 (n = 3) patients. Fractionation was mainly 12 Gy in 6 fractions of 2 Gy, usually twice-daily (n = 52), and once 1 fraction daily over 6 days. Twelve Gy in 4 daily fractions was given in 1 center, and 9.9 Gy in 3 fractions was preferred in case of sedation in 2 centers. Lung dose was reduced in 44 centers, mostly to 8-10 Gy. Other organs, especially kidneys, received dose-reduction as well in 10 centers. Patient positions were lateral decubitus (n = 15), supine (n = 17), supine and prone (n = 25), and sitting (n = 5). Beam setup was: conventional TBI with large fields at extended distance (n = 32); sweeping beam (n = 8), adjacent fields or moving couch (n = 11) with the patient underneath the gantry; and conformal modulated TBI at extended distance (n = 1), or with a conformal modulated rotational technique (n = 10). Some centers used multiple setups or switched techniques during the trial period. Conventional TBI beam direction was anterior-posterior/posterior-anterior for 28 centers, bilateral for 9, and from 4 sides in 7. Distance to the gantry was 5-6m (n = 3), 4-5m (n = 11), 3-4m (n = 11), 2-3m (n = 10), 1-2m (n = 15), or 1m (n = 6). Thirty-nine centers performed planning CT scans. Doses were calculated with a treatment planning system (n = 28), and/or with spreadsheet calculation (n = 30). Machines used were cobalt (n = 2), linear accelerator (n = 49), and/or tomotherapy (n = 4). Beam energies were ≤6 MV in 33, 6-15 MV in 16, and >15 MV in 6 centers. Dose rates at patient midplane varied from 0-5 cGy/min (n = 8), to 6-10 cGy/min (n = 13), 11-15 cGy/min (n = 7), 16-25 cGy/min (n = 13), or 60-80 cGy/min (n = 4), and variable high dose rates in conformal techniques (n = 12). Interventions to improve dose homogeneity over the body were performed in 38 centers, beam spoilers to increase surface doses in 33. Dose measurements on the patient during treatment occurred in 43 centers.

Conclusions: In the FORUM trial, radiotherapy centers used multiple known variations in setup of conventional TBI techniques. Conformal rotational TBI was used in a fifth of the centers, and its implementation is increasing. Fractionation and lung dose reduction were mainly consistent with the study protocol. To which extent different radiobiological effects due to variations in TBI setup, technique, fractionation, and timing may have led to potential differences in outcome or toxicities will be the object of further investigation in this homogeneous FORUM cohort.

Clinical Trial Registry: This is not a clinical trial, but a survey among centers who performed TBI during conditioning of children in the trial: NCT01949129

Disclosure: Conflict of interest: nothing to declare.

16 - Conditioning Regimens

P151

RETROSPECTIVE COMPARATIVE ANALYSIS OF TWO DIFFERENT FORMS OF ANTI THYMOCYTE GLOBULIN (ATG) IN PEDIATRIC AND YOUNG ADULT PATIENTS UNDERGOING ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANT

Gaurav Kharya[1], Ravi Shankar[1], Saksham Singh[1], Varsha Mishra[1], Garima Nirmal[1], Atish Bakane[1], Bharti Sharma[1], Manju Joseph[1], K K Swathymon[1], Mohit Chaudhary[2], Himshikha Yadav[1]

[1]Centre for Bone Marrow Transplant & Cellular Therapy, Indraprastha Apollo Hospital, Delhi, India, Indraprastha Apollo Hospital, Delhi, India

Background: Anti-thymocyte Globulin (ATG) is an integral part of conditioning chemotherapy for pediatric and young adult patients undergoing HSCT. With increasing use of alternate donor sources, role of ATG to prevent graft failure and graft versus host disease (GvHD) is becoming even more relevant. Although used widely but the data on comparative analysis of different forms of ATG is sparse, thus leaving the transplant physicians with multiple unanswered questions. In a retrospective analysis, we tried to look at the comparative efficacy and safety of two different forms of ATG namely Thymoglobulin® and Grafalon®. Thymglobulin® is obtained after administration of human thymocytes in pathogen free rabbits whereas Grafalon® is produced by immunizing the rabbits with Jurkat T-cell leukemia line.

Methods: We retrospectively analyzed a total of 155 patients who underwent allogenic-HSCT at our center, for both benign and malignant conditions, from August 2019 to November 2022. The primary objectives of the study were to compare the overall survival (OS), event free survival (EFS), engraftment kinetics, graft

failure (GF) and GVHD between the two different cohort. The secondary objective was to assess the immune reconstitution and to compare the complications in the two groups.

Results:

Patient variables	Thymoglobulin n = 63	Grafalon n = 92
Graft failure	3	1
Acute GVHD	18 (8)	10 (4)
Chronic GVHD	8	6
CMV reactivation	32	45
Bacterial infections	15	19
PRES	6	1
Engraftment syndrome	13	6
Median time to neutrophil engraftment (days)	13 (9-20)	15 (9-28)
Median time to platelet engraftment (days)	13 (9-35)	16 (6-48)

A total of 63 patients received Thymglobulin® and 92 received Grafalon®. Patient and donor characteristics have been highlighted in table 1. There was no significant difference in OS ($p = 0.09$), EFS ($p = 0.1$), grade III-IV acute GVHD ($p = 0.06$) and chronic GVHD ($p = 0.25$) in between the two groups. However, GF ($p = 0.04$), grade II-IV acute GVHD ($p = 0.02$) were significant less in Grafalon® cohort. Neutrophil and platelet engraftment were however better in Thymoglobulin cohort ($p = 0.0001$ and 0.0055) respectively. Reconstitution of CD3, CD4, CD8, CD19 and CD 56 subsets at day +100 were not statistically different between the two groups. Immunoglobulin profile at day +100 was in favor of Grafalon® for IgM ($p = 0.02$), however for IgG and IgA there was no significant difference. There was no significant difference in bacterial, fungal or viral (CMV, BKV, adenovirus) infections between the two group. Among other complications, we observed PRES and engraftment syndrome occurred more in Thymoglobulin® cohort ($p = 0.01$).

Conclusions: We observed Grafalon® cohort to have significantly less graft failure and overall grade II-IV GVHD whereas Thymoglobulin® cohort showed better engraftment kinetics. However, there was no significant difference in OS, EFS and grade III-IV GVHD in between the two groups. Also, there was no significant difference for immune reconstitution at day +100 in between the two groups except for IgM reconstitution, which was in favor of Grafalon®. There was no difference in the two groups for any infections. PRES was seen more in Thymoglobulin cohort but that might be confounded by concurrent use of CNI's.

Clinical Trial Registry: Not applicable, retrospective analysis.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P152

TREOSULFAN BASED CONDITIONING IN PEDIATRIC PATIENTS WITH NON-MALIGNANT HAEMATOLOGICAL INDICATIONS FOR TRANSPLANT IS ASSOCIATED WITH VERY LOW TREATMENT RELATED MORTALITY AND HIGH OVERALL SURVIVAL

Daniel Farrugia[1], Salah Ali[1], Persis J. Amrolia[2], Catriona Brook[1], Ben Carpenter[3], Rachael Hough[4], Anna-Maria Ewins[5], Oana Mirci-Danicar[6], Brenda Gibson[7], Katharine Patrick[8], Geoff Shenton[9], Sanjay Tewari[10], Robert F. Wynn[11], Robert Chiesa[2], Kanchan Rao[2], Mary Slatter[9], Su Han Lum[9], Beki James[1]

[1]Leeds Children's Hospital, Leeds, United Kingdom, [2]Great Ormond Street Hospital for Children, London, United Kingdom, [3]University College, London, United Kingdom, [4]University College London, London, United Kingdom, [5]University of Glasgow, Glasgow, United Kingdom, [6]Bristol Royal Hospital for Children, Bristol, United Kingdom, [7]Royal Hospital for Children, Glasgow, United Kingdom, [8]Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom, [9]Great North Children's Hospital, Newcastle, United Kingdom, [10]Royal Marsden Hospital, London, United Kingdom, [11]Royal Manchester Children's Hospital, Manchester, United Kingdom

Background: Treosulfan (L-treitol-1,4-bis-methanesulfonate) is a myeloablative alkylating agent with a comparatively favorable toxicity profile and more predictable pharmacokinetics than busulfan, which historically formed the backbone of many conditioning regimens. It is increasingly used in pediatric haematopoietic stem cell transplantation (HSCT) although there remains a paucity of data regarding toxicity and outcomes according to disease-specific pediatric cohorts.

Methods: A retrospective multi-center analysis was performed for consecutive pediatric patients who underwent a treosulfan conditioned HSCT in 9 BSBMTCT centers in the UK (Bristol; Glasgow; Great Ormond Street; Leeds; Manchester; Newcastle; Sheffield; Royal Marsden Hospital and University College, London) for non-malignant haematological indications between 2015 and 2021 inclusive, to determine the incidence of key treatment related toxicities, as well as treatment related mortality (TRM) and overall survival (OS).

Results: 96 patients met the criteria, with haemoglobinopathy being the most common indication: 32 (33%) had thalassaemia major; 22 (30%) had sickle cell disease; followed by bone marrow failure in 32 (33%). The majority, 57 (60%), had a matched family donor, the source was bone marrow in 70 (93%) and the most common combination was fludarabine/ treosulfan/thiotepa in 87(90%). The OS was 95% with a median follow up of was 4 years, and EFS was similarly high at 87%. There were no significant predictors on univariate analysis. The 5 deaths were due to: respiratory failure ($n = 2$); thrombotic microangiopathy with multi-organ failure (MOF; $n = 1$); sepsis with MOF ($n = 1$); and cerebral fungal infection associated with GVHD ($n = 1$). Only 1% had Grade II-IV GVHD, and 6% chronic GVHD. VOD occurred in 2 (2%). Five patients (5%) had second procedures: 3 had an unconditioned stem cell boost; 1 had donor lymphocyte infusions and 1 patient with thalassaemia had a second transplant for primary aplasia. They are alive and well.

Conclusions: These results for treosulfan based conditioning are very encouraging, with high overall survival and very low treatment related mortality and low graft failure. The poorer outcomes in osteopetrosis are not dissimilar to other cohorts, reflecting the need for timely diagnosis and transplantation. A prospective randomized comparison with busulfan containing regimens is unlikely to happen, but this real world data suggests a superiority over historical busulfan conditioned cohorts. Further, as the data matures it will inform understanding of late effects, including on fertility and development.

Disclosure: No disclosures.

16 - Conditioning Regimens

P153

COMPARISON OF FLUDARABINE/MELPHALAN(FM140) WITH FLUDARABINE/MELPHALAN/BCNU(FBM110) IN PATIENTS WITH RELAPSED/REFRACTORY AML UNDERGOING

ALLOGENEIC TRANSPLANTATION – A REGISTRY STUDY ON BEHALF OF THE EBMT ACUTE LEUKEMIA WORKING PARTY

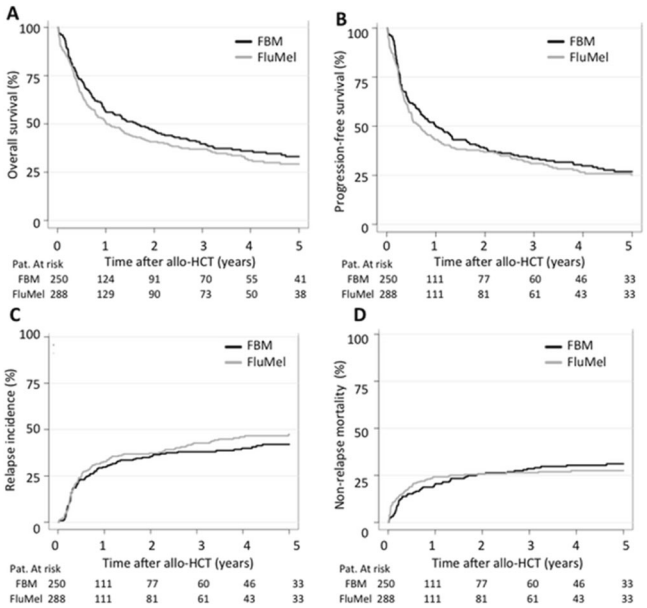
Jesus Duque-Afonso[1], Jürgen Finke[1], Maud Ngoya[2], Jacques-Emmanuel Galimard[2], Martin Bornhäuser[3], Matthias Eder[4], Wolf Rösler[5], Gesine Bug[6], Andreas Neubauer[7], Matthias Edinger[8], Gerald G. Wulf[9], Pavel Jindra[10], Herman Einsele[11], Matthias Stelljes[12], Dominik Selleslag[13], Eva Maria Wagner-Drouet[14], Donald Bunjes[15], Alexandros Spyridonidis[16], Eolia Brissot[2], Arnon Nagler[17], Fabio Ciceri[18], Mohamad Mohty[2]

[1]University of Freiburg, Freiburg, Germany, [2]Hôpital Saint Antoine, Sorbonne University, Paris, France, [3]University of Dresden, Dresden, Germany, [4]University of Hannover, Hannover, Germany, [5]University of Erlangen, Erlangen, Germany, [6]University of Frankfurt, Frankfurt, Germany, [7]University of Marburg, Marburg, Germany, [8]University of Regensburg, Regensburg, Germany, [9]University of Göttingen, Göttingen, Germany, [10]University of Pilsen, Pilsen, Czech Republic, [11]University of Würzburg, Würzburg, Germany, [12]University of Münster, Münster, Germany, [13]University of Brugge, Brugge, Belgium, [14]University of Mainz, Mainz, Germany, [15]University of Ulm, Ulm, Germany, [16]University of Patras, Patras, Greece, [17]Chaim Sheba Medical Center, Tel Hashomer, Israel, [18]IRCCS San Raffaele Scientific Institute, Milan, Italy

Background: The treatment of relapsed/refractory AML is associated with a dismal prognosis. The allogeneic hematopoietic cell transplantation (allo-HCT) is frequently performed as salvage therapy in this scenario. Conditioning protocols have been developed with the aim to reduce the leukemia burden without increasing their toxicity, especially in older patients or those with comorbidities. In our previous studies, we showed that AML patients in complete remission (CR) had better outcomes including overall survival (OS) after conditioning based on two alkylating agents (FBM110/FTM110) compared to conditioning with FM140 from the intermediate transplantation conditioning index (TCI) score.

Methods: In the present study, we compared the conditioning protocol FM140 (fludarabine, median 150 mg/m2; melphalan, median 140mg/m2) with a conditioning protocol based on FM140 with an additional alkylating agent i.e. FBM110 (fludarabine, median 150mg/m2; BCNU/carmustine 300-400mg/m2; and melphalan, median 110 mg/m2). From the registry of the EBMT Acute Leukemia Working Party, we identified 538 adult patients (288 patients with FM140 and 250 patients with FBM110) with acute myeloid leukemia (AML) with active disease (primary induction failure, relapsed or progressive disease), and transplanted with unmanipulated peripheral blood grafts from related or unrelated donors. Impacts of these two regimens on the outcomes were evaluated using Cox multivariable models.

Results: Patients in the FBM110 group were older (63.4 years vs. 58.9 years, $p < 0.001$) and had a worse Karnofsky performance score (KPS < 90, 50.4% vs. 41.7%, $p < 0.05$). Patients conditioned with FBM110 received more often in vivo T-cell depletion (TCD, 89.2% vs 63.9%, $p < 0.001$) of which they received more often ATG (75.6% vs. 46.9%) compared to patients conditioned with FM140, who received more frequently alemtuzumab (17% vs. 13.6%). No differences were observed between FBM110- compared to FM140-treated patients regarding OS (2y OS: 46.7% vs. 40.8%, hazard ratio (HR) for FM140 1.05, $p = 0.74$), progression-free survival (PFS) (2y LFS: 38.7% vs 36.8%, HR 1.06, $p = 0.66$), non-relapse mortality (NRM) (2y NRM: 25.8% vs 25.9%, HR: 1.07, $p = 0.8$) and relapse incidence (RI) (2y RI: 35.5% vs. 37.2%, HR: 1, $p = 0.98$). Despite FBM110 patients received more frequently in vivo TCD, there were no significant differences in aGvHD II-IV incidence (100d aGvHD II-IV: 34.1% vs 28.7%, HR 0.87, $p = 0.53$), aGvHD III-IV (100d aGvHD III-IV: 17% vs. 11.3%, HR 0.66, $p = 0.13$) and cGvHD (2y cGvHD: 31.7% vs. 32.7%, HR 0.94, $p = 0.73$)



Conclusions: In conclusion, despite differences on age and KPS, AML patients with active disease undergoing allo-HCT after FBM110 and FM140 conditioning show similar outcomes. We speculate that the reduced dose of melphalan is compensated by the addition of the second alkylating agent (BCNU) in FBM110 without increasing toxicity. Future studies should address the efficacy of melphalan containing regimens in combination with other drugs and/or using different dosing.

Disclosure: JD-A has received speaker's honoraria from Roche, Amgen, AstraZeneca, Riemser, Lilly, Ipsen and Sobi and travel support from AstraZeneca, Gilead and Sobi. JF has received research support and speaker's honoraria from Medac, Neovii, and Riemser.

16 - Conditioning Regimens

P154

OUTCOMES OF TBI 8-GRAY CONDITIONING IN ADULT PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA IN FIRST COMPLETE REMISSION

Sarah Tan[1], Henry Ngu[2], Lauren Child[1], Nicole Chien[1], Claire Hemmaway[1], Peter Browett[3], Timothy Hawkins[1], Leanne Berkahn[1], Richard Doocey[1], Clinton Lewis[1]

[1]Auckland City Hospital, Auckland, New Zealand, [2]BC Cancer Agency, Vancouver, Canada, [3]University of Auckland, Auckland, New Zealand

Background: Allogeneic haematopoietic stem cell transplantation (allo-HSCT) remains the primary curative option for adults with acute lymphoblastic leukaemia (ALL). Total body irradiation (TBI) based conditioning regimens are preferred but balancing the intensity of the preparative regimen to achieve optimal disease control with non-relapse mortality remains challenging.

Methods: The bone marrow transplant unit at Auckland City Hospital introduced a reduced toxicity 8-Gray (Gy) TBI-based conditioning regimen for ALL in 2017. We report our initial experience by conducting a retrospective review including adult patients ≥ 18 years with ALL in first complete remission (CR1) who underwent allo-SCT from sibling, matched unrelated (MUD) or haploidentical donors using different intensity conditioning regimens from 1 January 2015 and 31 December 2021. All patients provided consent for data submission and use in local and international data registries.

Results: Thirty patients met inclusion criteria. The median age was 51 years for both 8-Gy and Fludarabine/Melphalan (Flu/Mel) cohorts, while the median age was 26 years in 12-Gy cohort. There was a sex imbalance between the 8-Gy and Flu/Mel cohorts. There were significantly more patients with an elevated comorbidity index (HCT-CI) of 3 or more in the 8-Gy cohort. The majority of patients achieved flow MRD negativity pre-transplant.

With a median follow up of 40 months, the 2-year overall survival was 50% in TBI 8-Gy cohort, and 55% in Flu/Mel cohort (Figure 1a). The myeloablative TBI 12-Gy cohort had an improved 2-year overall survival numerically at 80%, although it did not reach statistical significance. The cumulative incidence of relapse (CIR) is the highest in TBI 8-Gy group (Figure 1b) with 2 out of 9 patients relapsing at 1 year of follow up. The 2-year GVHD and relapse free survival (GFRS) were higher at 69% in TBI 12-Gy cohort, whereas TBI 8-Gy and Flu/Mel have similar GRFS at 50% and 62%, respectively (Figure 1c). Non-relapse mortality (NRM) was highest in Flu/Mel cohort at 32% and no NRM event was noted in TBI 8-Gy cohort at 2 years (Figure 1d).

	12-Gy	8-Gy	Flu/Mel	p value
n	10	9	11	
Median Age, **y (range)**	26 (20-38)	51 (42-55)	p = 0.6 between 8-Gy vs Flu/Mel p = <0.01 between 12-Gy vs Flu/Mel	
Female, **no. (%)**	5 (50)	2 (22)	9 (82)	p = 0.025
ALL Subtype, **no. (%)**				
B-ALL	10 (100)	7 (78)	10 (100)	p = 0.081
T-ALL		2 (22)		
Comorbidity Index, **no. (%)**				
0	4 (40)	0	3 (30)	p = 0.112
1-2	6 (60)	5 (55)	8 (70)	p = 0.285
3+	0	4 (45)		p = 0.002
Donor Type, **no. (%)**				
Matched sibling	4 (40)	6 (67)	4 (36)	P = 0.376
Matched unrelated	5 (55)	1 (11)	7 (64)	P = 0.054
Haploidentical		2 (22)		P = 0.085
Mismatched MUD	1 (5)			P = 0.381
Pre-transplant MRD, **no. (%)**				
Positive (>/= 0.01%)	4 (40)	2 (22)	5 (45)	P = 0.570
Negative (< 0.01%)	6 (60)	7 (78)	6 (55)	P = 0.570

Conclusions: For patients with high-risk ALL in CR1, TBI 8-Gy conditioned allo-SCT resulted in a lower treatment related mortality rate, no early in-hospital death with similar OS and GFRS as the RIC conditioning cohort. While the cohorts are small, this data supports our clinical experience that the TBI 8-Gy is a well-tolerated and effective regimen for patients with ALL not fit for full dose myeloablative TBI.

The CIR at 1 year in older and more co-morbid patients using TBI 8-Gy is higher than those who received myeloablative TBI 12-Gy. The combination of reduced TBI dose and increased comorbidities may account for the difference in overall survival. Interestingly, the NRM in the 8-Gy cohort was much lower than that seen in the RIC cohort. Prospective studies comparing the efficacy of 8-Gy TBI to a comparable chemotherapy regimen (e.g., Flu/Mel or FluBu3) should be pursued to understand the benefit of reduced toxicity radiotherapy-based conditioning for ALL.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P155

COMBINATION OF FLUDARABINE AND CYCLOPHOSPHAMIDE AS A CONDITIONING REGIMEN IN SECOND HSCT FOR GRAFT FAILURE

Tatiana Rudakova[1], Ivan Moiseev[1], Elena Morozova[1], Julia Vlasova[1], Alina Vitrishchak[1], Alexander Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation

Background: Primary (PGF) and secondary (SGF) graft failure is associated with poor outcomes after allogeneic HSCT. The second allo-HSCT (2HSCT) may be only therapeutic option for GF. However, there are no established conditioning regimens for the 2HSCT. This study aimed to analyze the efficacy and safety adopted from aplastic anemia reduced-intensity conditioning regimen based on fludarabine (Flu) and cyclophosphamide (Cy) for salvage 2HSCT.

Methods: The study evaluated conditioning regimen consisting of Flu (30 mg/m2) (days−5 to−2) and Cy (300 mg/m2/day) (days−5 to−2). Thirty-five patients (pts) (F43%, M57%) with acute leukemia (66%), myeloproliferative (29%) and non-malignant (5%) diseases received the 2HSCT for GF from 2014 to 2022. Median age was 31 years 18-62). Median follow up was 77 (range 4-2531) days. GVHD prophylaxis was Cy-based (28 pts, 80%) and other protocols (7 pts, 20%). Donors were haploidentical siblings or parents in 20 (57%) cases, matched unrelated donors 9 (26%), mismatched unrelated 4 (11%), matched related 2 (6%) cases. Twenty-two (62%) pts were re-transplanted from the same donor, a new donor was used for 13 (38%) pts. PGF was defined as failure to achieve an absolute neutrophil count >0,5x10^9/l by 30 days after allo-HSCT and absence of donor chimerism. SGF was defined as cytopenias after initial engraftment with loss of donor chimerism less than 5%. Donor-specific anti-HLA-antibodies were detected in 4 pts. Indication for the 2HSCT was PGF in 21 (60%) pts, SGF - in 14 (40%) pts. BM and PBSC was used in 18 (49%) and 16 (48%) pts, respectively, and 1 pt (3%) received BM with PBSC.

Results: Median time from the first and second HSCT was 42 (30-237) days. Neutrophil engraftment was documented in 16 (46%) pts with median time of 30 (18-55) days. A total of 23 pts died (9 of them before D + 30 after 2HSCT), causes of death were infections (20) and relapse (3). Non-relapse mortality rate (NRM) was 37% (95% CI, 21-53) at 100 days and 61% (95%CI, 42-76) at two years. Two-year event free and overall survival (OS) was 21% (95% CI, 9–38) and 31% (95% CI, 18-52), respectively. The only factor associated with better OS and lower NRM was Cy-based GVHD prophylaxis in the 2d HSCT compared to other protocols (55% vs 87%, p = 0.013). Eleven pts received the 3d HSCT (PGF in 8 cases, and SGF in 3 cases). Infectious episodes

were documented in 31 cases; 26 pts had active infection at the time of the 2HSCT. Toxicity included mucositis 22 (63%) pts, cystitis 8 (23%) cases, cytokine release syndrome 2 (6%) cases, VOD 3 (9%) cases, TMA 2 (6%) cases, hemorrhagic complications 14 (40%) cases. CI of aGVHD grade III-IV was 16% (95%CI 5-31).

Conclusions: The 2HSCT with FluCy conditioning might be an option as a salvage therapy after GF. Infectious complications due to prolonged cytopenia remain the major problem in the setting of patients with PGF.

Disclosure: None.

16 - Conditioning Regimens

P156

COMPARISONS OF ATG-THYMOGLOBULIN (ATG-T) WITH ATG-FRESENIUS (ATG-F) TO OPTIMIZE CONDITIONING REGIMENS FOR HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Xing-Yu Cao[1], De-Yan Liu[1], Jian-Ping Zhang[1], Min Xiong[1], Zhi-Jie Wei[1], Jia-Rui Zhou[1], Yue Lu[1], Rui-Juan Sun[1], Yan-Li Zhao[1]

[1]Hebei Yanda Lu Daopei Hospital, Langfang, China

Background: Adding anti-human T lymphocyte or thymocyte immunoglobulin (ATG) to haploidentical HSCT (haplo-HSCT) conditioning regimens can decrease the incidence of graft-versus-host disease (GVHD) and promote implantation in T-cell acute lymphoblastic leukemia (T-ALL) patients. ATG-F (formerly called ATG-Fresenius, Grafalon, Neovii Biotech GmbH) and ATG-T (Thymoglobulin, Genzyme Polyclonals S.A.S.) are commonly used ATGs with different metabolic properties. ATG-F has been shown to have the anti-leukemic activity in vitro. We conducted a study comparing the anti-leukemic activities of two doses of ATG-T vs ATG-F, used as part of the conditioning regimens in T-ALL haplo-transplantation.

Methods: From July 2012 to June 2020, 152 patients with T-ALL in Hebei Yanda Lu Daopei Hospital who underwent haplo-HSCT with either a ATG-T 5mg/kg (n = 18), ATG-T 7.5mg/kg (n = 37) or ATG-F 20mg/kg (n = 97) conditioning regimen were enrolled. The total ATG dose was equally divided over 4 days (from the day -2 to day -4).

Results: The median age was 15 years (range: 2-61) and 107 (70.4%) of patients were male. All patients achieved complete remission (CR) before transplantation (first CR [CR1] =106; ≥ second CR [CR2] = 46) and received total body irradiation (TBI)-based conditioning regimens. There were no significant differences in age, gender, time from diagnosis to transplantation, number of chemotherapy cycles to obtain remission, disease status (CR1 or ≥CR2) before transplant among the three ATG groups. The median time to neutrophil and platelet engraftment in the ATG-T 5 mg, ATG-T 7.5mg and ATG-F 20mg groups was 15 days, 14 days and 14 days (p = 0.075) and 15 days, 12 days and 13 days, (p = 0.193), respectively.

The median follow-up time was 700 days (range:24-3126). Patients who received ATG-F 5mg had superior overall survival (OS) and leukemia free survival (LFS) compared to the ATG-T 7.5mg and ATG-F 20mg groups (5-year OS: 80.8% vs 53.4% vs 67.3%, p = 0.052; 5-year LFS: 80.8% vs 50.7% vs 65.5%, p = 0.046). The ATG-T 5mg group had a lower 5-year relapse incidence (RI) but this difference was not statistically significant compared to the ATG-T 7.5 mg and ATG-F 20 mg groups (0% vs. 8.1% vs.10.8%, p = 0.401). The 5-year non-relapse mortality (NRM) of ATG-T 5mg group was lower compared to the ATG-T 7.5mg and ATG-F 20mg groups (19.2% vs. 23.8% vs. 43.9%, p = 0.027).

There was no difference in grade 3-4 acute GVHD incidence and extensive chronic GVHD among the ATG-T 5mg, ATG-T 7.5mg and ATG-F 20mg groups (8.11% vs 10.31% vs 27.78%, p = 0.068; 29.4% vs 22.2% vs 21.6%, p = 0.369). No statistical difference was observed in the 100-day cytomegalovirus (p = 0.231) or Epstein-Barr virus reactivation (p = 0.262). By multivariate analysis, ≥CR2 before transplant, ATG-T 7.5mg, and the use of tacrolimus for GVHD prophylaxis were independent prognostic factors in reducing LFS. Infections in the ATG-T 7.5mg group resulted in an increased risk of mortality.

Conclusions: Our results demonstrate that despite its anti-leukemic activity in vitro, ATF-F did not reduce recurrence rate for T-ALL patients undergoing haplo-HSCT, compared to ATG-T. ATG-T 5mg resulted in better OS and LFS by reducing NRM compared to ATG-T 7.5mg and ATG-F 20mg.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P157

SEQUENTIAL ALLOGENEIC TRANSPLANTATION IN ACUTE MYELOID LEUKAEMIA AND MYELODYSPLASTIC SYNDROME: EXPERIENCE FROM A SINGLE CENTRE

Rebeca Jurado[1], Mireia Morgades[1], Alejandro de Jaureguizar[1], Marta Canelo[1], Blanca Xicoy[1], Susana Vives[1], María Josefa Jiménez[1], Maria Huguet[1], Christelle Ferrà[1], Josep Maria Ribera[1], Juan Manuel Sancho[1], Anna Torrent[1]

[1]Institut Català d'Oncologia Badalona, Hospital Germans Trias i Pujol, Josep Carreras Research Institute., Badalona, Spain

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative option for acute myeloid leukemia (AML) and high-risk myelodysplastic syndromes (HR-MDS). A proportion of patients fail to achieve a satisfactory response to undergo allo-HSCT, compromising the response to the procedure. In these cases, there is the possibility of sequential treatment schemes, including a first phase of chemotherapy to reduce the leukaemia cell burden, followed by allo-HSCT with reduced-intensity conditioning to take advantage of the graft-versus-leukaemia effect. We show the results of allo-HSCT with sequential conditioning (allo-SEQ) regimen from a single centre.

Methods: This study included all 15 patients with relapsed/refractory (R/R) AML or HR-MDS who underwent an allo-SEQ between July 2007 and September 2021 at the ICO-Hospital Universitari Germans Trias i Pujol. Patient's characteristics and outcomes after allo-HSCT with a sequential conditioning regimen were analysed.

Results: The characteristics of the patients and allo-HSCT data are summarized in Table 1. There were 8/15 females (53%), and the median age was 60 years old (range 28-69). The reasons for allo-SEQ were: early relapse (< 6 months) after high dose chemotherapy (n = 6); lack of complete response (> 5% bone marrow blasts) after two induction regimens, including high-dose cytarabine (n = 3); <50% reduction of blasts after the first induction (n = 3); HR-SMD (> 10% blasts or unfavourable cytogenetics) after two cycles of hypomethylating agents (n = 1); to avoid adding toxicity after a first partial response (PR) with slow hemoperipheral recovery post-induction therapy (n = 1); and to avoid toxicity in an MRD-positive patient with multiple

complications in induction and consolidations (n = 1). In 67% of patients the allo-SEQ were HLA identical.

Seven out 13 (54%) patients presented acute graft-versus-host disease (GVHD), of grade ≥3 in 4 of them, predominantly affecting the skin and gastrointestinal tract. Of the 7 patients who had received post-transplant cyclophosphamide, only 2 presented acute GVHD. Likewise, a high percentage of chronic GVHD was observed in 4/8 patients, being severe in 2/4.

Overall survival probabilities at 100 days and 5 years were 60% (95% CI: 32-80%) and 20% (95% CI: 5-42%), respectively (Figure 1). Twelve patients died, 9 transplant-related (infections (n = 3) GVHD (n = 2), graft failure (n = 2), hepatic obstructive sinusoidal syndrome (n = 1) and cerebral haemorrhage (n = 1)) and 3 due to disease relapse. The cumulative incidence of relapse (CIR) at one year was 20% (95% CI: 5%-42%).

TABLE 1: Patients and transplant characteristics.

Patients and Allo-HSCT characteristics		N = 15
Diagnosis	Acute myeloid leukaemia	13 (86%)
	Myelodysplastic syndrome	1 (7%)
	Acute panmyelosis with myelofibrosis	1 (7%)
Previous neoplasm	Yes	2 (13%)
ECOG score	0/1	12 (80%)/ 3 (20%)
Sorror score	≥4	3 (20%)
EBMT score	≥5	5 (33%)
Number of prior lines	1/2	10 (67%) / 5 (33%)
Disease status at allo-HSCT	Relapse / NR / PD / PR / MRD	6 (40%) / 4 (27%) / 1 (7%) / 3 (20%) / 1 (7%)
% Blasts at allo-HSCT	Median [range]	12.5% [1% - 35%]
Donor	MRD / Haploidentical / MUD	8 (53%) / 5 (33%)[1] / 2 (13%)
Stem cells source	PB / BM	14 (93%) / 1 (7%)
Type of conditioning	Myeloablative / Non myeloablative	5 (33%)/10 (67%)
Conditioning scheme	Fludarabine+Cytarabine+ Busulfan	9 (60%)
	Fludarabine+Cytarabine +Idarubicin+ Melphalan	4 (27%)
	Fludarabine+Cytarabine +Idarubicin+ Busulfan	2 (13%)
Graft versus host disease prophylaxis	CNI + others	7 (47%)
	PT-Cy based	7 (47%)
	CsA+MMF+Thymoglobulin	1 (7%)

1: Of which four were 5/10 and one 9/10; NR: non-response; PD: progression disease; PR: partial response; MRD: positive minimal residual disease. MRD: matched related donor; HSCT: hematopoietic stem cell transplantation; MUD: matched unrelated donor; PB: peripheral blood; BM: bone marrow; CNI: Calcineurin inhibitors; others: methotrexate or mycophenolate; PT-Cy: posttransplantation cyclophosphamide; CsA: cyclosporine; MMF: mycophenolate; MTX: methotrexate.

Conclusions: Although allo-SEQ is a valid therapeutic option for some selected high-risk patients diagnosed with R/R-AML or HR-MDS, it was associated to high mortality. The adequate selection of patients and the implementation of measures to reduce the toxicity are essential to improve the results.

Disclosure: *Nothing to declare.*

16 - Conditioning Regimens

P158

RECIPIENT STEM CELL MOBILIZATION WITH PLERIXAFOR IN PRE-HSCT CONDITIONING REGIMEN FOR NON-MALIGNANT CONDITIONS

Dmitry Balashov[1], Alexandra Laberko[1], Elvira Sultanova[1], Aishat Idarmacheva[1], Svetlana Radygina[1], Svetlana Kozlovskaya[1], Yulia Skvortsova[1], Larisa Shelikhova[1], Michael Maschan[1], Alexei Maschan[1]

[1]Dmitriy Rogachev National Center for Pediatric Hematology, Oncology, and Immunology, Moscow, Russian Federation

Background: Graft failure (GF) is one of the most common problems after allogeneic HSCT in non-malignant inherited diseases, which may reach up to 15%. Treosulfan-based conditioning and T-cell graft depletion are effective options to reduce risk of transplant-related toxicity and GVHD, which, however, may lead to increased incidence of GF. Addition of hematopoietic stem cell mobilizer - plerixafor to pre-HSCT preparative regimen may enhance myeloablation without escalation of chemo-associated organ toxicity. Here we present an experience of pre-HSCT plerixafor usage in non-malignant conditions.

Methods: Between May 2016 and January 2022, 81 patients (median age 2,5 years; range 0.5-13.4) with non-malignant diseases (Wiskott-Aldrich syndrome (WAS) 48, chronic granulomatous disease (CGD) 23, severe combined immunodeficiency (SCID) 4, severe congenital neutropenia 2, X- linked adrenoleukodystrophy 1, thalassemia 1, ataxia-telangiectasia (AT) 1, WHIM syndrome 1) underwent 84 allo-HSCT with plerixafor in conditioning regimen. 67 patients received plerixafor before first, 11 before second, 3 before first and second HSCTs.

The source of stem cells was PB (n = 79) or BM (n = 5); all PB grafts were TCRab/CD19 depleted. MMRD were used in 43 transplants, MUD in 34, and MSD in 7. Most patients received myeloablative doses of treosulfan (n = 76) or busulfan (n = 3) with fludarabine and melphalan (or thiothepa) in conditioning regimen. Other 5 patients (4 SCID, 1 AT) received minimally intensive conditioning (MIC) due to severe clinical status. For serotherapy, 79 of 81 patients received anti-thymocyte globulin. In all cases were used G-CSF 10 μg/kg (from day −8 to −4) and plerixafor 240 μg/kg (from day −6 to −4). 45 patients received post-transplant GVHD prophylaxis.

Results: Engraftment was achieved in 82 (97,6%) cases with a median time of 14 days (range 6-28) for neutrophils and 12 days (range 9-33) for platelets.

Acute GVHD was observed in 26 of 84 cases, but probability of acute GVHD grade ≥III was only 8,4% (95%CI 3,5-16,6%). 6 patients (7%) had chronic GVHD (limited, n = 4; extensive, n = 2).

GF was observed in 8 (9,7%) cases (non-engraftment, n = 2; graft rejection, n = 6) with a median time of 4 months post-HSCT (range 1-7). GF was observed in 2 (4,1%) of 48 WAS patients, in 2 (8,6%) of 23 CGD patients, and in 4 (40%) of 10 other patients. No difference in GF rates after first and second HSCT with plerixafor was seen (p = 0,6).

Median follow-up time was 37 months, range 1-79. OS was 78,6% (95%CI 68,3-86,8%) and varied between the diseases: 90% (95%CI 78,2-96,7%) in WAS, 75% (95%CI 53,3-90,2%) in CGD, and 30% (95%CI 6,7-65,2%) in other. The causes of death were bacterial sepsis (n = 4), GVHD or associated viral infections (n = 9) and TA-TMA (n = 2).

Conclusions: Most patients received TCRab/CD19-depleted graft after treosulfan-based conditioning, and the incidence of severe GVHD and transplant-related toxicity was low. Addition of plerixafor to conditioning regimen led to decreased incidence of GF in WAS (4,1%) and CGD (8,6%). Apparently, high incidence of GF in other patients might be caused by inadequate myeloblation of MIC regimens used in half of the patients.

Disclosure:
There are no conflicts of interest to report.

16 - Conditioning Regimens

P159

INCIDENCE OF HEMORRHAGIC CYSTITIS USING CYCLOPHOSPHAMIDE VERSUS ETOPOSIDE COMBINED WITH TOTAL BODY IRRADIATION AS CONDITIONING FOR HEMATOPOIETIC STEM CELL TRANSPLANT IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA

Sushil Gunaseelan[1], Arina Lazareva[1], Maria Gabelli[1], Khushnuma Mullanfiroze[1], Robert Chiesa[1], Persis Amrolia[1], Giovanna Lucchini[1], Kanchan Rao[1]

[1]Great Ormond street hospital NHS Trust, London, United Kingdom

Background: Total body irradiation (TBI) is commonly used as conditioning in Hematopoietic stem cell transplant (HSCT) for acute lymphoblastic leukaemia (ALL) in children. TBI is most frequently administered in combination with either cyclophosphamide (Cy/TBI) or etoposide (VP16/TBI). While both regimens are reported in literature to be well tolerated and with equivalent survival (Gassas et al. Bone marrow transplantation 2008); we observed an excess of troublesome Haemorrhagic cystitis (HC) in the Cy/TBI arm and sought to study this is more detail.

Methods: We conducted a retrospective analysis of patients with ALL, between ages 0-18 years, undergoing an HSCT in CR1 or CR2 at Great Ormond Street Hospital between 2009 and 2018. Primary objective was to compare the incidence of HC in both arms. The secondary objective was to analyse the outcomes following HSCT in the Cy/TBI arm compared to the VP16/TBI arm. The dose of Cyclophosphamide was 120mg/kg and TBI was administered to majority (69%) of the patients at 14.4Gy in 8 fractions and remaining (31%) at 12Gy in 6 fractions. Etoposide was given at 60mg/kg along with 12Gy TBI in 6 fractions. Patients were identified in the department database and relevant demographic and clinical data were extracted, these were compared using Chi-square test or Fisher's exact test as appropriate. Event-free survival (EFS), overall survival (OS), Transplant-related mortality (TRM) and relapse were analysed using Kaplan Meier method and Log rank test.

Results: A total of 75 patients who underwent Allogeneic HSCT for ALL were identified. 8 patients were excluded as they had different conditioning regimens. Out of 67 remaining patients, 32 were conditioned with VP16/TBI and 35 received Cy/TBI. The median age at HSCT in both groups were 7.7 and 7.8 years respectively. Majority of the patients had B-ALL and were transplanted in CR2 in both groups. There were no significant differences in incidence of GvHD and AKI in both the groups. However, 60% of patients who received Cy/TBI developed HC compared to 12% in those who received VP16/TBI ($p < 0.0001$). The incidence of BK virus in urine was also significantly higher in the Cy/TBI group (60%) as compared to VP16/TBI (16%)($p < 0001$). At a median onset of 19.5 days (Range 3-106) after HSCT, 28 patients (41%) developed HC and 17(60%) were of grade 1-2 and were managed conservatively. Grade 3-4 HC were observed in 11 patients (40%) with 6 patients requiring surgical intervention. The 3 year event-free survival and overall survival were 51.5 % and 54% for those receiving VP16/TBI, and 48% and 49.5 % for the Cy/TBI group (p value not significant). There was no significant difference in the TRM between the two groups (13% in VP16/TBI and 23% in Cy/TBI).

	VP16 based (32pts)	Ciclophosphamide based (35 pts)	p value
Median follow up (years)	3.2 (0.2-8.9)	0.9 (0.1-8.6)	
Median time to N recovery (days)	24 (14-37)	22.5 (13-84)	
GVHD Yes No	 29 (90%) 3 (10%)	 33 (94%) 2 (6%)	 ns
HC Yes No	 4 (12%) 28 (88%)	 21 (60%) 14 (40%)	 <0.0001
AKI Yes No	 9 (28%) 23 (72%)	 11 (31%) 24 (69%)	 ns
BK urine Yes No	 5 (16%) 27 (84%)	 21 (60%) 14 (40%)	 <0.0001
Relapse Yes No	 11 (34%) 21 (69%)	 9 (26%) 26 (74%)	 ns
Outcome Dead Alive	 14 (44%) 18 (56%)	 18 (51%) 17 (49%)	 ns
TRM Yes	 4 (13%)	 8 (23%)	 ns

Conclusions: We were able to identify a higher incidence of Hemorrhagic cystitis and BK viruria in patients conditioned with Cy/TBI compared to VP16/TBI. This did not determine the survival outcomes and transplant related mortality of the patients. If large prospective studies show equivalent survival with both these conditioning regimens; VP16/TBI may be preferable in order to minimise the incidence of troublesome HC.

Disclosure: 1. Sushil Gunaseelan- Nothing to declare.
2. Arina Lazareva- Nothing to declare
3. Maria Gabelli- Nothing to declare
4. Khushnuma Mullanfiroze-Nothing to declare
5. Robert Chiesa- Nothing to declare
6. Persis Amrolia- ADC Therapeutics -Patents & Royalties: named inventor WO2022063853A1
Autolus- Patents & Royalties and Research Funding
Bluebird Bio- Research Funding
Pierre Fabre- Consultancy
UCLB- Patents & Royalties
7. Giovanna Lucchini- Nothing to declare
8. Kanchan Rao- Nothing to declare

16 - Conditioning Regimens

P160

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION USING REDUCED TOXICITY VS MYELOABLATIVE CONDITIONING FOR THE TREATMENT OF CHILDREN WITH MYELOID MALIGNANCIES

Asaf D Yanir[1,2], Yoad Prokocimer[1], Yotam Dizitzer[1], Shlomit Barzilai Birenboim[1,2], Anat Yahel[1], Aviva Krauss[1,2], Jerry Stein[1,2]

[1]Schneider Children's Medical Center of Israel, Petach Tikva, Israel, [2]Tel Aviv University, Tel Aviv, Israel

Background: Allogeneic hematopoietic stem cell transplantation (aHSCT) is the definitive treatment for children with high-risk myeloid malignancies, but there is no consensus regarding the optimal conditioning regimen in this clinical setting. The addition of melphalan to the busulfan-cyclophosphamide regimen (Bu-cy-mel), introduced in the early nineties, has been adopted by many groups to reduce relapse rates. Nevertheless, concerns regarding the high toxicity of this regimen, especially in adolescents, has compelled the search for a less toxic regimen that does not sacrifice efficacy for tolerability. Most studies to date have focused on comparison between reduced intensity (RIC) regimens to fully myeloablative (MAC) regimens in these patients; the use of what is often termed "reduced toxicity conditioning" (RTC) has not been studied rigorously. Here we report results with a RTC using fludarabine, thiotepa and either melphalan or treosulfan (Flu-TT-Mel or Flu-Treo-TT) versus the use of the traditional Bu-CY- Mel conditioning for 1st aHSCT in children with myeloid malignancies.

Methods: This retrospective cohort included all children who received a 1st aHSCT for myeloid malignancies at Schneider Children's Medical Center of Israel between 2010 and 2021. The default conditioning regimen was MAC for patients < 12 years and RTC for patients ≥12 years, but was ultimately left to HSCT physician discretion, based on clinical evaluation of toxicity versus relapse risk. In a few cases, Treosulfan was used due to non-availability of melphalan. Serotherapy with ATG (Grafalon)was added for matched unrelated (MUD) or haploidentical donors. GVHD prophylaxis consisted of cyclosporin A alone (matched sibling donors, MSD), or in combination with low dose Methotrexate (MUD).

Univariate statistical analyses were performed to compare demographic and clinical characteristics, including outcomes of treatment. Kaplan-Meier estimates were utilized to assess cumulative incidence of relapse (CIR), treatment-related mortality (TRM), event-free survival (EFS) and overall survival (OS). Results are presented by log-rank and hazard ratio (HR) with 95% confidence interval (CI), and depicted using survival graphs.

Results: Twenty patients were transplanted using MAC and 24 using RTC. The MAC group included significantly fewer patients with AML and more JMML cases; patients in this group were significantly younger. All other pre aHSCT variables were comparable. Neutrophil and platelet engraftment occurred earlier in the RTC group, but the difference reached statistical significance only for platelet engraftment. Relapse rate was significantly higher in the MAC group, resulting in worse EFS. TRM and long-term organ toxicity were comparable between the 2 groups. OS was better in the RTC group, though the difference didn't reach statistical significance.

	MAC N = 20 (45.5%)	RTC N = 24 (54.5%)	p-value	Total N = 44 (100%)
AML/MDS/JMML	6/10/4 (30/50/20%)	15/9/0 (63/37%)	0.03/0.68/0.03	21/19/4 (47/43/10%)
Age (years)$_{2}$;	2.4 [1.4-9.1], 0.3-15.2	13.6 [9.9-15.6], 0-19.2	<0.001	9.9 [1.8-14.7], 0-19.2
Age < 12 (years)$_{1,3}$; n(%)	17 (85.0%)	8 (33.3%)	0.001	25 (56.8%)
Sex (male)$_{1}$; n(%)	13 (65.0%)	12 (50.0%)	0.317	25 (56.8%)
MSD/MUD/Haplo	9/10/1 (45/50/5%)	11/8/5(46/33/21%)	0.95/0.29/0.12	20/18/6 (45/40/15%)
CR1/CR2/Active disease	5/3/12(25/15/60%)	12/2/10 (50/8/42%)	0.09/1.0/0/22	18/4/22 (38/12/50%)
Neutrophil engraftment day$_{2,3}$;	17 [14-22], 8-53	14 [12-17], 8-32	0.056	15 [13-19], 8-53
Platelet engraftment day$_{2,3}$;	29 [17.5-41.5], 14-171	17.5 [13-22], 10-234	0.016	19 [16-33], 10-234
VOD$_{1}$; n(%)	7 (35.0%)	5 (20.8%)	0.293	12 (27.3%)
aGVHD Grade 1-2/ 3-4/ None	6/2/12 (25/15/60%)	2/8/14(8/32/60%)	0.145	7/11/26 (16/25/60%)
cGVHD :None/Limited/ Extensive	16/4/0 (80/20%)	18/4/2 (75/17/8)	1.000	34/8/2 (77/19/4%)
Relapse$_{1}$; n(%)	7 (35.0%)	2 (8.3%)	0.029	9 (20.5%)
Time to relapse (months)$_{2,3}$;	9 [2-17], 2-47	4 [1-7], 1-7	0.242	7 [2-14], 1-47
Treatment related mortality$_{1}$;n (%)	3 (15.0%)	2 (8.3%)	0.646	5 (11.4%)
Long term organ toxicity	6 (30.0%)	9 (37.5%)	0.601	15 (34.1%)
Total follow-up time$_{2,3}$;	29 [15-55], 1-98	28 [13-52], 2-87	0.906	29 [14-54], 1-98
Alive at last follow-up$_{1,3}$; n(%)	13 (65.0%)	21 (87.5%)	0.076	34 (77.3%)

[1]Pearson's chi-square or Fishers exact test
[2]Mann-Whitney U test
[3]Continuous variables are presented as median [IQR], range

Conclusions: In this small cohort, the use of 3 alkylating agents in a MAC protocol did not lead to better disease control, and EFS was worse compared to a RTC regimen. There was no improvement even in patients with MDS who received no therapy prior to HSCT. The optimal conditioning regimen for high-risk pediatric myeloid malignancies should be investigated in large prospective clinical trials.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P161

PREVIOUS BUSULFAN IS NOT A CONTRAINDICATION FOR SECOND ALLOGRAFT WITH REDUCED INTENSITY TREOSULFAN-BASED CONDITIONING REGIMEN FOLLOWED BY ALLOGENEIC HAEMATOPOIETIC STEM-CELL TRANSPLANT FROM UNRELATED DONORS

Adrian Maraj[1], Daniele Avenoso[1], Michelle Kenyon[1], Pramila Krishnamurthy[1], Varun Mehra[1], Austin Kulasekararaj[1], Shreyans Gandhi[1], Francesco Dazzi[1], Ye Ting Leung[1], Sandra Anteh[1], Maria Cuadrado[1], Mili Naresh Shah[1], Hayat Ullah[1], Styliani Bouziana[1], Christianne Bourlon[1], Oana Diana Dragoi[1], Antonio Pagliuca[1], Victoria Potter[1]

[1]King's College Hospital NHS Foundation Trust, London, United Kingdom

Background: Despite the improvement in the treatment of relapsed myelodysplastic syndromes with excess of blasts(MDS-EB) and acute myeloid leukaemia(AML), second hematopoietic stem cell transplant(HSCT) is still associated with increased transplant related mortality(TRM) and relapse rate if compared to first transplants. Therefore, actions are needed to improve the safety and efficacy of second HSCT.Within the alkyl sulfonates used in conditioning, Treosulfan has better marrow penetration than Busulfan and also an high activity on both myeloid progenitors and blasts; also, its hydrophilic properties are associated with less tissue damage and therefore with decreased incidence of graft-versus-host disease (GVHD)and veno-occlusive disease(VOD) of the liver.

Based on these encouraging promises, between December 2020 to May 2022, 10 consecutive second HSCT conditioned with fludarabine and treosulfan(FluTreo) were performed at King's College Hospital, London, with the aim to offer a less toxic second transplant. All the patients were firstly transplanted with busulfan based regimens and had a complete remission(CR) period more than 12 months after first HSCT.

Methods: Second HSCT was performed using GCSF mobilized peripheral blood stem cells as consolidative strategy following re-induction therapy. Conditioning protocol was with Fludarabine 30mg/m^2 on days-6,-5,-4,-3,-2 and Treosulfan 10g/m^2 on days-4,-3,-2;GVHD prophylaxis consisted of ATG 2.5mg/kg on days-2,-

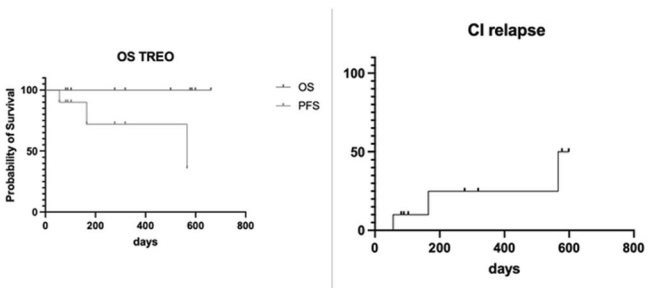
1,Ciclosporin 1.5mg/kg BD from day-1and post-HSCT Methotrexate 10mg/m^2 on days+1, + 3, + 6. Donors were 6matched unrelated donors and 4mismatched unrelated donors. Probabilities of overall survival(OS) was calculated using the Kaplan-Meier method. Relapse incidence(RI) and transplant related mortality(TRM)rates were estimated using cumulative incidence(CI) functions and considered as competing risks. For GvHD, death and relapse were considered competing events. Statistical analyses were performed with GraphPad Prism Version 9.4.1.

Results: Table 1 summarizes the demographic of the population. Median follow up was 344 day(range 100 – 661).

The 100 and 365 days OS were 100%, with median OS not reached(figure 1) and with absent TRM. No septic death before engraftment or primary graft failure were noted.

The 12 months and 18months leukemia-free survival(LFS) were 80%and70% respectively(figure 1), median LFS was 566 days. Median time to neutrophils>1000/mL was 13 days(12-16), and 16 days(13-35) to platelets > 20.000/m. Median CD3 and CD15 chimerism at day 365 were 98%and 100%. Incidence of acute GVHD was 60% (grade III-IV 10%); 90% of observed acute GVHD was skin grade I-II. Overall chronic GVHD rate was 10% (n = 1) and there were no moderate to severe cases. no VOD cases were recorded. Cumulative incidence of relapse was 30% with a relapse rate at 1 year of 20%. The median time to relapse was 165days(56-566) (figure 2). EBV reactivation rate was 90% (n = 9)and 56% of these patients (n = 5)required treatment with Rituximab, with 44% (n = 4) having biopsy proven post-transplant lymphoproliferative disorder(PTLD).

Characteristic	Number of patients n = 10
Age at HSCT in years, median (IQR)	55 (33-71)
Male	5 (50%)
Female	5 (50%)
Diagnosis	
AML	6 (60%)
MDS-EB	4 (40%)
Adverse cytogenetic risk (ELN)	
Favourable/Intermediate	4 (40%)
Adverse	6 (60%)
Disease status at second HSCT	
CR 1/2 (MRD negative)	5 (50%)
CR 1/2 (MRD positive)	5 (50%)
HCT-CI	
0-2	7 (70%)
3+	3 (30%)
Follow up in days, median (IQR)	409 (100-661)



Conclusions: Outcomes for this high-risk population are favorable with no deaths recorded from TRM, infection or graft failure. While follow-up has been limited, the OS is encouraging and the LFS and incidence of acute GVHD are comparable to recorded rates in the literature.

Previous conditioning with Busulfan does not preclude the efficacy of Treosulfan-based conditioning in second HSCT as it seems to offer an excellent anti-leukaemia effect without life threatening toxicities.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P162

SINGLE CENTRE REVIEW OF THE OUTCOME, MORBIDITY AND HEALTH RESOURCE UTILISATION USING BEAM-ALEMTUZUMAB CONDITIONING IN LYMPHOID MALIGNANCIES; A BASIS FOR IMPLEMENTING CHANGE

Louisa Shackleton[1], Conor Hughes[1], Andrew Houston[1], Mary Barrett[1], Greg Lee[1], Brendan Crowley[1], Christopher Laurence Bacon[1], Elisabeth Vandenberghe[1], Robert Henderson[1]

[1]St James's Hospital, Dublin, Ireland

Background: BEAM (carmustine, etoposide, cytarabine, melphalan)-Alemtuzumab allogeneic conditioning is used for chemo-refractory lymphoma patients treated in the Irish National Allogeneic Stem Cell Transplant (AlloSCT) unit, with post-transplant donor lymphocyte infusion (DLI) given to attain 100% total/CD3 donor chimerism and reduce relapse. This study of outcome and morbidity assessed by survival, chimerism, Graft versus host disease (GvH), viral reactivation, DLI and bed utilisation provides a baseline to benchmark new salvage strategies including CAR-T therapy and PTCy alloSCT.

Methods: Retrospective sequential BEAM-Alemtuzumab conditioned alloSCT patients from 2012-2021 (follow-up censor date 22/7/22) was collected from institutional patient files and transplant database. Data points included demographics, diagnosis, date of diagnosis, treatment history, disease status at alloSCT, outcome at 100 days and censor date or death, incidence/type of viral infections in first post-SCT year, GvH incidence, total(T)/CD3 chimerism, indication/number of DLI infusions given. Kaplan Meier curves were used for overall survival (OS) and progression free survival (PFS).

Results: 40 patients were included, see table for demographics, diagnosis, alloSCT variables. The median OS and PFS have not been reached with a 44 (range 2-125) months follow-up. The total OS and PFS were 87.4% and 70.9% at the censor date; the Hodgkin's lymphoma cohort had an OS/PFS of 87.7% and 83.3%. and diffuse large B cell lymphoma (DLBCL) cohort had an OS/PFS of 100% and 75%. Death occurred in 11(28%) patients; 3 of disease and 8(20%) with non-relapse related mortality including 2 GvH and 6 of infection (sepsis-2, fungal-1, viral-3 (adenovirus, COVID, JC virus)). 2 patients died within the first 100 days post-alloSCT (1-progressive disease, 1-sepsis).

T/CD3 Chimerism results were evaluable in 38(95%) patients; T/CD3 100% donor (n = 15, 39%), T/CD3 mixed (n = 22,58%) and 1 autologous recovery. DLI was given to 19(48%) patients, median infusion number 1(range 1-5), for mixed chimerism in 14(73%) and relapse in 6(31%). Ten (72%) mixed chimerism patients converted to 100% donor with one DLI and 8 developed GvH.

Morbidity evaluation

aGvH Grade II-IV developed in 27(68%) patients; 7(18%) Grade III-IV; skin(n = 7), upper/lower GI (n = 3 + 3), multi-organ aGvH 13 (30%). 15 (34%) patients developed extensive cGvH; 8 following aGVHD and 8 post-DLI. 9(24%) patients were steroid refractory.

One or more viral infection occurred in 38(95%) patients including EBV *(n = 16 (40%))*, CMV *(n = 7(17.5%))*, respiratory viruses (parainfluenza, RSV, influenza, COVID, Rhinovirus, metapneumovirus) *(n = 31(77%))*, HSV *(n = 22(55%))*, adenovirus *(n = 8(20%)*) and BK virus 5(12.5%).

Bed and day unit requirements included a mean inpatient stay of 34 days(range 22-60), median of 43 day-care visits (range 16-79) and a median of 3(range 0-9) inpatient readmissions in the first year post-alloSCT.

Baseline demographics	**n (%)**	**Transplant timeline**	**n (%)**
Total number of patients	40	**Median days diagnosis to transplant (range)**	
Median age at transplant (range)	45 (19-62)	Entire cohort	440 (140-3114)
Sex		Hodgkin's lymphoma	486 (143-3827)
Male	19 (42)	DLBCL	386 (149-1618)
Female	21 (58)	Follicular lymphoma	960 (246-2661)
Donor type		**No. lines prior therapy, median (range)**	3 (1-7)
Sibling- fully matched 10/10	17 (43)		
Sibling- 1 antigen mismatch	1 (2)	**Remission status at transplant** (1 unconfirmed)	
Unrelated- fully matched	20 (50)	Complete remission	25 (63)
Unrelated- 1 antigen mismatch	2 (5)	Partial remission	14 (35)
Diagnosis		**Day 100 remission status**	
Hodgkin's lymphoma	18 (45)	Complete remission	34 (85)
DLBCL	12 (30)	Partial remission	2 (5)
Follicular lymphoma	7 (18)	Progressive disease	2 (5)
Mantle cell lymphoma	2 (5)	Transplant related mortality	2(5)
NK/T cell lymphoma	1 (2)		

Conclusions: BEAM-Alemtuzumab is an effective conditioning regimen for chemo-refractory lymphomas but has significant associated morbidity resulting in appreciable GvH (aGvH-68% and cGvH-34%), frequent viral infections and high bed/day unit utilization. Chemo-refractory DLBCL can now be treated with CAR-T therapy and PTCy conditioned alloSCT updated at ASH2022 (BMT CTN Protocol 1703/1801 PROGRESS III) confirmed lower viral infection rates (62% versus 95%) and GvH with preserved survival. This supports our planned change from alemtuzumab to PTCy based conditioning and provides a baseline against which to assess new regimens.

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P163

IMPROVED CLINICAL OUTCOME OF ALLOGENEIC STEM CELL TRANSPLANTATION FOLLOWING TBI-BASED CONDITIONING REGIMEN. A SINGLE-CENTER EXPERIENCE

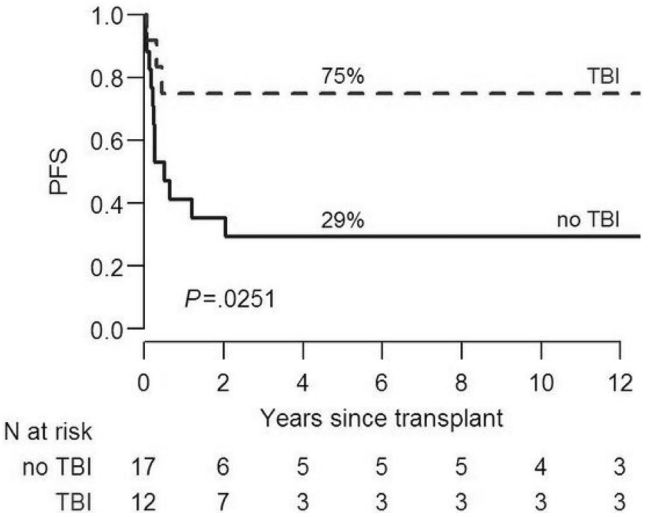
Alessandra Algarotti[1], Maria Caterina Mico'[1], Chiara Pavoni[1], Daniela Taurino[2], Giuseppe Gritti[1], Maria Chiara Finazzi[1], Gianluca Cavallaro[1], Francesco Romeo Filippone[3], Anna Grassi[1], Alessandro Rambaldi[4,1]

[1]Division of Hematology ASST Papa Giovanni XXIII, Bergamo, Italy, [2]IRCCS, Humanitas Cancer Center, Rozzano, Italy, [3]Division of Radiotherapy, Bergamo, Italy, [4]University of Milan, Milano, Italy

Background: Peripheral T-cell lymphomas (PTCL) comprise a group of morphologically and clinically heterogeneous disorders with a generally unfavorable outcome for patients failing front-line treatment. Allogeneic hematopoietic stem cell transplantation (AlloHSCT) remains a valuable treatment option to consolidate a salvage treatment strategy.

Methods: We retrospectively evaluate the impact of TBI-based conditioning regimens on the clinical outcome of 29 PTCL patients consecutively transplanted at our center between 1998 and 2021.

Results: The PTCL diagnoses were the following: PTCL-not otherwise specified (PTCL-NOS n = 10, 34%), anaplastic large cell lymphoma (ALCL n = 10, 34%), angioimmunoblastic lymphoma (AITL n = 4, 14%), cutaneous T-cell lymphomas (CTCL n = 4, 14%; Mycosis Fungoides n = 3 and Sezary syndrome n = 1) and 1 patient with NK-nasal type lymphoma. The median age was 40 years, (range 23-64), 14 patients were male, and 15 female. At transplant, most patients showed active disease (62%), an advanced clinical status (stage IV n = 24, 86%), and an intermediate-high (n = 6) or high (n = 9) International Prognostic Index (IPI) (65%). The median number of therapies before ALLO-HSCT was 2 (range 1-5). Only three patients were transplanted in their first complete remission, as part of a clinical trial. Patients were allografted from related siblings (n = 11, 38%) or unrelated donors (7 matched and 11 mismatched, 62%). The conditioning regimen was reduced-intensity (RIC) (n = 16, 55%) or myeloablative (n = 13, 45%) and among these latter 12 patients (41%) received total body irradiation (TBI) (800-1200cGy). Most patients (22/29, 76%) received graft versus host disease (GVHD) prophylaxis with anti-Thymoglobulin (ATG). The cumulative incidence of acute graft versus host disease grade 2-4 and moderate-severe chronic GVHD was 45% and 21% respectively. With a median follow-up of 2,5 years (range 0,1-25), 14 of 29 patients died (9 due to disease progression and 5 to infections or GVHD). At five-year, both OS and PFS are 48% while relapse and non-relapse mortality are 35% and 17%, respectively.



At univariate analysis, we observed a significantly better PFS (p = 0,03, HR 0,26) and a trend for a better OS (p = 0,15, HR 0,39) in patients who received a TBI-based conditioning regimen. No other factors, including disease status at the time of Allo-HSCT, number of treatment lines before HSCT, or specific histology influenced the outcome.

Conclusions:

In this patient's cohort, allogeneic HSCT confirmed its therapeutic potential and NRM was low despite the advanced clinical status. Disease recurrence was a rare event for patients surviving 2 years, suggesting the important role of graft versus lymphoma effect to control the disease. The use of a TBI-based conditioning regimen was associated with an improved outcome.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P164

TREOSULFAN, THIOTEPA AND FLUDARABINE CONDITIONING REGIMEN PRIOR TO ALLOGENEIC STEM CELL TRANSPLANTATION IN ACUTE MYELOID LEUKEMIA AND HIGH-RISK MYELODYSPLASTIC SYNDROMES: A SINGLE CENTER EXPERIENCE

Giulio Cassanello[1], Filippo Bagnoli[2], Giorgia Saporiti[2], Maria Goldaniga[2], Fabio Serpenti[1], Francesca Cavallaro[2], Kordelia Barbullushi[1], Giulia Galassi[2], Wilma Barcellini[2], Francesco Onida[1,2]

University of Milan, Milan, Italy, [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Background: Treosulfan-based conditioning prior to allogeneic transplantation has been shown to have myeloablative, immunosuppressive and antineoplastic effects associated with reduced transplant-related mortality (TRM) in adults. Emerging data are available for its use in myeloid malignancies.

Methods: We included patients diagnosed with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) who underwent first allogeneic hematopoietic stem cell transplantation (HSCT) at a single hematologic center from 2016 to 2022.

All patients received treosulfan-thiotepa-fludarabine (TTF) conditioning regimen, followed by allogeneic peripheral blood stem cell (PBSC) infusion. Treosulfan at 10, 12 or 14 g/m^2/day per 3 days and thiotepa 5 mg/Kg/day per one or two days were administered based on patient age and fitness. Fludarabine was administered at 30 mg/m^2/day for 5 days in all patients.

For non-haploidentical donors, graft versus host disease (GvHD) prophylaxis consisted of cyclosporine (CsA) and short-course methotrexate; anti-thymocyte globulin (ATG) was administered in matched sibling donor (MSD), matched unrelated donor (MUD) 10/10 and MUD 9/10 at 2.5, 5 and 7.5 mg/Kg, respectively.

Haploidentical patients received ATG 2.5 mg/Kg, post-transplant cyclophosphamide (PTCy) 50 mg/Kg on days 3 and 4, CsA and mycophenolate mofetil from day 5.

GvHD was graded according to MAGIC and NIH criteria for acute and chronic forms, respectively.

Results: We included 37 consecutive patients, mainly affected by AML (86%), with a median age of 59 years (24-74) (table 1).

Treosulfan at 14, 12 and 10 g/m^2/day was administered to 13 (35%), 13 (35%) and 11 (30%) patients respectively, while dose reduced thiotepa at 5 mg/Kg/day was administered in 18 patients (48%), most frequently combined with treosulfan 10 g/m^2/day.

Haploidentical donors were selected for 15 patients (40%), which mirrors the widespread use and favourable results reported with PTCy in recent years. 29 patients (78%) underwent HSCT in hematologic complete remission, the remaining were in partial remission (11%) or non-response (11%). Nearly half of patients were considered at high risk for TRM, as reflected by a comorbidity index (HCT-CI) ≥ 3 in 17 patients (46%) and an EBMT score ≥4 in 18 (49%).

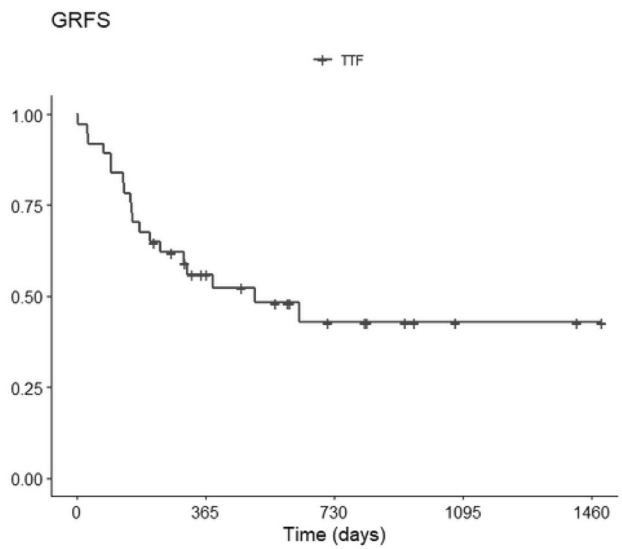
Grade 2-4 acute GVHD was observed in 6 patients (16%), with only one experiencing an overall grade 3. A concomitant sinusoidal obstruction syndrome was observed in two patients (5%), consistent with the endothelial origin of both complications. 5 patients (14%) developed chronic GvHD, none of them of severe overall grade.

The only TRM cause was infection, occurring in 4 patients (11%). After a median follow up of 507 days (5-2469), 18 patients (49%) remained relapse- and GvHD-free (GRFS). The estimated 2-year relapse free survival (RFS) and overall survival (OS) were 59% and 67%, respectively.

Conclusions: In conclusion, despite an elevated HCT-CI and EBMT score in half of patients, TTF conditioning resulted in low TRM rate. Relapse was the main cause of death, hence a higher treosulfan dosing and/or a faster immunosuppression tapering might be considered given the low GVHD incidence. Finally, we observed a high rate of GRFS with this transplant platform, which may deserve further study if confirmed on large cohorts.

Table 1. Baseline features and outcome after TTF conditioning

TTF conditioned patients (N = 37)	
Median age, years (range)	59 (24-74)
AML, N (%) / MDS, N (%)	32 (86%) / 5 (14%)
Graft source	
Matched sibling donor (MSD), N (%)	7 (19%)
MUD 10/10, N (%) / MMUD 9/10, N (%)	10 (27%) / 5 (14%)
Haploidentical donor, N (%)	15 (40%)
Pre-transplant risk assessment	
HCT-CI > 2, N (%)	17 (46%)
EBMT > 3, N (%)	18 (49%)
DRI intermediate, N (%) / High or Very high, N (%)	26 (70%) / 11 (30%)
Post-transplant complications	
Acute GvHD (grade 2-4), N (%) / (grade 3-4), N (%)	6 (16%) / 1 (3%)
Chronic GvHD, N (%)	5 (14%)
Sinusoidal obstruction syndrome (SOS), N (%)	2 (5%)
Transplant outcome	
Transplant related mortality (TRM) incidence, N(%)	4 (11%)
2-year relapse free survival (RFS), %	59%
2-year graft-relapse free survival (GRFS), %	49%
2-year overall survival (OS), %	67%



Clinical Trial Registry: not applicable
Disclosure: Nothing to declare

Clinical Trial Registry: not applicable

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P165

THIOTEPA, TREOSULFAN AND FLUADARABNE (TTF) VERSUS THIOTEPA, BUSULFAN AND FLUDARABINE (TBF) CONDITIONING FOR MATCHED RELATED DONOR PERIPHERAL BLOOD STEM CELL TRANSPLANT FOR THALASSEMIA MAJOR

Upasana Karthik[1], Neha Rastogi[1], Dhwnee Thakker[1], Sunisha Arora[1], Rachit Khandelwal[1], Satya Prakash Yadav[1]

[1]Medanta, The Medicity Hospital, Gurgaon, India

Background: Traditionally used busulfan (BU) and cyclophosphamide (Cy) based conditioning for Haemopoietic Stem Cell Transplantation for Thalassemia Major is associated with higher veno-occlusive diseases (VOD) and mortality. Thus, recently Cy free reduced toxicity regimens – Thiotepa, Treosulfan, Fludarabine (TTF) and Thiotepa, Busulfan, Fludarabine (TBF) have been used. Here, we discuss the head-to-head comparison between TTF and TBF conditioning in children with thalassemia major who underwent matched related donor (MRD) Peripheral blood stem cell transplant (PBSCT).

Methods: Medical records of all children who underwent MRD PBSCT for Thalassemia Major from January 2018 to October 2022 were retrospectively analyzed. Patients received either TTF or TBF conditioning along with Anti-Thymocyte Globulin (ATG) after an informed written consent. Total doses were-Fludarabine-160mg/m^2, Thiotepa-10mg/kg and Rabbit ATG(Thymoglobulin)- 4.5mg/kg. Dose of Busulfan was 3.2mg/kg/day for 4 days and Treosulfan-14g/m^2/day for 3 days. Graft vs. host disease (GVHD) prophylaxis was with cyclosporine and methotrexate (Day+1,3,6 and 11). From January 2022 all children received a single dose of Peg-GCSF on day+6. The two groups were analyzed for differences in various transplant related outcomes. Statistical analysis was conducted with IBM-SPSS version 21.0. $p < 0.05$ was taken to be significant.

Results: Our cohort comprised of 20 children, 10 in each group. Median age- 5.7 years (TBF) and 5.1 years (TTF). Male: Female was 1:1 in both groups. TBF group had 80%, 0% and 20% in Pesaro Class I, II and III respectively. TTF group had 80% class-I, 20% class-II and none class-III patients. Median pre-transplant ferritin was 1370 ng/ml (TBF) and 1520 ng/ml (TTF). Basic characteristics were similar in both groups without statistically significant differences. However, mean neutrophil engraftment was significantly different between two groups which can be attributed to administration of Peg-GCSF to all TTF patients. There was no statistically significant difference in platelet engraftment, acute or chronic GVHD, VOD, Transplant Associated Thrombotic Microangiopathy, mucositis, need for narcotic analgesics, diarrhea, central nervous system complications, pulmonary complications, poor graft function, sepsis, chimerism on last follow up, viral re-activation, duration of hospital stay and re-admissions post discharge between TBF and TTF groups (Table1). Only one patient (Class-III) died in TBF group with sepsis on day+140. None died in TTF. No primary graft failure in either group. Mixed chimerism at last follow up was seen in none and two patients (20%) in TBF and TTF respectively ($p = 0.330$). Viral reactivation was seen in five patients in TBF and three patients in TTF ($p = 0.646$). Overall survival (OS) was 90% for TBF group at a median follow up of 41 months. OS was 100% for TTF group at follow up of 5 months. The duration of follow up for TTF groups is short as it is recently adopted conditioning regimen in our unit.

Table1: Comparison of Transplant Related Outcomes between the 2 groups.

Parameters	TBF	TTF	P value
Neutrophil Engraftment (days)	14.80 ± 3.05	11.70 ± 0.95	0.007
Platelet Engraftment (days)	15.22 ± 2.22	16.60 ± 7.59	0.607
aGvHD	3(30%)	2(20%)	1.00
cGvHD	1(10%)	0(0%)	1.00
Veno-occlusive disease	3(30%)	0(0%)	0.211
HLH	2(20%)	0(0%)	0.474
Thrombotic micro-angiopathy	1(10%)	1(10%)	1.00
Mucositis	6(60%)	1(10%)	0.057
Need for narcotics for analgesia	5(50%)	1(10%)	0.141
Diarrhea	3(30%)	4(40%)	1.00
CNS Complication	1(10%)	1(10%)	1.00
Pulmonary Complication	1(10%)	0(0%)	1.00
Poor Graft Function	2(20%)	0(0%)	0.474
Sepsis	4(40%)	3(30%)	1.00
Mixed Chimerism at last follow-up	0(0%)	2(20%)	0.330
Viral Reactivation	5(50%)	3(30%)	0.646
Duration of Hospital stay (Mean ± SD)	25.20 ± 3.01	23.20 ± 4.08	0.228
Post-transplant Readmissions	8(80%)	4(40%)	0.170

Conclusions: Both TBF and TTF conditioning regimens are safe and effective for children with thalassemia major undergoing MRD PBSCT.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P166

POST-TRANSPLANTATION CYCLOPHOSPHAMIDE-BASED GVHD PROPHYLAXIS AFTER FLU-TBI MYELOABLATIVE CONDITIONING IS ASSOCIATED WITH FAVORABLE OUTCOMES IN ADULT PATIENTS WITH ALL TREATED WITH CONTEMPORARY INDUCTION REGIMENS

Nadia Bambace[1], Yuliya P.L. Linhares[1], Ariel Perez Perez[1], Tiba Al Sagheer Pharm[1], Talia Zahra[1], Muni B Rubens[1]

[1]Miami Cancer Institute, Miami, United States

Background: The optimal myeloablative conditioning regimen for adults with acute lymphoblastic leukemia (ALL) in the haploidentical and mismatched setting remains undefined. Our institution has adopted the FLU-TBI regimen with post-transplantation cyclophosphamide (PTCY) to treat most patients undergoing allogeneic stem cell transplants for ALL. We sought to describe our real-world experience with this regimen across all donor sources.

Methods: Adults undergoing allogeneic stem cell transplantation for ALL having received FLU-TBI (fludarabine 30 mg/m^2 x 3 days and TBI 150cGy BID on D-4 to D-1) followed by the infusion of an unmanipulated peripheral stem cell graft between April 2020 and August 2022 were retrospectively identified. All patients received cyclophosphamide 50mg/kg on d + 3 and +4, mycophenolate (MMF) and tacrolimus as immunosuppression.

Results: A total of 10 patients were included in the study. The median age was 49 years (range, 20 - 67). Fifty percent of patients were aged ≥ 50. Philadelphia-positive ALL comprised 50% of the cohort, of which 40% received a chemotherapy-free induction combining steroids, a TKI and blinatumomab. Prior exposure to novel immunotherapeutics was 90% (Inotuzumab, n = 2; blinatumomab, n = 5; both agents, n = 2). A median of 2 cycles of blinatumomab were administered prior to HSCT. Five patients received a haploidentical graft, 1 patient received an HLA- match-related graft, 2 patients received an HLA-matched unrelated graft while 2 patients received an HLA-mismatched unrelated graft. Eighty percent of the cohort had intermediate risk disease. Disease control at time of transplant was excellent with 90% of patients in MRD neg complete remission (CR). The median HCT-CI score was 2 (0-10). Ninety percent of patients had a KPS ≥ 90%. Median time to neutrophil and platelet recovery were 15d (13-17d) and 22d (16-32d). All patients achieved complete donor T cell and myeloid chimerism by day +30.

At D + 100, 8 out of 8 evaluable patients were in MRD negative CR. One patient died at 5 months post-HSCT from sepsis in the setting of acute graft-vs-host-disease (GVHD). Acute GVHD grades I to II and III to IV was seen in 40% and 10% respectively. The cumulative incidence of chronic GVHD was 10% with no severe cases. The most common post-HSCT infectious complications were COVID infection (40% of patients) and viral reactivations. Asymptomatic CMV reactivation was noted in 20% of patients, despite 90% seropositivity. This lower incidence is attributed to the routine use of post-transplant letermovir.

At a median follow up of 289 days (94-942), the estimated 1-year OS was 83.3% (53.5-100). Median OS was not reached. There were no documented disease relapses.

Baseline Characteristics (n = 10)	Value/n
Age, median, range	49 (20-67)
Gender	
Male	5(50%)
Female	5(50%)
Disease status	
CR1	8
CR2	2
PH positive	5
CNS involvement	2
DRI index	
Low	8
Intermediate	2
High	2
MRD status at HSCT	
Negative	9 (90%)
Positive	1 (10%)
Stem cell source	
PBSC	10 (100%)
HLA match	
12/12 Match	3
9/12 Match	2
6/12 Match	5
HCT-CI	
< 3	6
3-5	3
>5	1
KPS	
< 90%	1
CMV serostatus	
D + R+	9
D-R-	1
Engraftment	
Median ANC	15d
Median ANC	18d
Acute GVHD	
Grade I-II	4 (40%)
Grade I-II	1(10%)
Chronic GVHD	1 (10%)
Infections	
CMV viremia	2
Adenoviremia	1
COVID	4
Respiratory, other	1
GI, other	1

Conclusions: Within the limits of a small but homogeneously treated population of adult ALL, the FLU-TBI regimen was well tolerated and associated with favorable outcomes in the haploidentical, HLA-matched and mismatched setting. Our experience illustrates that a cumulative TBI dose of 1200cGy can be safely administered to patients ≥ 50 years old without significant toxicity. The absence of relapse and low TRM is likely related to the high MRD-negative pretransplant rate achieved in this cohort with the utilization of less intensive chemotherapy regimens incorporating early immunotherapy use.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P167

INFERIOR OUTCOMES WITH MELPHALAN BASED CONDITIONING COMPARED TO BUSULFAN WITH FLUDARABINE IN CHILDREN UNDERGOING HSCT

Revathi Raj[1,2], Ramya Uppuluri[2], Venkateswaran Vellaichamy Swaminathan[2], Sohini Chakraborty[2], Satishkumar Meena[2], Kavitha Ganesan[2], Suresh Duraisamy[2], Vikas Hegde[2], Usha Surianarayanan[2], Indira Jayakumar[2]

[1]Tamilnadu, Chennai, India, [2]Apollo Cancer Hospitals, Chennai, India

Background: The efficacy of a reduced toxicity regimen (RTC) with Fludarabine and Melphalan compared to a Myeloablative regimen (MAC) with Fludarabine and Busulfan has not been studied extensively in children. We performed a retrospective analysis of the outcomes of the first transplantation in patients who had underwent an allogeneic HSCT after RTC or MAC at our centre

over the last ten years with specific emphasis on chimerism after HSCT.

Methods: Our study analysed the outcome of children under 18 years between December 2015 to December 2021 who underwent allogeneic HSCT following a RTC with Fluadarabine 40 mg /m2 for 4 days and Melphalan 140 mg/m2 for 1 day or a MAC regimen with Fluadarabine 40 mg/m2 for 4 days with intravenous Busulphan at a dose of 4.8 mg/kg/day in above two years and 3.2 mg/kg/day in children less than 2 years old. We did not perform Busulfan pharmacokinetics. Data collected included demographics and the indications for HSCT. We documented mixed chimerism or graft rejection as an event at Day 100 and 1 year and complete chimerism as event free survival. We also recorded data on overall survival and the cause of mortality. The study was approved by Institutional Ethics Committee.

Results: We analysed data on 85 children aged between 2 months and 17 years with 59 (69%) male and 26 (31%) females. The indication for HSCT was a malignancy in 50 (58%) and a non-malignant disorder in 35(42%) children. We used Melphalan based RTC in 31 (36%) and Busulfan based MAC in 54 (64%). The EFS and OS did not differ based on malignant or non- malignant indication, age less than 3 years or over 3 years or the sex of the child. The EFS on Day 100 was 48.4% in the RTC group versus 72.2% in the MAC group and this was statistically significant (p 0.025). The EFS at one year was also superior in the MAC group at 77.8% versus 45.2% in the RTC group (p 0.003). The overall survival was similar in both groups at 45.2% in the RTC group and 37% in the MAC group and this was not statistically significant (p 0.30). Relapse or rejection was the main cause of mortality 10/34 (31%) in the RTC group and 11/54 (20%) in the MAC group.

Conclusions: The results suggest that the Melphalan based RTC regimen is an inferior conditioning strategy for children as the there is a higher incidence of mixed chimerism and the need for donor lymphocyte infusions and post-transplant graft manipulation. Our cohort did not receive targeted busulfan with fludarabine and hence the reduced EFS in this group. Busulfan with pharmacokinetics with fludarabine is the most effective option for children undergoing MAC conditioning HSCT.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P168

LOMUSTINE, ETOPOSIDE AND CYCLOPHOSPHAMIDE IN CONDITIONING REGIMEN FOR LYMPHOMAS: THE EXPERIENCE OF A BRAZILIAN INSTITUTION

Christianne Toledo de Souza Leal[1], Kelli Borges dos Santos[1], Juliana Pereira[2], Fernando Barroso[3], Ana Paula Pinheiro[1], Maria Carolina Nascimento Pires[1], Abrahao Elias Hallack Neto[1]

[1]Juiz de Fora Federal University, Juiz de Fora, Brazil, [2]Sao Paulo University, Sao Paulo, Brazil, [3]Ceara Federal University, Fortaleza, Brazil

Background: Due to the lack of evidence regarding the best conditioning regimen for the realization of autologous stem cell transplantation (ASCT) in patients with lymphoma, new schemes have been proposed as alternative to traditional regimens, mainly in the context of the shortage of drugs, which frequently occurs in Brazil. We evaluated a conditioning protocol with lomustine, etoposide and cyclophosphamide (LEC) for ASCT in patients with lymphoma.

Methods: In the first step, the maximum tolerated dose of lomustine was set at 400 mg/m^2, by means of a 3:3 scale. The second step consisted of evaluating the protocol with the use of lomustine (400 mg/m^2) and etoposide (1 g/m^2) on day -5, followed by cyclophosphamide (6 gr/m^2 days -4 to -2). The results were compared with the historical series of patients submitted to conditioning with carmustine, cyclophosphamide and etoposide (CBV) and lomustine, etoposide, cytarabine and melphalan (LEAM). The mortality related to treatment (MRT), progression-free survival (PFS) and overall survival (OS) were calculated.

Results: Of the 139 patients evaluated, 31 received LEC, 37 LEAM and 71 CBV. Eighty-three (60%) patients had Hodgkin's lymphoma, with a homogeneous distribution between the three protocols CBV: 63%; LEAM: 56.75%; and LEC: 58% ($p = 0.7$). At the time of ASCT, 15 patients had refractory disease, without statistically significant difference between treatment groups ($p = 0.21$), as well as for age ($p = 0.19$). With an average time of neutropenia of 9.4 days, only one patient in the LEC group died within the first 100 days of the ASCT, with a trend to lower MRT. For 139 patients evaluated, OS at 24 and 60 months, was, respectively, 67% and 52.8%. OS at 2 years for the 3 conditioning protocols was 83%, 75.7% and 58.6% for those receiving LEC, LEAM and CBV, respectively ($p = 0.018$).

Conclusions: Although longer follow-up time is required, LEC proved to be a secure protocol, with higher overall survival rates than protocols used previously in our environment. The LEC protocol proves to be an option to traditional conditioning regimens and may be an alternative to cytarabine protocols or in situations where frequently used medications are lacking.

Clinical Trial Registry: RBR-10bj7s98
https://ensaiosclinicos.gov.br

Disclosure: There are no conflicts of interest to declare.

16 - Conditioning Regimens

P169

PREVIOUS BUSULFAN EXPOSURE IS NOT A CONTRAINDICATION FOR SECOND ALLOGRAFT WITH REDUCED INTENSITY TREOSULFAN BASED CONDITIONING FOLLOWED BY IN-VIVO T-CELL DEPLETED UNRELATED DONOR HAEMATOPOIETIC TRANSPLANT

Adrian Maraj[1], Daniele Avenoso[1], Michelle Kenyon[1], Pramila Krishnamurthy[1], Varun Mehra[1], Austin Kulasekararaj[1], Shreyans Gandhi[1], Francesco Dazzi[1], Ye Ting Leung[1], Sandra Anteh[1], Maria Cuadrado[1], Mili Naresh Shah[1], Hayat Ullah[1], Styliani Bouziana[1], Christianne Bourlon[1], Oana Diana Dragoi[1], Antonio Pagliuca[1], Victoria Potter[1]

[1]King's College Hospital, London, United Kingdom

Background: Despite the improvement in the treatment of relapsed myelodysplastic syndromes and acute myeloid leukaemia, second hematopoietic stem cell transplant (HSCT) remains associated with increased transplant related mortality (TRM) and relapse rate compared to first transplants. Therefore, actions are needed to improve the safety and efficacy of second transplants. Within the alkyl sulfonates used in conditioning, Treosulfan has better marrow penetration than Busulfan and high activity on both myeloid progenitors and blasts; also, its hydrophilic properties are associated with less tissue damage and therefore

decreased incidence of graft-versus-host disease (GVHD) and veno-occlusive disease (VOD) of the liver.

Based on these encouraging promises, between December 2020 to May 2022, 10 consecutive second HSCT conditioned with fludarabine and treosulfan (FluTreo) were performed at King's College Hospital, London with the aim to offer a less toxic second transplant. All the patients were firstly transplanted with busulfan based regimens.

Methods: Second HSCT was performed using GCSF mobilized peripheral blood stem cells. Conditioning protocol was with Fludarabine 30mg/m^2 on days-6,-5,-4,-3,-2 and Treosulfan 10g/m^2 on days-4,-3,-2; GVHD prophylaxis consisted of ATG 2.5mg/kg on days-2,-1, Ciclosporin 1.5mg/kg BD from day -1 and post-HSCT Methotrexate 10mg/m^2 on days$+1, +3, +6$. Donors were 6 matched unrelated donors and 4 mismatched unrelated donors. Probabilities of overall survival (OS) were calculated using the Kaplan-Meier method. Relapse incidence (RI) and transplant related mortality (TRM) rates were estimated using cumulative incidence (CI) functions and considered as competing risks. For GvHD, death and relapse were considered competing events. Statistical analyses were performed with GraphPad Prism Version 9.4.1.

Results: Table 1 summarizes the demographic of the population. Median follow up was 344 days(range 100 – 661).

The 100 and 365 days OS were 100% with median OS not reached (figure 1) and with absent TRM. No septic deaths before engraftment or primary graft failures were noted.

The 12 months and 18 months leukemia-free survival (LFS) were 80% and 70% respectively (figure 1), median LFS was 566 days. Median time to neutrophils>1000/uL was 13 days(12-16), and 16 days(13-35) to platelets >20000/uL. Median CD3 and CD15 chimerism at day 365 were 98% and 100%. Incidence of acute GVHD was 60% (grade III-IV 10%); 90% of observed acute GVHD was skin grade I-II. Overall chronic GVHD rate was 10% (n = 1) and there were no moderate to severe cases. No VOD cases were recorded. Cumulative incidence of relapse was 30% with a relapse rate at 1 year of 20%. The median time to relapse was 165 days(56-566) (figure 2). EBV reactivation rate was 90%(n = 9) and 56% of these patients (n = 5) required treatment with Rituximab, with 44%(n = 4) having biopsy proven post-transplant lymphoproliferative disorder(PTLD).

Table 1

Characteristic	Number of patients n = 10
Age at HSCT in years, median (IQR)	55 (33-71)
Male	5 (50%)
Female	5 (50%)
Diagnosis	
AML	6 (60%)
MDS / MDS-MPN	4 (40%)
Adverse cytogenetic risk (ELN)	
Favourable/Intermediate	4 (40%)
Adverse	6 (60%)
Disease status at HSCT	
CR 1/2 (MRD negative)	3 (30%)
CR 1/2 (MRD positive)	5 (50%)
Primary induction failure	2 (20%)
Relapsed disease	0
HCT-CI	
0-2	7 (70%)
3+	3 (30%)
Follow up in days, median (IQR)	409 (100-661)

Figure 1

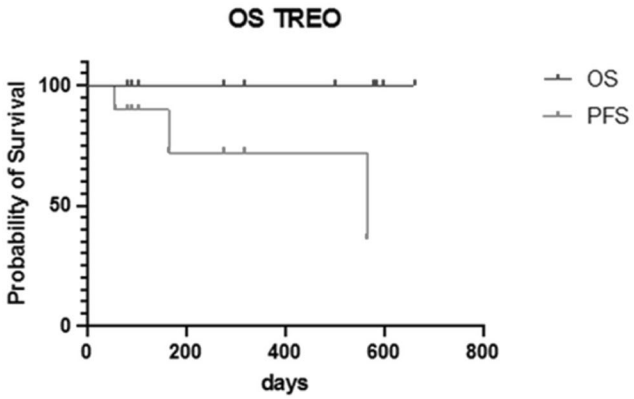
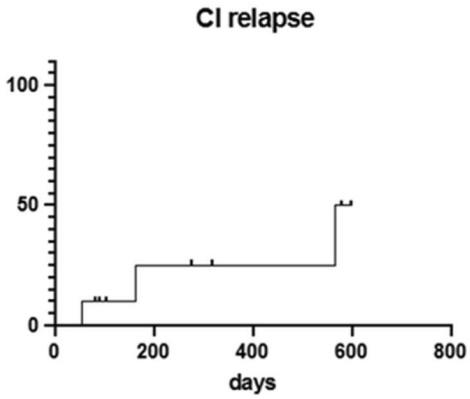


Figure 2



Conclusions: Outcomes for this high-risk population are favorable with no deaths recorded from TRM, infection or graft failure. While follow-up has been limited, the OS is encouraging and the LFS and incidence of acute GVHD are comparable to recorded rates in the literature.

Previous conditioning with Busulfan does not preclude the efficacy of Treosulfan-based conditioning in second HSCT as it seems to offer an excellent anti-leukaemia effect without life threatening toxicities.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P170

COMBINATION OF FLUDARABINE WITH TOTAL BODY IRRADIATION IS ASSOCIATED WITH REDUCED EARLY TRANSPLANT-RELATED TOXICITIES IN ACUTE LYMPHOBLASTIC LEUKEMIA ADULT PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION

Gianluca Cavallaro[1], Anna Grassi[1], Maria Caterina Micò[1], Alessandra Algarotti[1], Paola Stefanoni[1], Daniela Taurino[2], Maria Chiara Finazzi[1], Federico Lussana[1], Giuliana Rizzuto[1], Benedetta Rambaldi[1], Marta Castelli[1], Francesco Romeo Filippone[1], Chiara Pavoni[1], Alessandro Rambaldi[1]

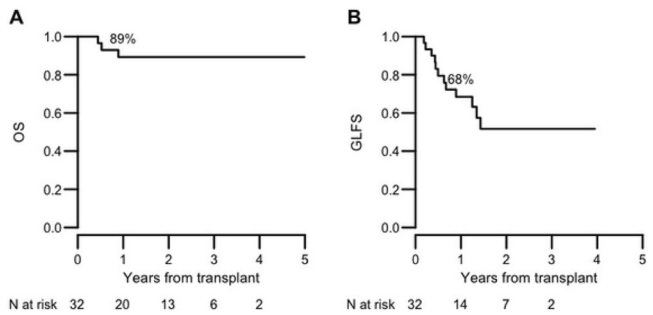
[1]ASST Papa Giovanni XXIII, Bergamo, Italy, [2]IRCCS Humanitas Cancer Center, Rozzano, Italy

Background: Hematopoietic stem cell transplant (HSCT) represent the best consolidation therapy for acute lymphoblastic leukemia (ALL) patients achieving a first complete remission (CR), especially in high-risk and very high-risk disease or in case of standard risk disease with minimal residual disease (MRD) positivity during first line therapy and in case of relapsed/refractory disease. Current EBMT guidelines on HSCT for ALL suggest the adoption of a myeloablative conditioning regimen combining total-body irradiation (TBI) at the dose of 12 Gray (Gy) with an alkylating agent, such as cyclophosphamide (CY), especially in patients aged less than 45 years. Clinical experiences with the TBI-CY conditioning regimen show excellent outcomes in terms of disease control, with relevant rates of non-relapse mortality (NRM) and short and long-term side effects. We report our experience with the combination of fludarabine and TBI as conditioning regimen in ALL patients undergoing HSCT.

Methods: We analyzed 32 ALL patients consecutively undergoing HSCT in our Institution from April 2017 to October 2022. We selected only patients who received a 12 Gy and 8 Gy TBI doses. We collected data concerning NRM, overall survival (OS), leukemia-free survival (LFS), incidence of grade 2-4 acute graft versus host disease (GvHD), incidence of moderate/severe chronic GvHD, graft-and-leukemia free survival (GLFS). Outcomes were evaluated at 1 year after transplant. We also reported the incidence of specific early transplant-related toxicities with a retrospective comparison with a cohort of 42 patients undergoing a TBI-CY regimen. The analyzed toxicities were hemorrhagic cystitis, veno-occlusive disease (VOD), grade 3-4 mucositis and infectious complications.

Results: Median follow-up for the study population was 1.3 years (range 0.03-5). 13/32 patients received TBI 8Gy due to older age or significant comorbidities. 1-year NRM of whole population was 11%. 1-year OS (Fig.1 panel A) and LFS were 89% and 86%, respectively. Concerning GvHD, we observed 13/32 cases of grade 2-4 aGvHD, with skin being the most frequently affected organ; moderate or severe cGvHD occurred in 5/32 patients. 1-years GLFS was 68% (Fig.1 panel B). Regarding toxicities, we made a retrospective comparison with an age-matched cohort of 42 patients undergoing HSCT in the years 2007-2016 with TBI-CY as conditioning regimen. In TBI-fludarabine group, we observed a reduction in grade 3-4 mucositis (51.6% vs 94.7%, $p = 0.0015$) and hemorrhagic cystitis (9.4% vs 31.7%, $p = 0.0221$). VOD rates were lower in TBI-fludarabine (1 case vs 4 cases), but we did not observe a statistical significance probably because of the global low number of events ($p = 0.3814$). Incidence of infectious complication within 100 days after transplant were similar between the two groups (28.1% vs 36.6%, $p = 0.4452$). Death events were lower in TBI-fludarabine group (9.4% vs 40.5%, $p = 0.0028$).

Figure 1: 1-year OS (A) and GLFS (B)



Conclusions: With the limitation of a retrospective analysis, our experience confirms that fludarabine-TBI conditioning regimen is feasible and possibly leads to lower rates of early transplant-related toxicities without a detrimental effect on relapse rate.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P171

THE IMPACT OF TREOSULFAN -BASED CONDITIONING FOR PRIMARY IMMUNE DEFICIENCIES: SINGLE CENTER EXPERIENCE

Gizem Zengin Ersoy[1], Funda Cipe[2], Basak Adakli Alsoy[1], Nazlı Hashemi[1], Ozlem Basoglu Oner[1], Selime Aydogdu[3], Gurcan Dikme[4], Melek Erdem[5], Ceyhun Bozkurt[6], Tunc Fisgin[1]

[1]Altinbas University, Mediacal Park Bahcelievler Hospital Pediatric Bone Marrow Transplantation Unit, Istanbul, Turkey, [2]Altinbas University, Park Bahcelievler Hospital, Istanbul, Turkey, Umraniye Training and Research Hospital, Istanbul, Turkey, [4]Istanbul Aydın University, Istanbul, Turkey, [5]Istınye University, Medical Park Gaziosmanpasa Hospital, Istanbul, Turkey, [6]Istinye University, Bahcelievler Medical Park Hospital, Istanbul, Turkey

Background: The use of treosulfan-based conditioning for hematopoietic stem cell transplantation (HSCT) in pediatric practice is increasing because of its effective myeloablative and immunosuppressive properties while proposing less systemic toxicity. Reduced-toxicity conditioning is preferred in patients with primary immune deficiency (PID), many of whom enter HSCT with chronic infection and end-organ comorbidities. This study aims to explore the relationship between systemic treosulfan exposure and early and long-term clinical outcomes in patients undergoing allogeneic HSCT for PID.

Methods: This retrospective observational study is conducted in the Pediatric Stem Cell Transplantation Unit of Altinbas University Medical Park Bahcelievler Hospital. Our cohort comprised 58 PID patients who underwent HCST with treosulfan-based conditioning between April 2018 and April 2022. Collected data included age at the time of transplantation, sex, type of PID, transplantation type, donor relatedness, human leukocyte antigen (HLA) donor matching, stem cell source, treosulfan dose, and area under curve ratio (AUC) of treosulfan, the presence, and grade of treatment-related early toxicity (mucositis, hepatic, neurologic and skin toxicity); acute graft-versus-host disease (aGVHD), and chronic GVHD (cGVHD), chimerism status, event-free survival (EFS) and overall survival (OS). All patients received homogenous conditioning containing treosulfan (14 gr /m2 for patients > one-year-old, 12 gr/m2 for patients < one-year-old) for three days and fludarabine 30 mg/m2 for five days. Serotherapy was done with anti-thymocyte globulin (ATG). GVHD prophylaxis consists of calcineurin inhibitors (cyclosporine for MSD and MUD; tacrolimus for MMD) and micofenolat mofetil (MMF) for MMD. Blood samples for treosulfan measure were collected at 0,1,2 and 4th hours of treosulfan exposure, and AUCs were calculated and divided into three based on tertiles; low: <625 m.h/L; medium:625-950 m.h/L and high: >950 m.h/L.

Results: Treosulfan dose groups (12 gr/m2:27 patients-14 gr/m2:30 patients) and AUCs are compared according to mucositis grade, early hepatic, neurologic, and skin toxicity; donor chimerism at 1st, 3rd, 6th months and last chimerism; the presence of acute or chronic GVHD and its grade; the presence of transplant-related mortality and overall survival. Treatment-related toxicities and the presence of acute or chronic GVHD were similar for each dose and AUC group. The 1st-month and last chimerism ratios were identical in all groups and >90% in 51 patients (89,6%). Mixed chimerism increased in the 14 gr/m2 group (OR:5). 2 years of overall survival for PID patients who underwent treosulfan-based conditioning was 76%.

Conclusions: Treosulfan-based conditioning regimens are effective and cause reduced toxicity for PIDs. Like the previous literature, we did not find any significant change in toxicities or outcomes related to HSCT according to AUCs. Although the efficacy of 12gr/m2 and 14 gr/m2 doses is the same, mixed chimerism rates are higher in the 14 gr/m2 group. This study raised whether the dose of treosulfan could be modified in the > one-year-old group who take the dose of 14 gr/m2. However, this conclusion might have been affected by the retrospective structure of this study and should be supported with prospective trials.

Clinical Trial Registry: Not applicable

Disclosure: The authors disclose no conflict of interest.

16 - Conditioning Regimens

P172

POST-TRANSPLANT CYCLOPHOSPHAMIDE IN UNRELATED DONOR PERIPHERAL BLOOD STEM CELL TRANSPLANT RESULTS IN SUCCESSFUL ENGRAFTMENT AND SUBSTANTIALLY LOW INCIDENCE OF CHRONIC GRAFT VERSUS HOST DISEASE

Ifigeneia Tzannou[1], Ioannis Tsonis[1], Tatiana Tzenou[1], Anna Roumelioti[1], Natasa Eleni Loutsidi[1], Maria Katsareli[1], Maria Eleni Karatza[1], Maria Garofalaki[1], Zoi Poulopoulou[1], Soultana Tryfonidou[1], Eirini Tziotziou[1], Eirini Grispou[1], Dimitrios Karakasis[1], Stavros Gigantes[1], Ioannis Baltadakis[1]

[1]Evangelismos Hospital, Athens, Greece

Background: The Post-Transplant Cyclophosphamide (PTCY) approach was first studied in the haploidentical transplant setting and resulted in high percentages of engraftment and reduced frequency of acute and chronic Graft versus Host Disease (GvHD) and non-relapsed mortality (NRM), without T-cell depletion. PTCY is increasingly being used in HLA-matched (MUD) and mismatched unrelated donors (MMUD). The aim of this study was to investigate the impact of PTCY on the incidence of chronic GvHD, which remains an important issue in the unrelated donor transplant setting.

Methods: Thirty-seven consecutive patients who underwent allogeneic hematopoietic stem cell transplant from unrelated donors were studied. PTCY was administered on days +3 and +4 post-transplant at a dose of 50 mg/kg/day. Additional GvHD prophylaxis included tacrolimus and mycophenolate mofetil starting on day +5. Anti-thymoglobulin was not given. In patients with no evidence of GvHD, immunosuppression was gradually tapered, and eventually stopped by day +90. We evaluated the safety and efficacy of PTCY, focusing on toxicity, engraftment, aGvHD and cGvHD frequency, relapse, non-relapse mortality and survival.

Results: We performed 37 unrelated donor transplants with PTCY from January 2021 to August 2022 in patients with a median age of 53 (18-69) years. The reason for transplant was AML/MDS (n = 27), NHL/CLL, (n = 2), pMF (n = 2), CML (n = 1) και ALL (n = 5). 22/37 patients had intermediate Disease risk index (DRI), 9 high and 6 had low. Twenty-five patients received myeloablative conditioning and 12 reduced-intensity. HLA-allele matching was 8/8 in 26 cases and 7/8 in 11. Of note all patients received a peripheral blood graft and the median CD34+ cell dose was 6,68×10e6/kg (3,27-11,58). The most common toxicities observed were oral mucositis (n = 22), diarrhea (n = 26), vomit (n = 7) and liver toxicity (n = 3) – in all cases grade I-II. Engraftment, defined as neutrophils >500/μl, was achieved in 34 cases in a median of 16 (13-25) days. Two patients died before day +28 due to NRM and one additional patient with myelofibrosis had primary graft failure. The cumulative incidence of aGvHD, grade II-IV at 100 days was 51,4% (95%CI: 37,3-70,7). However, aGvHD grade III-IV was only 5,4% (95%CI: 1,4-21,2). The cumulative incidence of cGvHD was 13,2% (95%CI: 5,2-33,5), with only one case of extensive cGvHD. In a median follow-up of 13,8 (3-22) months, disease free (DFS) and overall survival (OS) at 1 year were 71,8% (95%CI: 58,4-88,4) and 71,6% (95%CI: 58,6-88,3) respectively. There was no statistically significant difference in survival rates for patients who received a MUD versus MMUD transplant. DFS at 1 year was 73,7% (95%CI: 58,7-92,5) and 64% (95%CI: 37,4-100) and OS at 1 year was 73,5% (95%CI: 58,4-92,5) and 64% (95%CI: 37,4-100) for MUD and MMUD respectively.

Conclusions: We used PTCY for GvHD prophylaxis in MUD and MMUD peripheral blood stem cell transplants. This approach was well tolerated. Engraftment was documented in all but 2 patients, with a low incidence of grade III-IV aGvHD. cGvHD, which is an important barrier in unrelated donor transplant, was also substantially low. Overall, there are implications that PTCY may revert the negative impact of HLA mismatch on the outcomes of unrelated donor transplantation.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P173

LONG-TERM SAFETY AND EFFICACY OF REDUCED TOXICITY CONDITIONING REGIMENS IN OLDER RECIPIENTS OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR ACUTE LEUKEMIAS

Eleni Gavriilaki[1], Christos Demosthenous[1], Despina Mallouri[1], Ioannis Batsis[1], Anna Vardi[1], Zoi Bousiou[1], Eleni Papchianou[1], Elina Mouratidou[1], Christos Varelas[1], Alkistis Panteliadou[1], Anastasia Marvaki[1], Maria Papathanasiou[1], Apostolia Papalexandri[1], Chrysavgi Lalayanni[1], Chrysanthi Vadikoliou[1], Anastasia Athanasiadou[1], Evangelia Yannaki[1], Achilles Anagnostopoulos[1], Ioanna Sakellari[1]

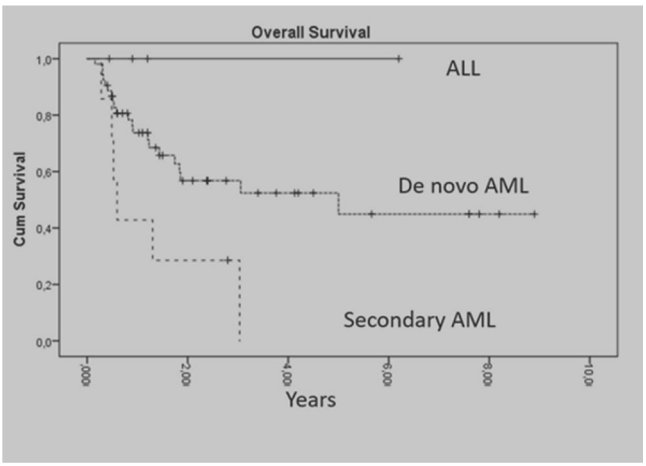
G Papanikolaou Hospital, Thessaloniki, Greece

Background: Reduced toxicity regimens have expanded the transplant population with outcomes comparable to other myeloablative conditionings, even in older patients. However, the long-term safety and efficacy of these regimens remain unknown.

Methods: We retrospectively studied consecutive patients aged 60 years or older that received allogeneic hematopoietic cell transplantation (alloHCT) for acute leukemia in our JACIE-accredited center (2014-2019). Patients with acute myeloid leukemia (AML) received FT14 (Fludarabine 150mg/m^2-Treosulfan 42mg/m^2) or FB4 (Fludarabine 150 mg/m^2-Busulfan 12.8 mg/kg), while patients with acute lymphocytic leukemia (ALL) Fludarabine-Melphalan (180 mg/m^2) or modified Thiotepa-Fludarabine-Busulfan. Post-transplant Cyclophosphamide was added in haploidentical donors and ATG (Thymoglobiulin 5mg/kg) in patients with unrelated donors. The following factors were studied: age, type of disease/donor/graft, phase at transplant, CD34 cells infused, infections, cumulative incidence/CI of graft-versus-host disease (GVHD), overall (OS) and disease-free survival (DFS).

Results: We studied 64 patients, with a median age of 64 (60-71) years, transplanted for de novo AML (53), secondary AML (7), ALL (4). The majority was transplanted in first complete remission/CR (40/63), while 13 in second CR, and 11 in refractory/relapsed disease. Grafts were peripheral blood stem cells from matched

unrelated (32), sibling (23) and haploidentical (9) donors. Full donor chimerism was achieved in all patients at median 30 (12-90) post-transplant days. We calculated acceptable rates of CI in acute (gr 2-4) and extensive chronic GVHD (28.1% and 45.3%, respectively). Disease relapse was observed in 13/64 (20.3%) patients. With a median follow-up of 1.9 (range 0.4-8.9) years in surviving patients, 2-year DFS and OS (Figure) were 100% in ALL; 51.8% and 56.8% in de novo AML; 20.1% and 28.6% in secondary AML ($p = 0.032$ and $p = 0.020$). Secondary AML ($p = 0.013$) and haploidentical donors ($p = 0.009$) predicted poor OS in the multivariate analysis, independently of acute GVHD. No secondary malignancy was observed.



Conclusions: Our real-world study confirms that alloHCT with reduced toxicity regimens is feasible in older patients with acute leukemias. The choice of alloHCT in this special patient population of a rather older age needs to be personalized.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P174

WOULD MONITORIZING TREOSULFAN LEVELS IN PATIENTS TRANSPLANTED FOR TRANSFUSION DEPENDENT THALASSEMIA BE BENEFICIAL IN TERMS OF CHIMERIZM? A SINGLE CENTER EXPERIENCE

Basak Adaklı Aksoy[1], Gizem Zengin Ersoy[1], Mariam Elsayed[1], Ozlem Basoglu Oner[1], Selime Aydogdu[2], Gurcan Dikme[3], Melek Erdem[4], Tunc Fisgin[1], Ceyhun Bozkurt[4]

[1]Altinbas University, Istanbul, Turkey, [2]Umraniye Training and Research Hospital, Istanbul, Turkey, [3]Istanbul Aydın University, Istanbul, Turkey, [4]Istinye University, Istanbul, Turkey

Background: Allogeneic stem cell transplantation (SCT) is the only curative option for thalassemia major patients. Experience of allogeneic SCT in transfusion dependent thalassemia patients (TDT) using treosulfan based preparative regimen, a retrospective analysis of 23 patients' data, was presented in our study.

Methods: All TDT patients with HLA identical related (%52)/ unrelated (%48) donor who underwent an allogeneic SCT at our center between September 2018- April 2022 were included. Conditioning regimen was treosulfan; 12 g/m2/day under age 1 and 14 g/m2/day above age 1, thiotepa 10 mg/kg/day, fludarabine 30 mg/m2 /day -5 days (TreoFluT). Treosulfan levels measured for every patient at 0,1,2,4. hours of infusion and area under curve (AUC) was calculated in mg*h/L.

Results: Treosulfan AUC levels (mg*h/L) was obtained for every patient and divided into three major groups as low (< 850 (mg*h/L)), medium (850-1100(mg*h/L)), and high (> 1100(mg*h/L)). Fifteen patients for low AUC group, 2 patients for medium and 6 patients for high AUC levels were compared for the effect of treosulfan AUC levels on transplant related toxicity as mucositis and sinusoidal obstruction syndrome (SOS) or transplant related mortality (TRM) along with mixed chimerism. Grade 3-4 mucositis was seen only one patient for low AUC group while 3(%50) patients had in high AUC group. None of the patients experienced SOS for each group. Transplant related mortality was %8.6 and no significant difference was detected between AUC groups. Mixed chimerism was detected for 7/23 patients (%30) and 6 patients (%25) belong to low AUC group although it has no difference statistically ($p < 0,357$).

Conclusions: There are few studies which correlates treosulfan AUC level with posttransplant consequences in pediatric age group. Although there are publications state that no correlation is needed for treosulfan, expanding patient group and repeating study for follow up in terms of posttransplant toxicity and long term consequences will be beneficial.

Clinical Trial Registry: none

Disclosure: none.

16 - Conditioning Regimens

P175

HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH EARLY ANTITHYMOCYTE GLOBULIN AND LOW DOSE POST-TRANSPLANT CYCLOPHOSPHAMIDE IN CHILDREN AND YOUNG ADULTS

Hee Young Ju[1], Hong Hoe Koo[2], Hee Won Cho[1], Nahee Kim[1], Kyungmi Kim[1], Ji Won Lee[1], Ki Woong Sung[1], Keon Hee Yoo[1]

Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of, [2]Korea Hemophilia Foundation, Seoul, Korea, Republic of

Background: Hematopoietic stem cell transplantation from a haploidentical donor (haplo-HCT) are increasingly used in patients lacking a matched donor, but the optimal strategy needs to be defined. This study aims to review the outcome of haplo-HCT with early antithymocyte globulin and low dose post-transplant cyclophosphamide (ATG/LD-PTCy) in a single center.

Methods: A retrospective analysis was done on patients who underwent haplo-HCT with ATG/LD-PTCy at the Department of Pediatrics, Samsung Medical Center between 2019 and 2022. Rabbit ATG was administered 2 mg/kg/day for 2 days (d-7, d-6) and cyclophosphamide 14.5 mg/kg/day was given for 2 days (d-3, d-2). The conditioning regimen was chosen between busulfan/ fludarabine and total body irradiation/cytarabine/cyclophosphamide based on the patient's diagnosis. As for PTCy, cyclophosphamide 25 mg/kg/day was administered at d3 and d4, and tacrolimus with mycophenolate mofetil was given from d5 for graft-versus-host disease (GVHD) prophylaxis.

Results: A total of nineteen patients (9 male) underwent haplo-HCT with ATG/LD-PTCy. Patients' median age at haplo-HCT was 10.1 years (range, 1.3-21.6). The most common diagnosis was acute myeloid leukemia (AML; $n = 4$), followed by acute lymphoblastic leukemia (ALL; $n = 3$) and severe aplastic anemia ($n = 3$). Among the 10 leukemia patients, 2 patients had refractory leukemia and 4 patients were in second complete remission. Neutrophil and

platelet engraftment was achieved at a median of 16 and 35 days in 18 patients. One patient with engraftment failure underwent 2nd haplo-HCT, but ALL relapsed at 3 months despite successful engraftment. Two patients with AML and one patient with acute undifferentiated leukemia relapsed within 4 months. In patients with successful engraftment, the natural killer cells recovered most early, followed by B cell recovery. The overall and relapse-free survival rates of the total patients were 80.8% and 75.0% at 12 months, respectively, with a median follow-up of 12 months. Acute GVHD occurred in 15 patients, of which 13 were grade I or II.

Conclusions: Considering the patients' highly advanced disease status, haplo-HCT with ATG/LD-PTCy demonstrated potential with a high engraftment rate and favorable outcome. ATG/LD-PTCy might be a feasible option for patients undergoing haplo-HCT.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P176

HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCIES USING FLUDARABINE AND TOTAL BODY IRRADIATION CONDITIONING AND POS-TRANSPLANT CYCLOPHOSPHAMIDE-BASED GVHD PROPHYLAXIS RESULTS IN HIGH DISEASE-FREE SURVIVAL

Afraa Fadul[1], Naziha Menasria[2], Sara Salim[3], Saloua Hmissi[3], Amna Gameil[1], Mohammad Bakr[1], Deena Mudawi[1], Amaal Gulied[4], Anas Hamad[4], Medhat Askar[5,6], Samira Saleh[5], Saju Divakar[7], Suparna Chandramouli[7], Anu Korula[1], Rula Ghasoub[4], Nancy Kassem[4], Maria Benkhadra[4], Omar Ismail[1], Honar Cherif[1], Anita Kasthuri Amudhavalli[8], Suja Pillai[1], Fatima Taloozy[1], Nahrida Nazir Bandi[1], Nayel Al Tarawneh[8], Eman Hassanein[9], Javid Gaziev[1]

National Center for Cancer Care and Research, HMC., Doha, Qatar, [2]Cell Therapy Laboratory. Hamad Medical Corporation, Doha, Qatar, [3]Hematopathology and Transfusion. Hamad Medical Corporation, Doha, Qatar. National Center for Cancer Care and Research, HMC., Doha, Qatar, [5]Clinical Immunology. Hamad Medical Corporation, Doha, Qatar, [6]National Marrow Donor Program, Minneapolis, United States, [7]Radiotherapy. National Center for Cancer Care and Research. Hamad Medical Corporation, Doha, Qatar, [8]National Center for Cancer Care and Research. Hamad Medical Corporation, Doha, Qatar, [9]Academic Health System. Hamad Medical Corporation., Doha, Qatar

Background: Haploidentical stem cell transplantation (Haplo-HSCT) using post-transplant cyclophosphamide (PTCy) is a readily available alternative option for patients who do not have HLA matched donors. This is an attractive approach in developing countries which usually do not have an unrelated donor registry and/or cannot afford the cost associated with the procurement of stem cells from an unrelated donor. Almost universal availability of haploidentical donor has made it possible for every patient in need of a transplant. Accumulated experience showed that outcomes of Haplo-HSCT in acute leukemias and lymphomas are similar to those obtained after matched related and unrelated transplants. We report our experience of Haplo-HSCT in hematologic malignancies.

Methods: 17 consecutive patients with median age of 34 years (range, 16-53), 9 with myeloid (AML, CMML, CML) and 8 with lymphoid (ALL, NHL) malignancies received Haplo-HSCT at our Center. Donors were sibling (n = 12), parent (n = 3) and child (n = 2). Only one patient had DSAs. At the time of transplantation 14 patients were in CR1/CR2 and 3 had relapsed/refractory disease.16 patients were intermediate-high risk. All patients received myeloablative conditioning regimen- 15 Fludarabine 160 mg/m^2 total dose and TBI 1200 cGy (Flu160TBI1200), 1 Flu160TBI1200 and Thiotepa, and 1 patient Cy100TBI1200 due to shortage of fludarabine. GVHD prophylaxis consisted of PTCy on days +3 and +4, CSA starting from day -1 and MMF from day 0. Sixteen patients received PBSC and 1 patient bone marrow grafts. The median CD34 cell dose was 7.55 x 10^6/kg (range, 5.2-13), and CD3 cell dose was 157 x 10^6/kg (range, 46.5-257).

Results: All patients achieved sustained engraftment with complete donor chimerism. The median follow-up for surviving patients was 10 months (range, 3-30). 2-year OS and DFS were 88%, and GRFS was 74%. The cumulative incidence of grade 2-3 acute GVHD and mild chronic GVHD was 29% and 7%, respectively. None of the patients has developed moderate or severe chronic GVHD. None of the patients had relapse. One patient died 11 months after transplantation due to pneumonia (while in his home country). All but 2 patients are off immunosuppression therapy. Only one patient had grade 3 CRS requiring tocilizumab. The incidence of grade 1 or grade 3 CRS was 47% and 6%, respectively. One patient developed secondary poor graft function successfully treated with romiplostim and G-CSF. The incidence of clinically significant CMV infection was significantly high in patients who did not receive letermovir prophylaxis (92%) compared with patients receiving letermovir (3%). Two patients developed grade 3 BK-virus associated hemorrhagic cystitis, 2 TA-TMA. Pneumonia occurred in 5 patients, one of them had successfully treated Covid-19 pneumonia. One patient developed tuberculosis.

Conclusions: Haplo-HSCT with PTCy leads excellent survival for patients with hematologic malignancies who lack matched donors. Myeloablative FluTBI regimen is safe, well tolerated and is associated with strong antileukemic effect leading to high relapse-free survival.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P177

BE-EAM HIGH-DOSE CHEMOTHERAPY FOLLOWED BY ASCT: A SINGLE CENTER EXPERIENCE

Handan Haydaroglu Sahin[1], Abdi Ibrahim Sonmez[1], Vahap Okan[1]

[1]Gaziantep University, Gaziantep, Turkey

Background: BEAM (carmustine, etoposide, cytarabine, and melphalan) is used as the most accepted preparation regimen before autologous bone marrow transplantation (ASCT) in patients with relapsed/refractory non Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). This trial examined the feasibility, efficacy and safety analysis of Bendamustine-EAM (Be-EAM), a new preparation regimen for ASCT in patients with advanced lymphoid malignancies.

Methods: Fifteen patients with Hodgkin's disease (n = 5) and non-Hodgkin's lymphoma (n = 10) were treated in this study. We retrospectively analyzed the data of patients who underwent ASCT with the Be-EAM regimen between January 2021 and December 2022. Bendamustine was substituted for carmustine. The preparatory regimen consisted of bendamustine on day -5 and -4 (160-200 mg/m^2/d) cytarabine daily from day -6 to day -3 (75 mg/m^2 every 12 hours), etoposide daily from day -6 to day -3 (150 mg/m^2 every 12 hours) and melphalan on day -2 (100-140mg/m^2). Peripheral blood progenitor cells and/or bone marrow were infused on Day 0.

Results: A total of 15 patients, i.e. 4 females and 11 males, were included in the study. Median age was 39,5 years. Bendamustine 160 mg/m2 and melphalan 100 mg/m2 were used in 3 patients with HL and 5 patients with NHL, while bendamustine 200 mg/m2 and melphalan 140 mg/m2 were used in other patients. High-dose administration was preferred in more aggressive subtypes and in patients cured with multiple-line therapy. The median time to engraftment was 11 days (range, 9-18) for neutrophils and 15 days (range, 13-35) for platelets. Febrile neutropenia developed in three patients, while bacteremia was observed in only one patient (6.6%). Four patients experienced grade 1-2 diarrhea. The incidence of mucositis was 45% with grade 1-2 mucositis 74.4%, and grade 3 mucositis 26.6%. Median time to hospital discharge was 20 days (range, 9-26 days). After a median follow-up of 11 months, 13 of 15 patients (86.6%) are in complete remission, whereas 1 of 15 relapsed and 1 of 15 did not respond. The 100-day transplantation-related mortality was 0%. Be-EAM was well tolerated in all patients with no significant toxicity specific to this regimen.

Conclusions: Be-EAM conditioning regimen followed by ASCT seems to be is active with tolerable toxicity in the treatment of patients with advanced lymphoid malignancies, and can be used safely as an alternative to BEAM regimen.

Disclosure: All authors have read and approved the manuscript. None of the authors have any potential conflicts of interest regarding this paper.

16 - Conditioning Regimens

P178

CYCLOPHOSPHAMIDE FOLLOWED BY BUSULFAN CONDITIONING FOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION – UMC LJUBLJANA, SLOVENIA SINGLE CENTER EXPERIENCE

Njetočka Gredelj[1], Klara Šlajpah[1], Luka Čemazar[1], Polona Novak[1], Neda Gržinič[1], Nika Kraljić[1], Martina Tomažin[1], Tereza Urdih[1], Matjaž Sever[1]

[1]University Medical Center Ljubljana, Ljubljana, Slovenia

Background: Busulfan with cyclophosphamide (BuCy) protocol is widely used and proven standard for myeloablative conditioning (MAC) in allogeneic hematopoietic stem cell transplantation (HSCT) patents with AML and MDS. Though BuCy has superior conditioning results and relative low long term sequelae, it is known to be toxic regimen which carries a high risk of sinusoidal obstruction syndrome (SOS) as well as high early mortality rate. There are many attempts to minimizing regimen-related toxicity, reduce non-relapse mortality (NRM) and keep or improve progress free survival (PFS) and overall survive (OS). One of the approaches is to reverse the order of application of Bu and Cy which showed to improve outcome in HSCT.

Methods: We retrospectively analysed data from 69 patients who received cyclophosphamide and busulfan (CyBu) as conditioning protocol for allogeneic HSCT in period from January 2017 to December 2021. All patients received intravenous cycloposhamide in dose of 60 mg/m2 daily on days -7 and -6 followed by a fixed dose intravenous busulfan 3,2 mg/kg/daily in 4 divided doses on days -5 to -2. GvHD prophylaxis was cyclosporine A (from day -1), methotrexate (on days +1, +3, +6 and +11) and in patients with unrelated HSCT antithymocyte globulin (Grafalon) in cumulative dose of 30 mg/kg. SOS prophylaxis was ursodeoxycholic acid 250 mg po 3 times daily.

Results: The characteristics of all patients and transplants are summarized in Table 1. The majority of patients (73,9%) were transplanted for AML. High risk AML had 51%, intermediate 25,5%, and 23,5% of patients. 56,5% of patients were transplanted in the first complete remission, 18,8% in the second or higher remission and 15,9% without achieving remission of the disease. All patients engrafted at a median of 12 (range 10–20) days after HSCT. The incidence of aGvHD (grades II-IV) and cGvHD was 24,6% and 39,1%, respectively. SOS occurred in 3 (4,3%) patients with no death caused by SOS. Sixteen (23,2%) patients relapsed. The median OS and PFS were not reached at a median follow-up of 35 months. Overall mortality rate was 17,4% with 2,9% early mortality by day 100. Main cause of death was relapse in 13% of patients with remaining causes for death infection and GvHD both in one patient.

Table 1

Variables	Categories	Patients n = 69 (%)
Age at Transplant (Years)	Median (Range)	44 (19-64)
Gender	Female	36 (52%)
	Male	43 (48%)
Underlying disease	AML	51 (73,9%)
	MDS	12 (17,3%)
	APL	4 (5,8%)
	CML	2 (2,9%)
Donor	MRD	17 (24,6%)
	MUD	36 (52,2%)
	MMUD	16 (23,2%)
Acute GVHD	Grade 2-4	17 (24,6%)
Chronic GVHD	All	27 (39,1%)
	Mild	18 (26%)
	Moderate	3 (4,3%)
	Severe	6 (8,7%)

Conclusions: CyBu conditioning regimen was safe with low NRM and relapse rate as well as low incidence of acute and chronic GvHD. The incidence of severe SOS was 4,3% which is comparable to 2-5% from the literature. Earlier studies showed that CyBu regimen is a good option in patients undergoing allogeneic HSCT for myelofibrosis, however, there is still open question about increased risk of relapse in patients with AML/MDS as all our relapses were in this patient group. Our data support CyBu conditioning protocol for AML/MDS even in a setting with no access to determine target dose of busulfan.

Disclosure: Nothing to declare.

16 - Conditioning Regimens

P179

ANTI-THYMOCYTE GLOBULIN IN CONDITIONING IN PATIENTS WITH ACUTE MYELOID LEUKEMIA UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION – A RETROSPECTIVE SINGLE CENTER ANALYSIS

Lazar Chadievski[1], Irina Panovska - Stavridis[1], Lidija Chevreska[1], Borche Georgievski[1], Aleksandra Pivkova Veljanovska[1]

[1]University Clinic for Hematology, Skopje, North Macedonia, The Republic of

Background: Acute myeloid leukemia (AML) is a malignant hematological disease characterized by accumulation of malignant hematopoietic immature precursors in the bone marrow, resulting in failure of the marrow. Timely diagnosis and treatment are of the highest importance because of the acute course of the disease and the mortality rates that are unacceptable, especially if the disease is misdiagnosed or left untreated. Allogeneic hematopoietic stem cell transplant (HSCT) is the treatment with the biggest curative potential and must be included in post-remission treatment of patients with AML. Up to 70% of patients undergoing allogeneic HSCT will suffer graft versus host disease (GvHD) to some extent, acute or chronic, significantly contributing to the mortality rates. One of the options of GvHD prophylaxis is to do in vivo T cell depletion by application of anti-thymocyte globulin (ATG) during conditioning. The major drawback is the fear of increased rates of infectious complications, mainly reactivation of Epstein-Barr virus (EBV) and cytomegalovirus (CMV), and fatal fungal infections that will not result in improved TRM and overall survival (OS). Also, there are studies confirming the„fear" that the use of ATG worsens relapse rates, even in patients receiving myeloablative conditioning.

Methods: In our study we analyzed 40 patients with AML diagnosed and treated in the University Clinic for Hematology in Skopje in the period between 2014 and 2021. The median age of patients was 40.9 years. As far as the conditioning, we used myeloablative conditioning (MAC) in almost all patients (38 patients – 98%). ATG was administered on days -3-2-1 before transplant in 19 patients (47%). We made a comparative analysis of the GvHD rates, infectious complications rates and survival rates in patients receiving and not receiving ATG in conditioning. All our patients were on standard fungal prophylaxis with fluconazole 200 mg, and ciprofloxacin 500mg twice daily for gastrointestinal decontamination. We used a standard dose of ATG -thymoglobuline at 5 to 10 mg/kg.

Results: In the ATG group, 15.8% of patients were diagnosed with acute GvHD, and the same percentage accounted for the chronic GvHD. The non-ATG group had significantly higher rates of acute GvHD (29%) and chronic GvHD (24%). The worse grades of GvHD III-IV were detected in the non-ATG group *vs*. the ATG group (19% *vs*. 10%) and contributed more to the mortality rates of the patients. No inferiority was confirmed regarding fatal infectious rates in the ATG group compared to the non-ATG group. The same accounted for the relapse rates (in the non-ATG group (19%) compared to the ATG group (16%)).

Conclusions: This analysis concludes that ATG in conditioning of patients with AML undergoing allogeneic HSCT as a method of in vivo T cell depletion is a justified therapeutic approach contributing to treatment benefits to the patients.

Disclosure: No disclosures.

6 - Experimental Transplantation and Gene Therapy

P180

INITIAL FIRST-IN-HUMAN RESULTS: CD33-DELETED HEMATOPOIETIC STEM AND PROGENITOR CELLS DISPLAY NORMAL ENGRAFTMENT AFTER HEMATOPOIETIC CELL TRANSPLANT (HCT) AND TOLERATE POST-HCT GEMTUZUMAB OZOGAMICIN (GO) WITHOUT CYTOPENIAS

Ben Tomlinson[1], Hyung C. Suh[2], Divya Koura[3], Guenther Koehne[4], Christina Cho[2], Nadia M Bambace[4], Léa Bernard[5], Nirali Shah[6], Roland B. Walter[7], John F. DiPersio[8], Miguel-Angel Perales[9], Michael Loken[10], Sritama Nath[11], Glen Raffel[11], Brenda Cooper[1]

[1]Seidman Cancer Center, University Hospitals Cleveland Medical Center, Cleveland, United States, [2]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, United States, [3]UCSD Moores Cancer Center, San Diego, United States, [4]Miami Cancer Institute, Baptist Health, Miami, United States, [5]Hôpital Maisonneuve-Rosemont/Université de Montréal, Montreal, Canada, [6]National Cancer Institute, Bethesda, United States, [7]Fred Hutchinson Cancer Research Center, Seattle, United States, [8]Washington University School of Medicine, St. Louis, United States, [9]Memorial Sloan Kettering Cancer Center, New York, United States, [10]Hematologics, Seattle, United States, [11]Vor Biopharma, Cambridge, United States

Background: In order to reduce AML relapse post-HCT, a *CD33* CRISPR/Cas9 gene-edited donor allograft, tremtelectogene empogeditemcel (trem-cel), formerly VOR33, was developed to enable post-HCT CD33-directed therapies while protecting healthy donor cells from on-target myelosuppression. VBP101 (NCT04849910) is a Phase 1/2a trial designed to evaluate the safety of trem-cel and GO (Mylotarg™), an anti-CD33 antibody-drug conjugate, in AML patients who are at a high risk of relapse post-HCT.

Methods: A 64 y-old F patient with relapsed $CD33^+$ *TP53* mutant AML, adverse cytogenetics, and CRi with measurable residual disease (MRD; 1.8% bone marrow [BM] blasts), underwent myeloablative busulfan/melphalan/fludarabine/ATG conditioning followed by HCT with trem-cel. Trem-cel was manufactured from G-CSF + plerixafor-mobilized cells from an HLA-matched (10/10) unrelated donor and was composed of 7.6 x 10^6 $CD34^+$ cells/kg with 88% CD33 deletion. The patient received GO at 0.5 mg/m^2 at 68 days post-HCT as part of the trial's initial dose escalation.

Results: Post trem-cel infusion, neutrophil engraftment and platelet recovery occurred at 10 and 22 days, respectively.

At the D28 assessment, whole blood and myeloid chimerism were 100% donor. Flow cytometry of peripheral blood (PB) demonstrated 95% of neutrophils and 94% of monocytes were CD33 negative. BM analysis showed 95% of maturing myeloid, 92% of maturing monocyte and 94% of CD34+ myeloblasts were CD33 negative with development patterns comparable to a reference non-edited post-HCT BM. Similar levels of PB and BM CD33 negativity were observed at the D60 assessment and PB chimerism remained 100% donor.

After dosing with 0.5 mg/m^2 of GO, no decrease in neutrophil or platelet counts was observed through D20 and no elevations in LFTs were observed. An additional 3 cycles of GO are planned.

No trem-cel-related or GO-related safety events were reported through 20 days after GO (D87 post-trem-cel infusion).

Conclusions: This is the first report of successful engraftment of a CD33-edited allogeneic donor graft and toleration of post-HCT GO. Engraftment was comparable to similarly treated patients who received non-edited CD34-selected grafts (median 11 days) (Luznik *et al* 2022, JCO 40:356-368). Consistent with high CD33 editing efficiency in trem-cel, the majority of PB and BM myeloid cells lacked CD33 expression. BM myeloid populations were similar to a reference patient transplanted with non-edited cells. At a 0.5mg/m^2 dose of GO, previously shown to saturate CD33 antigen (Mylotarg ODAC 2017), no cytopenias were observed, supporting the hypothesis that CD33 deletion can protect donor cells from GO. These initial data support the biologic dispensability of CD33 in myeloid development and a potential approach enabling post-HCT treatment with GO and other CD33-targeted therapies. Enrollment of additional patients is ongoing.

Clinical Trial Registry: NCT04849910

Disclosure: Ben Tomlinson: BMS- speaker bureau.
Hyung C Suh: No
Divya Koura: Cidara- consultancy
Guenther Koehne: No
Christina Cho: No
Nadia M Bambace:
1) Consultancy - AbbVie, BMS
Léa Bernard: No
Nirali N Shah - No
Roland B Walter:
1) Consultancy and research funding; - Agios, Amgen, Aptevo Therapeutics, Pzer, Inc, Macrogenics, Celgene, BioLineRx, LTd, Immunogen, Kura Oncology
2) Current equity holder in a publicly-traded company - Amphivena Therapeutics, Inc
3) Research Funding - Selvita, Stemline Therapeutics, Arog Pharmaceuticals, Janssen R&D
4) Consultancy - Race Oncology LTD, AbbVie, BerGenBio, Orum Therapeutics, Inc, Astellas Pharma US, Inc, Jazz Pharma, Kit Pharma, Kronos Bio, GSK, Janssen Global Services, BMS, Genentech, New Link Genetics, Boston Biomedical, Inc
John F DiPersio:
1) Current equity holder in a private company and Membership on an entity's Board of Directors or advisory committees - Magenta Therapeutics, WUGEN, hC Bioscience, Inc., Riverside Venture Partners
2) Incyte - Consultancy and Research Funding
3) Research Funding - NeoImmune Tech, Macrogenics, BioLineRx, Ltd, Amphivena Therapeutics
4) Patents & Royalties - CAR-T cell Product with Washington University and WUGEN, VLA-4 Inhibitor with Washington University and Magenta Therapeutics
Miguel-Angel Perales:
1) Consultancy - Nektar Therapeutics, Merck, Omeros, Orca Bio, Cidara Therapeutics, Sellas Life Sciences, MorphoSys, Medigene, Servier
2) Honoraria and research company - BMS, Incyte, Nektar Therapeutics, Kite, a Gilead Company, Miltenyi Biotec, Novartis, VectivBio AG, Vor Biopharma, Abbvie, Astellas, Celgene, Karyopharm, MorphoSys, Takeda, Bellicum
Michael Loken: Hematologics: Current Employment and Current equity holder in private company
Sritama Nath: Vor Biopharma - current Employment and Current holder of stock options in a privately-held company
Glen D Raffel: Vor Biopharma - current Employment and Current holder of stock options in a privately-held company
Brenda W Cooper: No

6 - Experimental Transplantation and Gene Therapy

P181

LENTIVIRAL-MEDIATED GENE THERAPY FOR SEVERE PYRUVATE KINASE DEFICIENCY: RESULTS FROM AN ONGOING GLOBAL PHASE 1 STUDY

José Luis López Lorenzo[1,2], Ami Shah[3,4], Julián Sevilla[5,6], Susana Navarro[2,6,7], Lucía Llanos[1,2], Begoña Pérez de Camino Gaisse[1,2], Sol Sanchez[1,2], Josune Zubicaray[5], Bertil Glader[3,4], May Chien[3,4], Oscar Quintana Bustamante[6,7,2], Miriam Zeini[8], Grace Choi[8], Eileen Nicoletti[8], Gayatri Rao[8], Maria Grazia Roncarolo[3,4], Juan Bueren[7,6,2], Jonathan Schwartz[8], José Carlos Segovia[6,7,2]

[1]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, [2]Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain, [3]Stanford University School of Medicine, Stanford, United States, [4]Lucile Packard Children's Hospital, Palo Alto, United States, [5]Fundación para la investigación Biomédica, Hospital Infantil Universitario Niño Jesús (HIUNJ), Madrid, Spain, [6]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain, [7]Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Madrid, Spain, [8]Rocket Pharmaceuticals, Inc., Cranbury, United States

Background: Pyruvate kinase deficiency (PKD) is a rare inherited hemolytic anemia caused by mutations in the PKLR gene. Manifestations include anemia, splenomegaly and iron overload, which may be life-threatening in severely affected individuals. Currently available treatments are limited to a recently-approved enzyme activator or palliative therapies limited to chronic blood transfusions, iron chelation therapy and splenectomy which are associated with significant side effects. Based on compelling preclinical data, a global Phase 1 clinical trial RP-L301-0119 (NCT04105166) is underway to evaluate lentiviral mediated hematopoietic stem and progenitor cell (HSPC)-targeted gene therapy for adults and children with severe PKD.

Methods: Splenectomized patients with severe PKD (severe and/or transfusion-dependent anemia) are eligible. Following apheresis, HSPCs are transduced with PGK-coRPK-WPRE lentiviral vector and cryopreserved. Myeloablative therapeutic drug monitoring-guided busulfan is administered and the gene therapy product (RP-L301) is thawed and infused. Patients are followed for safety assessments (replication competent lentivirus [RCL] and insertion site analysis [ISA]), and efficacy parameters (PB and BM genetic correction, decrease in transfusion requirements, clinically significant improvement in anemia and reduction of hemolysis) for 2 years post-infusion.

Results: As of October 2022, 2 patients (age 31 and 47 years at enrollment) with severe anemia have received RP-L301. Patient 1 received $3.9x10^6$ CD34+ cells/kg with mean vector copy number (VCN) of 2.73. Patient 2 received $2.4x10^6$CD34+ cells/kg with mean VCN of 2.08. Despite baseline hemoglobin (Hb) levels in the 7.0-7.5 g/dL range, at 24 months post-infusion both patients have normal-range hemoglobin (13.2 g/dL and 14.7 g/dL, respectively), improved hemolysis and no red blood cell transfusion requirements post-engraftment. Other parameters of hemolysis and anemia (LDH, bilirubin, erythropoietin) are improved. Peripheral blood mononuclear cell (PBMC) vector copy numbers (VCNs) were 1.75 and 1.65 at 24- and 18-months[CG1] [RM2], respectively. Both patients reported improved quality of life (QOL), also demonstrated by increases in both FACT-An and SF-36 scores, with marked improvement in SF-36 energy/fatigue, physical functioning, and general health components. No serious adverse events (SAEs) have been attributed to RP-L301. Hematopoietic reconstitution occurred within 2 weeks of administration. ISAs in PB and BM for both patients up to 12 months following gene therapy indicate highly polyclonal patterns.

Conclusions: Clinical efficacy and safety data indicate that RP-L301 is a potential treatment for patients with severe PKD, including those who did not derive benefit from available therapies. RP-L301 was successfully manufactured utilizing autologous HSPCs from patients with severe PKD. Robust and sustained efficacy in both pts at 24 months post-treatment was demonstrated by normalized hemoglobin, improved hemolysis parameters, and transfusion independence.

Clinical Trial Registry: NCT04105166

Disclosure: Lorenzo: There are no relationships to disclose. Shah: Vertex Pharmaceuticals: Advisory Board; Bluebird Bio: Advisory Board. Sevilla: Inventor on patents on lentiviral vectors filed by CIEMAT, CIBERER and Fundación Jiménez Díaz, and may be entitled to receive financial benefits from the licensing of such patents. Rocket Pharmaceuticals, Inc.: Consultant, Patents &

Royalties, Licensed Medical Products. Consultant/ Advisor/Honorarium for the following: Amgen, Novartis, Miltenyi, Sobi. Navarro: Rocket Pharmaceuticals, Inc.: Research Funding, Patents & Royalties, Equity Ownership. Llanos: There are no relationships to disclose. Gaisse: There are no relationships to disclose. Sanchez: There are no relationships to disclose. Zubicaray: Novartis: Consultancy. Glader: Agios Pharmaceuticals: Research Funding. Chien: There are no relationships to disclose. Bustamante: Rocket Pharmaceuticals, Inc.: Equity Ownership; Universidad Francisco de Vitoria: Teaching Activities. Zeini: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Choi: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Nicoletti: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Rao: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Roncarolo: There are no relationships to disclose. Bueren: Rocket Pharmaceuticals, Inc.: Consultancy and Research Funding. Other: Inventor on patents on lentiviral vectors filed by CIEMAT, CIBERER and Fundación Jiménez Díaz, may be entitled to receive financial benefits from the licensing of such patents and receives funding for research. Schwartz: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Segovia: Rocket Pharmaceuticals, Inc.: Consultancy and Research Funding.

6 - Experimental Transplantation and Gene Therapy

P182

LENTIVIRAL-MEDIATED GENE THERAPY FOR PATIENTS WITH FANCONI ANEMIA [GROUP A]: UPDATED RESULTS FROM GLOBAL RP-L102 CLINICAL TRIALS

Julián Sevilla[1,2], Claire Booth[3], Agnieszka Czechowicz[4,5], Rajni Agarwal[4,5], Josune Zubicaray[1], Paula Río[2,6,7], Kritika Chetty[3], Grainne O'Toole[3], Jinhua Xu-Bayford[3], Philip Ancliff[3], Elena Sebastián[1], Grace Choi[8], Miriam Zeini[8], Eileen Nicoletti[8], Cindy Eide[9], John Wagner[9], Gayatri Rao[8], Adrian Thrasher[3], Jonathan Schwartz[8], Maria Grazia Roncarolo[4,5], Juan Bueren[2,6,7]

[1]Fundación para la Investigación Biomédica, Hospital Infantil Universitario Niño Jesús (HIUNJ), Madrid, Spain, [2]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain, [3]UCL Great Ormond Street Institute of Child Health, London, United Kingdom, [4]Stanford University School of Medicine, Stanford, United States, [5]Lucile Packard Children's Hospital, Palo Alto, United States, [6]Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Madrid, Spain, [7]Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain, [8]Rocket Pharmaceuticals, Inc., Cranbury, United States, [9]University of Minnesota, Minneapolis, United States

Background: Fanconi anemia (FA) is an inherited deoxyribonucleic acid (DNA) repair disorder that results in progressive bone marrow failure (BMF) in 80% of patients within the first decade of life. Allogeneic hematopoietic stem cell transplant (alloHSCT) is potentially curative for FA-related BMF. Although survival exceeds 80% in experienced transplant centers, adverse effects including 100-day mortality and increased cancer risk limit overall success. The current gene therapy studies utilize autologous FA-A CD34+ enriched hematopoietic stem and progenitor cells (HSPCs) and rely upon the proliferative advantage of gene-corrected FA HSPCs, enabling engraftment without antecedent conditioning, as demonstrated in pre-clinical studies and the FANCOLEN-I clinical trial conducted in Madrid, Spain. We report results from global RP-L102 studies using "Process B" manufacturing optimizations.

Methods: Patients with FANCA mutations, age ≥1 year with no HLA-matched sibling donor and ≥30 CD34+ cells/μL in bone marrow (BM) are eligible. Peripheral blood (PB) mononuclear cells are collected via leukapheresis. Following CD34+ enrichment, HSPCs are subsequently transduced with a lentiviral vector carrying the FANCA gene, and infused without cryopreservation or conditioning. Patients are followed for 3 years post-infusion for safety assessments (including replication competent lentivirus [RCL] and insertion site analysis [ISA]) and for evidence of efficacy (increasing PB and BM vector copy number [VCN] and mitomycin-C [MMC] resistance in BM colony forming cells [CFCs]), along with stabilization/correction of cytopenias.

Results: As of October 2022, 12 patients age 2 to 6 years have received RP-L102. Sustained engraftment has been demonstrated in 7 of 10 evaluable patients with ≥12 months of follow up as indicated by peripheral blood mononuclear cell (PBMC) VCN. Six of these 7 patients have increasing BM CFC MMC resistance with concurrent hematologic stabilization. One additional patient with increasing PBMC and BM VCN has had recent development of BM CFC MMC resistance and relative hematologic stability. One patient without evidence of genetic correction had progressive BMF and underwent successful alloHSCT. A transient serious Grade 2 RP-L102 infusion-related reaction was observed in one patient and resolved without sequelae. No patients have developed RCL. One patient developed T cell lymphoblastic lymphoma determined to be unrelated to gene therapy. There has been no evidence of RP-L102 related bone marrow dysplasia, clonal dominance or insertional mutagenesis.

Conclusions: RP-L102 conferred phenotypic correction as demonstrated by sustained increase in BM CFC MMC resistance, concomitant genetic correction and hematologic stabilization in at least 6 patients with ≥1 year of follow up. Sustained engraftment, phenotypic correction, and hematologic stability was achieved in the absence of conditioning. RP-L102 represents a potentially curative therapy to prevent FA-related BMF, which can be administered without the need for a suitable allogeneic donor or transplant-conditioning related toxicities. Updated safety and efficacy data for patients with ≥12 months of follow up will be presented.

Clinical Trial Registry: NCT03814408; NCT04069533; NCT04248439

Disclosure: **Sevilla:** Inventor on patents on lentiviral vectors filed by CIEMAT, CIBERER and Fundación Jiménez Díaz, and may be entitled to receive financial benefits from the licensing of such patents; Amgen: Consultancy/Advisor, Honoraria; Novartis: Consultancy/Advisor, Honoraria; Miltenyi: Consultancy/Advisor, Honoraria; SOBI: Consultancy/Advisor, Honoraria; Rocket Pharmaceuticals, Inc.: Consultancy/Advisor, Honoraria.

Czechowicz: Beam Therapeutics: Consultancy, Equity Ownership; Decibel Therapeutics: Equity Ownership; Editas Medicine: Equity Ownership; Forty Seven Inc: Divested Equity in Last 24 Months; Gilead Sciences: Intellectual Property Rights; Global Blood Therapeutics: Equity Ownership; GV: Consultancy, Equity Ownership; Jasper Therapeutics: Intellectual Property Rights; Magenta Therapeutics: Equity Ownership, Intellectual Property Rights; Rocket Pharmaceuticals, Inc.: Research Funding; Spotlight Therapeutics: Consultancy, Equity; Stemodontics: Consultancy, Equity Ownership.

Booth: SOBI: Consultancy, Honoraria; Orchard Therapeutics: Consultancy, Honoraria; Takeda: Honoraria; Rocket Pharmaceuticals, Inc.: Consultancy; GSK: Honoraria.

Agarwal: No relationships to disclose.

Zubicaray: Novartis: Consultancy.

Río: Rocket Pharmaceuticals, Inc.: Equity Ownership, Patents & Royalties, Research Funding.

Navarro: Rocket Pharmaceuticals, Inc: Patents & Royalties, Research Funding, Equity Ownership.

Chetty: No relationships to disclose.

O'Toole: No relationships to disclose.

Xu-Bayford: No relationships to disclose.
Ancliff: No relationships to disclose.
Sebastián: No relationships to disclose.
Choi: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership.
Zeini: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership.
Nicoletti: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership.
Eide: No relationships to disclose.
Wagner: Rocket Pharmaceuticals, Inc: Consultancy, Equity Ownership; ASC Therapeutics: Consultancy; Bluebird Bio: Consultancy; Vertex Pharmaceuticals: Consultancy; Magenta Therapeutics: Consultancy. **Rao:** Rocket Pharmaceuticals: Employment, Equity Ownership.
Thrasher: Orchard Therapeutics: Consultancy and Equity Ownership; Rocket Pharmaceuticals, Inc.: Consultancy; 4Bio Capital: Consultancy; Generation Bio: Consultancy and Equity Ownership.
Schwartz: Rocket Pharmaceuticals: Employment, Equity Ownership.
Roncarolo: No relationships to disclose.
Bueren: Rocket Pharmaceuticals, Inc.: Consultancy; Other: Inventor on patents on lentiviral vectors filed by CIEMAT, CIBERER and Fundación Jiménez Díaz, and may be entitled to receive financial benefits from the licensing of such patents and receives funding for research.

6 - Experimental Transplantation and Gene Therapy

P183

FIRST-IN-HUMAN INTRAVENOUS FBX-101 (AAVRH10.HGALC) AFTER UCBT PREVENTS IMMUNE RESPONSE TO VECTOR'S CAPSID AND TRANSGENE, INCREASES GALC ACTIVITY, BRAIN AND MOTOR DEVELOPMENT IN KRABBE DISEASE

Maria Escolar[1,2], Mark Vander Lugt[3], Michele Poe[1], Melissa Greco[2], Keith Werling[2], Erandi De Silva[1], Juan Ruiz[1], Paul Szabolcs[2]

[1]Forge Biologics, Grove City, United States, [2]University of Pittsburgh, Pittsburgh, United States, [3]University of Michigan, Ann Arbor, United States

Background: FBX-101 RESKUE is a novel AAV-based gene therapy approach that takes advantage of myelo/immune-ablation to override the antibody response to intravenously administered AAVrh10-hGALC vector's capsid. Additionally, there is no antibody response to the transgene because the healthy donor immune system does not recognize the deficient enzyme as a foreign antigen. Infantile Krabbe disease (IKD) is the most common and aggressive presentation of this severe neurodegenerative disorder caused by galactocerebrosidase (GALC) deficiency. If left untreated, IKD leads to death by 2 years of age. Asymptomatic patients are diagnosed through newborn screening or family history. Allogeneic umbilical cord blood transplantation (UCBT), the current standard of care, improves outcomes in asymptomatic infants, but motor function declines due to peripheral neuropathy leading to death usually in teen years. FBX-101 is an intravenously administered AAVrh10-hGALC vector designed to "rescue" peripheral nerve disease. Currently, one of the most difficult challenges of AAV gene therapy is the antibody response to vector and transgene and immune-mediated toxicities. We attempt to address these difficulties by leveraging the myelo/immune-ablated environment after the infusion of allogeneic umbilical cord blood.

Methods: RESKUE is an open-label Phase 1/2 dose-escalating trial to evaluate safety and efficacy of FBX-101 after UCBT for the treatment of patients with IKD. Patients are diagnosed because of family history or through newborn screening which is available in 10 states across the US. Subjects in cohort 1 receive a single IV infusion of FBX-101 at a low dose of $3.0x10^{13}$ vg/kg post-UCBT, while cohort 2 subjects will receive a higher dose of $8.0x10^{13}$ vg/kg. There is a trial evaluation period of 2 years post administration, with an additional 3 years of follow-up. We report on the safety and preliminary efficacy of the first two patients treated in cohort 1.

Results: The first 2 subjects received FBX-101 at a dose of $3.0x10^{13}$ vg/kg 25 and 29 days after UCBT. FBX-101 was well tolerated, with no treatment-related serious adverse events observed up to 1 year and 9 months after administration. No antibodies to the capsid or transgene have developed and both subjects engrafted with full chimerism. We report an 80-fold increase in plasma GALC and 3-to-10-fold increase in CSF GALC enzyme activity following gene transfer. Additionally, this increase translated into normalization of motor skills measured by PDMS-II, and normal brain white matter growth measured by MRI diffusion tensor imaging.

Conclusions: Administration of FBX-101 after UCBT prevents antibody response to the vector allowing efficient AAV transduction, ensuring that GALC enzyme is available to support both brain and peripheral nerve development in patients, representing a novel gene therapy strategy for metabolic diseases in which transplant is indicated.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT04693598

Disclosure: Maria L Escolar, Paul Szabolcs: financial interest in Forge Biologics.

6 - Experimental Transplantation and Gene Therapy

P184

CRISPR-BASED TRANSCRIPTIONAL HEMATOPOIETIC STEM CELL EDITING FOR ENHANCED ANTI-LEUKEMIC GRAFT FUNCTION

Franziska Baatz[1], Jessica Herbst[1], Johann Meyer[1], Axel Schambach[1], Tobias Maetzig[1], Michael Hust[2], Martin Sauer[1]

[1]Hannover Medical School, Hannover, Germany, [2]TU Braunschweig, Braunschweig, Germany

Background: Fostering natural killer (NK) cell activity in the graft can enhance graft versus leukemia effects (GvL) without triggering graft versus host disease (GvHD). Enforced expression of chimeric antigen receptors (CARs) on NK cells is therefore a promising approach even for the use across HLA-barriers. However, NK cell cultivation and genetic engineering remains cumbersome. The transcription factor B cell CLL/lymphoma 11B (BCL11B) is one of the key regulators determining the fate of T versus NK cell development. We therefore hypothesized that the addition of CRISPR/Cas9-based *Bcl11b*-edited CAR-transduced lymphoid progenitors to the graft would allow for the development of CAR-expressing natural killer like cells (CARiK cells) mediating enhanced anti-leukemic effects in leukemia-bearing hematopoietic stem cell (HSCT) recipients.

Methods: Antigen binders against murine CD123 (antigen of interest on myeloid leukemic blasts) were identified using phage display technology. High affinity binders were cloned into a 2nd generation murine CAR backbone (CD28CD3zeta configuration) and comparatively assessed for expression strength, functionality, specificity, and the extent of tonic signaling activity. Aiming for an

all in one vector approach, a sgRNA sequence against *Bcl11b* was added to the construct for CRISPR-mediated gene disruption. Transduced murine LSK cells were then differentiated into lymphoid NK cell progenitors using the OP9-DLI feeder layer system. Double edited progenitors (8 x 10^6) and respective controls were co-transplanted into leukemia-bearing murine HSCT recipients. BCL11B suppression was assessed by Western-blotting, correlated with the appearance of a NK cell-like phenotype, and finally tested for in vivo functionality.

Results: A functional CD123 CAR of high expression strength, specificity, and devoid of tonic signaling activity was generated. Despite the lack of tonic signaling, early encounter with CD123 in culture already triggered some degree of NK-directed development. The extent of fratricide was limited. Early *Bcl11b* disruption allowed for further lymphoid cell differentiation. *Bcl11b* editing only let to complete BCL11B suppression as did the combined all in one vector construct. CAR transduction w/o *Bcl11b* editing resulted in incomplete BCL11B suppression. After transduction with the lentiviral all in one construct, a strong developmental NK cell shift was observed. After co-transplantation of these CARiK cells up to 100% leukemia-free survival was achieved. Unexpectedly, the relative low expression strength of CD123 on physiologic hematopoiesis allowed regular myelopoietic recovery when compared to controls.

Conclusions: BCL11B editing of hematopoietic stem cell-derived CAR-engineered lymphoid progenitors allows the generation of a NK cell-like cell product with considerable anti-tumor activity. Genetic stability remains to be determined.

Disclosure: Nothing to declare.

6 - Experimental Transplantation and Gene Therapy

P185

HAPLOIDENTICAL STEM-CELL TRANSPLANTATION FOR CHILDREN WITH NON-MALIGNANT DISORDERS, USING AB+ T CELL /CD19 + B-CELL DEPLETION, A SINGLE CENTER EXPERIENCE

Gal Hai Dadi[1,2], Etai Adam[1,2], Elad Jacoby[1,2], Sarah Malkiel[1], Daphna Hutt[1], Nira Varda-Bloom[3], Amos Toren[1,2], Bella Bielorai[1,2]

[1]Division of Pediatric Hematology and Oncology, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel, Tel Aviv University, Tel Aviv, Israel, [3]Stem Cell Laboratory, Sheba Medical Center, Ramat Gan, Israel

Background: Hematopoietic stem cell transplantation using an allogeneic donor (allo-HSCT) is the definitive therapy for a wide range of non-malignant disorders (NMD)- severe combined immune deficiency (SCID), inborn errors of immunity (IEI), bone marrow failure (acquired/congenital) and familial Hemophagocytic lymphohistiocytosis (HLH). Some of these patients present with acute, rapidly progressive and life-threatening disease, necessitate immediate transplant, and the need for a readily available donor is crucial.

A novel approach of allo-HSCT, using a haploidentical donor along with ex-vivo depletion of αβ-TCR + T cell /CD19 + B cells (αβ + TCR depleted haplo-HSCT) has been utilized in malignant and non-malignant disorders, with results comparable to traditional allo-HSCT donors.

Methods: Data was collected retrospectively regarding thirty-six children age <21 years with non-malignant disorders underwent αβ + TCR depleted haplo-HSCT between the years 2012-2021.

Results: Twenty-six of them (72%) engrafted and ten had either primary graft loss (did not achieved neutrophil count above 500 cells/uL at day 30) or low-level donor chimerism. Median time to neutrophils and platelet engraftment was ten and eleven days, respectively. Secondary rejection was observed in two patients. For all patients who engrafted and did not have secondary rejection, full donor chimerism was observed at day 30. Dose of CD34+ cells in the graft had no impact on engraftment kinetics nor on secondary rejection. Twenty-six patients conditioned with myeloablative conditioning (MAC)-Treosulphan/Busulfan based or combination of Fludarabine, Thiotepa and Melphalan, two patients conditioned with fludarabine based regimen (reduced-intensity conditioning, RIC) and eight patients, with SCID were transplanted without conditioning. GVHD prophylaxis did not negatively affect engraftment. Median length of follow-up for the whole cohort was 20 months (IQR 8.1-54.4 months). Five-year overall survival probability was 56% for the whole cohort. It was higher for patients without active infection at day 0 of transplant compared to patients with active infection (91.7% vs 33%, respectively, $p = 6.4*10\text{-}4$). Fourteen patients had died. Thirteen patients died from infection and one from veno-occlusive disease. Post-transplant de novo autoimmunity of autoimmune hemolytic anemia was recorded for two patients. Cumulative incidence of aGVHD and cGVHD was 30% and 19%, respectively. Eight patients underwent second transplant (patients' number 4, 5, 9, 13, 19, 22, 29, 32) of them four patients engrafted. Four patients did not engraft and eventually died from infectious complication.

Thirty-six patients underwent αβ + TCR depleted haplo-HSCT at our institute.

Conclusions: αβ + TCR depleted haplo-HSCT is feasible and effective for children with life threatening NMD. Children who undergo αβ + TCR depleted haplo-HSCT with active infections had poorer outcomes whereas children without an active infection had excellent outcomes. Thus, patients who have a clear indication for transplant should be evaluated for transplant as early as possible and αβ+ depleted Haplo HSCT should be considered as the preferred option.

Disclosure: Nothing to declare.

6 - Experimental Transplantation and Gene Therapy

P186

DISCOVERY OF NEOANTIGENS USING ARTIFICIAL INTELLIGENCE (NEO-ARS™) IN AML: A PILOT STUDY

Su-young Choi[1], Joo-Young Kang[2], Hyun-Jin Yang[2], Jeong-Yeon Park[2], Il-Oh Jeong[2], Jong Hui Hong[2], Jongsun Jung[2], Thi Thuy Duong Pham[1], Bu-Yeon Heo[1], Jeong Suk Koh[3], Myung-Won Lee[3], Jung-Hyun Park[4], Yunsun Jang[4], Deog-Yeon Jo[3], Jaeyul Kwon[5], Ik-Chan Song[3]

College of Medicine, Chungnam National University, Daejeon, Korea, Republic of, [2]Syntekabio Inc, Seoul, Korea, Republic of, College of Medicine, Chungnam National University, Daejeon, Korea, Republic of, [4]Translational Immunology Institute, College of Medicine, Chungnam National University, Daejeon, Korea, Republic of, College of Medicine, Chungnam National University, Daejeon, Korea, Republic of

Background: Neoantigens caused by somatic mutations in tumors are attractive therapeutic targets for cancer immunotherapy. However, research on neoantigens in acute myeloid leukemia (AML) is still lacking.

Methods: Leukemic blast DNA from bone marrow mononuclear cells (BMMC) at diagnosis was compared with Germline DNA from BMMC at time of complete remission (CR) using whole exome sequencing (WES) for the identification of patient-specific tumor mutations and MHC alleles. In addition, RNA sequencing (RNAseq) was performed to determine the level of expression of the genes with leukemic-specific mutations. Of all possible neopeptides-MHC class I (pMHC) combinations, neoantigen candidates were identified using a physics-informed deep learning algorithm NEO-ARS^{TM}. Briefly, 3D structural modeling and molecular dynamics simulations of pMHCs were conducted and followed by computation of solvent-accessible surface areas of neopeptides for T cell recognition. Neopeptides with low predicted binding energy (i.e., high predicted affinity) were selected as neoantigen candidates and prioritized using solvent-accessible surface areas. For the peptides assumed to be neoantigen, IFN-γ ELIspot experiments were performed using peripheral blood mononuclear cells from human leukocyte antigen (HLA)-matched donor of allogeneic hematopoietic stem cell transplantation.

Results: With this approach, we prioritized a list of 6 neoantigen peptide-HLA candidates from 2 AML patients each (peptide lengths of 9 amino acids) across the available HLA class I alleles for that patient. In one patient (54 years old male with HLA-A*02:01), 90 peptides derived from 15 somatic mutations were designed, and 6 of them were predicted as neoantigen candidates by NEO-ARS^{TM}. In the other patient (55 years old male with HLA-A*11:01), 198 peptides derived from 33 somatic mutations were designed, and 6 of them were predicted as neoantigen candidates by NEO-ARS^{TM}. We synthesized 6 predicted neo-peptides in each patient. In IFN-γ ELISpot assay, the first patient, peptide #1(2068.3), #2(2163.3), #4(2006.6) and #6(1886.6) had higher spot forming units (SFU) than DMSO (1393.3) alone (in the all peptide, $P < 0.0001$). In the second patient, peptide #3(1165, $P < 0.01$), #4(1043.3, $P < 0.05$) and #5(1813.3, $P < 0.001$) had higher spot forming units (SFU) than DMSO (653.3) alone.

Conclusions: The neoantigens predicted by NEO-ARS^{TM} showed a good immunogenicity against T cells in ELIspot assay. Thus, the neoantigens predicted by this AI algorithm have the potential to be used efficiently in novel therapies such as customized cancer vaccines or T cell receptor (TCR) T cell therapy for the patients with AML in the future.

Disclosure: I have no conflict of interest.

6 - Experimental Transplantation and Gene Therapy

P187

LOW DOSE OF FLUDARABINE IS AN EFFECTIVE CONDITIONING TREATMENT TO SUPPRESS RELAPSE RATE IN PT-CY-BASED HAPLOIDENTICAL PERIPHERAL BLOOD STEM CELL TRANSPLANTATION

Jeong A. Kim[1], Jinhang Kim[1], Nanyoung Yun[1], Jae-Yong Kwak[2]

St. Vincent Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea, Republic of, Chonbuk National University Hospital, Jeonju, Korea, Republic of

Background: Haploidentical related donors are alternative donors for patients in the absence of a HLA-matched donor and in an urgent need of transplantation. However, haploidentical PBSCT (haploPBSCT) pose significant challenges due to HLA mismatch, which often leads to increased risk of graft versus-host disease (GVHD) and non-relapse mortality (NRM). A recent study led by the Johns Hopkins group pioneered the use of post-transplant cyclophosphamide (PTCY) in the haploPBSCT setting. The study used mostly reduced-intensity conditioning (RIC) and reported significant reductions in NRM and GVHD. However, high rate of relapse is problem that still needs to be addressed. To resolve high rate of relapse, we used a low-dose of fludarabine (30mg/m^2 x 3 days, from 30mg/m^2 x 5 days) as a preparation regimen in PTCy-haploPBSCT settings, and report the outcome.

Methods: 19 patients (6 acute leukemia, 8 low-risk MDS (R-IPSS < 3.5), 3 high-risk MDS (R-IPSS > 3.5), and 2 severe aplastic anemia) were enrolled, and the median age was 51 (range, 24 to 69). The conditioning regimen consisted of a combination of busulfan (6.4 mg/kg), total body irradiation (TBI, 3Gy), and fludarabine (30mg/m^2 x 3 days or 30mg/m^2 x 5 days). High-dose cyclophosphamide (50 mg/kg/day on days 3 and 5), cyclosporine, and MMF were used for GVHD prophylaxis. The median number of CD34$^+$ cells of PBSCs was 10.64×10^6 cells/kg (range, $6.14–11.08 \times 10^6$ /kg).

Results: In all patients, PFS at 2 years was 77%. Neutrophil engraftment was achieved in 95% of patients with a median time of 14 days (range, 13–15 days). The cumulative incidence of grades III-IV acute GVHD at 100 days, chronic GVHD, and relapse at 2 years were 21%, 38%, and 22%, respectively.

12 patients received a regular dose of fludarabine (30mg/m^2 x 5 days); 7 patients received a low-dose of fludarabine (30mg/m^2 x 3 days). In the patient group who received a regular dose of fludarabine ($n = 12$), PFS at 1 year was 62%. The cumulative incidence of grades III–IV acute GVHD at 100 days, chronic GVHD, and relapse at 1 year were 17%, 43%, and 22%, respectively. In the low-dose fludarabine group ($n = 7$), PFS at 1 year was 100%. The cumulative incidences of grades III–IV acute GVHD at 100 days, chronic GVHD, and relapse at 1 year were 29%, 14%, and 0%, respectively.

Conclusions: Our results indicate that a low-dose fludarabine (30mg/m^2 x 3 days) in PTCy-haploPBSCT setting is a valid and safe strategy for preventing relapse rate and may provide better clinical outcomes in long-term disease control.

Disclosure: no conflict of interest.

6 - Experimental Transplantation and Gene Therapy

P188

DIFFERENT RECOVERY PATTERNS OF CMV-SPECIFIC AND WT1-SPECIFIC T CELLS IN PATIENTS WITH ACUTE MYELOID LEUKEMIA UNDERGOING ALLO-HSCT: IMPACT OF CMV INFECTION AND LEUKEMIA RELAPSE

Xiao-Hua Luo[1,2], Thomas Poiret[2], Zhenjiang Liu[2], Qingda Meng[2], Anurupa Nagchowdhury[3], Per Ljungman[4]

The First Affiliated Hospital of Chongqing Medical University, Yuzhong District, Chongqing, China, Karolinska Institutet, Stockholm, Sweden, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, Karolinska University Hospital, Stockholm, Sweden

Background: In allogeneic hematopoietic cell transplantation (allo-HSCT), both virus-specific T cells and leukemia-specific T cells need to be reconstituted to protect patients from virus infections and primary disease relapse. Cytomegalovirus (CMV) infection remains an important cause of morbidity and mortality after allo-HSCT. Emerging data indicate that CMV reactivation is associated with reduced risk of leukemia relapse in patients with acute myeloid leukemia (AML) undergoing allo-HSCT.

Methods: Adult HLA-A*0201-positive patients with AML in first (n = 22) or second complete remission (n = 2), who had a human leukocyte antigen (HLA)-identical sibling donor or an HLA-A-, HLA-B- or HLA-DRB1- allele-matched (6/6) unrelated donor (MUD) were included in this study. All of the patients were identified as WT1 positive prior to allo-HSCT as described previously. A quantitative PCR-based analysis of short tandem repeats was performed at 1, 3, 6 and 12 months after allo-HSCT. Measurable residual disease (MRD) assessments with flow cytometry were performed regularly in bone marrow and scheduled at the same intervals as the chimerism analyses when possible. CMV-specific T cells (CMV-CTL) and WT1-specific T cells (WT1-CTL) frequencies were quantified and phenotyped in patients by staining with PE-A*0201 $CMV_{NLVPMVATV}$ Dextramer, PE-A*0201 $WT1_{SLLFLLFSL}$ Dextramer and APC-A*0201 $WT1_{VLPLTVAEV}$ MHC (Immunex, Copenhagen, Denmark). The proportion and phenotype of CD8+ or CD4 + T cells producing IFN-γ and TNF-α in response to stimulation with the CMV pp65 protein or WT1 protein (15 mers, with 11 aa overlap, swiss prot: P06725 and PP19544; Peptides&Elephants) were measured by FACS analysis. CMV-specific T cell line (HD-2) and T cell clones (A1-8 and A1-9) specific for CMV pp65 protein were generated from a single HLA-A*0201+ healthy control. Aliquots of CMV-specific T cells (A1-8 and A1-9 cell lines) were stimulated with individual peptides of WT1 (5μg/ml) for 72h. Survivin peptides (15 mers, with 11 aa overlap, swiss prot: O15392; Peptides&Elephants) were used as a control.

Results: In a cohort of 24 WT1 + AML patients during the first year following HSCT, CMV specific CD8 + T cells (CMV-CTL) reconstituted much faster than WT1-specific CD8 + T cell (WT1-CTL) after allo-SCT. Moreover, CMV-CTL expressed lower levels of exhaustion markers and were more functional as identified by production of IFN-γ / TNF-α and expression of Eomes/ T-bet. Interestingly, our patients with CMV reactivation presented higher frequency of CMV-CTL, lower levels of Eomes+T-bet- and higher levels of Eomes+T-bet+ expression in response to WT1 and CMV pp65 antigen during the first year after transplantation as compared to patients without CMV reactivation. Kinetics of CMV-CTL and WT1-CTL after transplantation might be associated with measurable residual disease and later leukemia relapse.

Conclusions: Our results support that CMV reactivation, aside from the CMV-CTL reconstitution, could influence WT1-CTL reconstitution after allo-HSCT, thus potentially contributing to the remission/relapse of AML.

Disclosure: Nothing to declare.

6 - Experimental Transplantation and Gene Therapy

P189

ANALYSIS OF MARROW INFILTRATING T CELL AT 3 MONTHS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Thi Thuy Duong Pham[1], Su-Young Choi[1], Bu-Yeon Heo[1], Jeong Suk Koh[2], Myung-Won Lee[2], Jung-Hyun Park[3], Yunsun Jang[3], Deog-Yeon Jo[2], Jaeyul Kwon[4], Ik-Chan Song[2]

College of Medicine, Chungnam National University, Daejeon, Korea, Republic of, College of Medicine, Chungnam National University, Daejeon, Korea, Republic of, [3]Translational Immunology Institute, College of Medicine, Chungnam National University, Daejeon, Korea, Republic of, College of Medicine, Chungnam National University, Daejeon, Korea, Republic of

Background: With the introduction of immune checkpoint inhibitors, the importance of tumor-infiltrating lymphocytes has increased. However, few studies have analyzed the effect of marrow-infiltrating T cells on relapse after allogeneic hematopoietic stem cell transplantation (HSCT) in patients with hematologic malignancies.

Methods: We analyzed the marrow-infiltrating T cell at 3 months after allogeneic HSCT in consecutive patients who treated in Chungnam National University Hospital from April 2021 to May 2022. We classified T cells into five subtypes using CD45RA, CD95 and CCR7 by flowcytometry analysis: naïve, stem cell memory (SCM), central memory (CM), effector memory (EM) and effector memory with positive CD45RA (EMRA). And we measured the expression level of the inhibitor receptor (PD-1, LAG-3, CTLA-4, TIM-3 and TIGIT). And we analyzed regulatory T cell (Treg) by defining as $CD25^{high}CD125^{low}$ and divided them into three categories using CD25 and CD45RA; naïve, active and non-suppressive Treg. We defined early relapse (ER) as relapse within 6 months of allogeneic HSCT.

Results: With this approach, marrow-infiltrating T cells were analyzed in 33 patients with a median age of 58 year (ranged from 25 to 71). Stem cell source were 36.4% from matched sibling donor, 36.4% from haplo-identical donor and 27.3% from matched unrelated donor. All patients received mobilized peripheral blood stem cell transplantation. Marrow-infiltrating CD3 + T cell counts were lower in patients with allogeneic HSCT compared to normal subjects (CD3 + T cells: 5.5% in HSCT patient vs. 36.1% in normal subjects, $p = 0.0002$). However, CD3 + CD8 + T cells were similar in HSCT patients and normal subject. In patients with early relapse (ER), naïve and SCM was higher, and EM was lower than those in non-ER patients among CD4 + T cells (naïve; 1.0% in ER patients vs 12.9% in non-ER patients, $p = 0.0004$ /SCM; 3.3% in ER patients vs 15.8% in non-ER patients, $p = 0.0155$ /EM; 61.2% in ER patients vs 39.7% in non-ER patients, $p = 0.0284$). Of CD4 + T cell, the expression of TIM-3 was higher in ER patients than in those without (MFI; 1689.5 in ER patients vs 428.75 in non-ER patients, $p = 0.0080$). In patients with early relapse (ER), naïve and SCM was higher, and EM was lower than those in non-ER patients among CD8 + T cells (naïve; 7.8% in ER patients vs 1.1% in non-ER patients, $p = 0.0004$ /SCM; 11.7% in ER patients vs 4.3% in non-ER patients, $p = 0.0654$ /EM; 43.9% in ER patients vs 51.6% in non-ER patients, $p = 0.3522$). Of CD8 + T cell, the expression of TIM-3 was higher in ER patients than in those without (MFI; 748.5 in ER patients vs 301.6 in non-ER patients, $p = 0.0037$). Treg levels were slightly higher in ER patients, and naïve Treg levels were significantly higher than those in no-ER patient (naïve Treg; 2.3% in ER patients vs 0.3% in non-ER patients, $p = 0.0042$).

Conclusions: T cell differentiation was delayed in patients with early relapse compared to those without. And TIM-3 expression of effector T cell was higher in patients with early relapse. So, Patients with high risk of relapse after allogeneic HSCT may benefit from the use of TIM-3 inhibitors.

Disclosure: I have no conflict of interest.

12 - Graft-versus-host Disease – Clinical

P190

MULTICENTER RANDOMIZED PHASE II CLINICAL TRIAL TO COMPARE GRAFT-VERSUS-HOST DISEASE PROPHYLAXIS WITH TACROLIMUS AND MYCOPHENOLATE MOFETIL VERSUS RUXOLITINIB AFTER POST-TRANSPLANT CYCLOPHOSPHAMIDE (PTCYRUXO)

Ivan Moiseev[1], Yulia Kitaeva[2], Mikhail Drokov[3], Tatyana Rudakova[1], Maria Barabanshikova[1], Ksenia Afanasyeva[1], Elena

Morozova[1], Yulia Vlasova[1], Natalya Popova[3], Yulia Sveshnikova[2], Vera Vasilyeva[3], Larisa Kuzmina[3], Sergey Bondarenko[1], Tatyana Konstantinova[2], Elena Parovichnikova[3], Alexander Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation, Regional Hospital #1, Ekaterinburg, Russian Federation, [3]National Research Center for Hematology, Moscow, Russian Federation

Background: Background: Post-transplant cyclophosphamide (PTCY) is more and more broadly used graft-versus-host disease (GVHD) prophylaxis. The BMT CTN 1203 randomized trial demonstrated that combination of PTCY, tacrolimus and mycophenolate mofetil (MMF) improves GVHD-relapse-free survival compared to other regimens and may be considered among the standards of prophylaxis. Nonetheless, this regimen is associated with substantial toxicity and does not reduce the risk of relapse. Given the positive results of Phase I/II study of GVHD prophylaxis with PTCY-ruxolitinib combination (Morozova et al., Acta Hematologica, 2021) we conducted a randomized multicenter trial to compare these two types of GVHD prophylaxis in acute leukemia patients.

Methods: This is the planned interim analysis of PTCyRuxo (CINC424ARU01T, clinicaltrials.gov, NCT04669210) multicenter randomized trial involving first 90 patients (70% of target recruitment). Major inclusion criteria are age 18-70 years, complete remission of acute leukemia, haploidentical or unrelated donor. Major exclusion criteria are severe concurrent illness, uncontrolled infection. Study procedures include FB2-FB4 conditioning according to center standard operating procedures (SOPs), GVHD prophylaxis with PTCY 50 mg/kg on days +3, + 4, tacrolimus from day 5 to 100, MMF 30 mg/kg/day from day 5 to 35 (Control) and PTCY 50 mg/kg on days +3, + 4 with ruxolitinib 15 mg/day on days 5-21, and 10 mg/day on days 22-150 (PTCyRuxo). Patients were stratified by DRI and type of donor (unrelated/haploidentical). Other supportive care measures were performed according centers' SOPs. Among 90 enrolled patients 36% had acute lymphoblastic and 64% acute myeloid leukemia, median age was 34 years (range 19-58). Myeloablative conditioning was performed in 65% of patients, unrelated donor donated for 54%, haploidentical for 46%. Peripheral blood stem cells were used for 86% of patients.

Results: Median follow-up was 12 months. There was no difference in the incidence of engraftment (91% vs 89%, $p = 0.67$). PTCyRuxo prophylaxis was non-inferior to Control in the incidence of acute GVHD grade II-IV (11% [95%CI 4-23%] vs 24% [95%CI 13-37%], non-inferiority $p = 0.0036$, superiority $p = 0.12$) and moderate/severe chronic GVHD (26% [95%CI 13-40%] vs 35% [95%CI 19-51%], non-inferiority $p = 0.0469$, superiority $p = 0.61$). There was no difference in overall survival (82% [95%CI 53-85%) vs 73% [95%CI 65-91%], $p = 0.53$), event-free survival (76% [95%CI 57-88%] vs 68% [95%CI 51-81%], $p = 0.47$), non-relapse mortality (11% [95%CI 4-23%] vs 22% [95%CI 10-36%], $p = 0.34$) and relapse incidence (10% [95%CI 2-25%] vs 6% [95%CI 1-19%], $p = 0.57$) between PTCyRuxo and Control groups respectively. There was no difference in the incidence of major transplantation complications except no cases of veno-occlusive disease and transplant-associated microangiopathy were documented in the PTCyRuxo group (0% vs 15% combined, $p = 0.007$). Also less patients in the PTCyRuxo group experienced severe adverse events requiring prolonged hospitalization, readmission or transfer to the ICU (18% vs 37%, $p = 0.0468$). Preliminary analysis of immunological recovery by day+100 demonstrated more pronounced naïve T-cell depletion with higher prevalence of memory and effector CD8+ cells in the PTCyRuxo group.

Conclusions: The study continues to enroll patients, no futility or safety flags were triggered. Preliminary analysis demonstrates favorable safety profile of the novel GVHD prophylaxis regimen.

Clinical Trial Registry: NCT04669210, clinicaltrials.gov

Disclosure: The study is an investinator-initiated trial supported by Novartis. COI: M.I.: Novartis - honoraria; Janssenn - honoraria; Jazz- Honoraria; Sobi - honoraria; Takeda -honoraria.

12 - Graft-versus-host Disease – Clinical

P191

EFFICACY OF PTCY-BASED GVHD-PROPHYLAXIS IN ADULTS OLDER THAN 55 WITH MYELOID MALIGNANCIES UNDERGOING ALLO-HCT ACCORDING TO DONOR TYPE: STUDY FROM THE TCWP OF THE EBMT

Maria Queralt Salas[1], Christophe Peczynski2 Peczynski[2], Henrik Sengeloev[3], Didier Blaise[4], Tobias Gedde-Dahl[5], Igor Wolfgang Blau[6], Régis Peffault de Latour[7], Helene Schoemans[8], Thomas Schroeder[9], Nicolaus Kröger[10], David Burns[11], Stephan Mielke[12], Matthias Eder Eder[13], Fabio Ciceri[14], Marie Robin[15], Donal P McLornan[16], William Boreland[17], Ivan Moiseev[18], Penack Olaf[19], Christian Koenecke[13], Zinaida Peric[20]

[1]Hospital Clinic de Barcelona, Barcelona, Spain, [2]Saint Antoine Hospital, Paris, France, [3]Rigshospitalet, National University Hospital, Copenaghen, Denmark, [4]Centre de Recherche en Cancerologie de Marseille, Institut Paoli Calmettes, Marseille, France, [5]University of Oslo and Oslo University Hospital-Rikshospitalet, Oslo, Norway, [6]Charité Universitätsmedizin Berlin, Berlin, Germany, [7]Hôpital St. Louis, Paris, France, [8]University Hospitals Leuven and KU Leuven, Leuven, Belgium, [9]University Hospital Essen, Essen, Germany, [10]University Medical Center Hamburg/Germany, Hamburg, Germany, [11]University Hospital Birmingham, Birmingham, United Kingdom, [12]Karolinska University Hospital, Stockholm, Sweden, [13]Hannover Medical School, Hannover, Germany, [14]Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy, [15]Hopital Saint-Louis, APHP, Université de Paris, Paris, France, [16]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [17]EBMT Paris Study Office, Paris, France, [18]RM Gorbacheva Research Institute, Pavlov University, St Petersburg, Russian Federation, [19]Campus Virchow Klinikum, Charité Universitätsmedizin Berlin, Berlin, Germany, [20]University Hospital Zagreb, University of Zagreb, Zagreb, Croatia

Background: Due to demographic changes and optimized practices, an increasing cohort of patients beyond 55 years of age proceed to allo-HCT. PTCY is widely used for GVHD prevention in mismatched allo-HCT and is being evaluated in the matched setting. Particularly data from PTCY following RIC allo-HCT in elderly patients is limited.

Methods: The EBMT Transplant Complications Working Party performed a retrospective analysis comparing outcomes of PTCY-based versus conventional GVHD prophylaxis in RIC allo-HCT recipients with AML/MDS ≥ 55 years using data from the EBMT registry.

Results were analyzed separately depending on donor type. Each cohort was then divided into two groups according to GVHD prophylaxis (PTCY-based without ATG/Campath vs. other). A propensity score matching was applied in each donor type subgroup using cell source, disease risk index, patient and donor sex and CMV status, Karnofsky Performance Status, use of TBI, and patient age as matching factors.

Results: 10605 patients between 55 and 75 years with AML in CR or MDS undergoing their first RIC allo-HCT between 2014 and 2020 were identified. After performing the matching analysis, 454, 774, 465, and 656 patients were included, respectively, in MSD, MUD 10/10, 9/10 MMUD, and haploidentical donor comparison.

As shown in Table 1, using PTCY in adults receiving MSD grafts was associated with higher incidences of grades II-IV and III-IV aGVHD (HR 2.13, P < 0.001 and HR 2.48, P = 0.003) and comparable cGVHD (any grade) (HR 0.83, P = 0.25). PTCY was associated with comparable relapse risk (HR 0.84, P = 0.38) and NRM (HR 0.95, P = 0.84), and similar rates of OS (HR 0.95, P = 0.75) and GRFS (HR 1.02, P = 0.88).

Patients undergoing MUD allo-HCTs with PTCY had comparable grades II-IV and III-IV aGVHD (HR 1.05, P = 0.75 and HR 1.11, P = 0.73), lower incidences of any cGVHD (HR 0.67, P = 0.011) and similar extensive cGVHD (HR 0.84, P = 0.44). Using PTCY was associated with a lower relapse risk (HR 0.68, P = 0.04), comparable NRM (HR 0.90, P = 0.62), a trend to higher OS (HR 0.78, P = 0.093), and similar GRFS (HR 0.85, P = 0.15).

Using PTCY in MMUD allo-HCTs was associated with comparable grades II-IV and II-IV aGVHD (HR 1.14, P = 0.45 and HR 1.20, P = 0.55) and cGVHD (HR 0.83, P = 0.29), lower risks for relapse (HR 0.54, P = 0.025) and NRM (HR 0.58, P = 0.018), and higher OS (HR 0.60, P = 0.008), and GRFS (HR 0.7, P = 0.015).

Patients undergoing haplo-HCT with PTCY had comparable grade II-IV and III-IV aGVHD (HR 0.87, P = 0.41 and HR 1.26, P = 0.44) and cGVHD (HR 0.90, P = 0.52), and a lower relapse risk (HR 0.55, P < 0.001), comparable NRM (HR 0.96, P = 0.80), a trend to higher OS (HR 0.82, P = 0.066), and similar GRFS (HR 0.86, P = 0.13).

Conclusions: Using PTCY in patients beyond 55 years of age with AML in CR or MDS undergoing first RIC allo-HCT from MUD, MMUD, and haplo-HCT, provided comparable incidences of GVHD than other prophylaxis without PTCY, and a trend to better post-transplant results.

A higher aGVHD incidence was observed in MSD allo-HCTs receiving PTCY. Further analysis will investigate whether PTCY efficacy varies depending on the additional immunosuppressive drugs administered and how PTCY impacts on relapse risk.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P192

REFINED ANALYSIS AT THE PEPTIDE-BINDING GROOVE LEVEL OF HLA AND GRAFT-VERSUS-HOST DISEASE ASSOCIATION IN PATIENTS WITH ACUTE LEUKEMIA WHO UNDERWENT UMBILICAL CORD BLOOD TRANSPLANTATION

Wahid Boukouaci[1], Monica M. Rivera Franco[2], Fernanda Volt[2], Ching-Lien Wu[1], Hanadi Rafii[2], Barbara Cappelli[3,2], Graziana M. Scigliuolo[3,2], Chantal Kenzey[2], Vanderson Rocha[4,2], Annalisa Ruggeri[5,2], Eliane Gluckman[2,3], Ryad Tamouza[1]

[1]Univ Paris Est Créteil, INSERM U955, IMRB, F-94010, Créteil, France, [2]Eurocord, Hôpital Saint Louis APHP, Institut de Recherche de Saint-Louis (IRSL) EA3518, Université de Paris-Cité, Paris, France, [3]Monacord, Centre Scientifique de Monaco, Monaco, Monaco, [4]Service of Hematology, Transfusion and Cell Therapy, and Laboratory of Medical Investigation in Pathogenesis and Directed Therapy in Onco-Immuno-Hematology (LIM-31), Hospital das Clínicas, São Paulo University, São Paulo, Brazil, [5]Hematology and Bone Marrow Transplant Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

Background: The association between the human leukocyte antigens (HLA) and graft-versus-host disease (GVHD) has been studied but data in terms of diversity of peptide-binding pockets remain scarce. The objective of this study was to analyze whether genotypes, pocket motifs, and their amino acid positions of HLA class I HLA-A, -B, and -C (B and F pockets) and HLA-class II -DRB1 (P4, P6, and P9) and -DQB1 (P4 and P9) were associated with GVHD after umbilical cord blood transplantation (UCBT) in patients with acute leukemia.

Methods: A retrospective analysis was performed including 849 patients with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) undergoing a single UCBT. Demographics and genotyping data were obtained from the Eurocord/EBMT database. Easy-HLA web application was used for haplotype inference when needed. Pockets and amino acids were imputed from the four-digit HLA genotypes of patients using the IPD-IMGT/HLA database.

Results: Overall, 30.5% (n = 259) of the patients developed acute (a)GVHD with significant associations with the NN and KK genotypes of the amino acid positions 77 and 80 of the HLA-C (p = 0.003). The incidence of aGVHD was higher in case of KK genotype mismatch between UCB and recipient (p = 0.029). The pocket B "YSAVMENVHY" motif of HLA-A alleles was associated with severe aGVHD (p = 0.004). Further, NN and RR genotypes of the HLA-C amino acid positions 77 and 156, were both associated with severe aGVHD (p = 0.006 and p = 0.002, respectively). Mismatches between recipient and UCB in P4 and P9 pockets of HLA-DQB1 alleles also conferred more risk of severe aGVHD (p = 0.007). Chronic (c)GVHD was observed in 172 recipients (20.3%). The pocket B "YYAVMEISNY" motif of the HLA-B*15:01 allele was associated with lower incidence of cGVHD (p = 0.002) while two mismatches between HLA-B pocket B were associated with an increased risk (p = 0.002). The absence of mismatch between the recipient and the UCB in P4 and P9 of the HLA-DRB1 alleles was associated with a lower risk of cGVHD (p = 0.004). In terms of cGVHD grading, the "YFAVMENVHY" motif of the HLA-A pocket B of the CBU was found protective against the development of extensive cGVHD (p = 0.003) while the HLA-A pocket F "SIAYIDYTKW" motif was protective against any grade of cGHVD (p = 0.0003). In addition, one mismatch in P9 of the HLA-DRB1 alleles was associated with higher incidence of extensive cGVHD (p = 0.011).

Conclusions: Understanding the functional weight of the HLA molecules on the post UCBT complications is of major importance towards improvement of UCB selection and outcomes optimization. In transplantation settings, GVHD remains a major cause of morbidity and non-relapse mortality. Our observations, at the peptide binding groove level, not only confirm and replicates previous findings but also uncover new associations altogether ultimately allowing a fine dissection of the underlying mechanisms of this clinical entity.

Clinical Trial Registry: Not applicable.

Disclosure: None of the authors have any conflict of interest to disclose.

12 - Graft-versus-host Disease – Clinical

P193

TWO DISTINCT IMMUNE PROFILES ARE IDENTIFIED IN PEDIATRIC CHRONIC GVHD BY MACHINE LEARNING IN THE ABLE STUDY COHORT

Bernard Ng[1], Geoff DE Cuvelier[2], Sayeh Abdossamadi[3], Elena Ostroumov[3], Amina Kariminia[3], Kirk R. Schultz[3]

[1]University Of British Columbia, Vancouver, Canada, [2]CancerCare Manitoba/University of Manitoba, Winnipeg, Canada, [3]BC Children's Hospital Reserach Institute/UBC, Vancouver, Canada

Background: Significant heterogeneity is present in the biology of chronic graft-versus-host-disease (cGvHD), as result of various peri-transplant factors, age of the donor and recipient, graft

	Older adults undergoing RIC allo-HCT from MSD N = 454				Older adults undergoing RIC allo-HCT from MUD N = 774				Older adults undergoing RIC allo-HCT from MMUD N = 465				Older adults undergoing RIC haplo-HCT N = 656			
	PTCY-based prophylaxis N = 121 (26.7%)	Other Prophylaxis N = 333 (73.3%)	Cox-Pair Matched Analysis		PTCY-based prophylaxis N = 195 (25.2%)	Other Prophylaxis N = 579 (74.8%)	Cox-Pair Matched Analysis		PTCY-based prophylaxis N = 122 (26.2%)	Other Prophylaxis N = 343 (73.8%)	Cox-Pair Matched Analysis		PTCY-based prophylaxis N = 469 (71.5%)	Other Prophylaxis N = 187 (28.5%)	Cox-Pair Matched Analysis	
Descriptive information:			N/A				N/A				N/A				N/A	
Median age (range)																
Baseline Diagnosis	63 (56-74)	63 (55-74)			65 (55-74)	65 (55-75)			64 (56-75)	64 (55-74)			65 (55-75)	64 (55-73)		
AML in CR																
MDS																
High DRI	85 (70.2)	248 (74.5)			132 (67.7)	387 (66.8)			78 (63.9)	219 (63.8)			342 (72.9)	143 (76.5)		
KPS < 90%	36 (29.8)	85 (25.5)			63 (32.3)	192 (33.2)			44 (36.1)	124 (36.2)			127 (27.1)	44 (23.5)		
PBSC grafts	27 (22.3)	68 (20.4)			59 (30.3)	175 (30.2)			40 (32.8)	109 (31.8)			84 (17.9)	34 (18.2)		
	27 (22.3)	70 (21.0)			60 (30.8)	174 (30.1)			25 (20.5)	70 (20.4)			149 (31.8)	59 (31.6)		
	107 (88.4)	302 (90.7)			191 (97.9)	569 (98.3)			119 (97.5)	336 (98.0)			324 (69.1)	126 (67.4)		
Patients receiving ATG or Campath	0	144 (43.2%)	N/A		0	421 (72.7%)	N/A		0	296 (86.3%)	N/A		0	63 (33.7)	N/A	
	% (95% CI)	**% (95% CI)**	**HR**	**P value**	**% (95% CI)**	**% (95% CI)**	**HR**	**P value**	**% (95% CI)**	**% (95% CI)**	**HR**	**P value**	**% (95% CI)**	**% (95% CI)**	**HR**	**P value**
CIF of GVHD																
Gr. II-IV aGVHD (+100)	34 (26-43)	18 (14-22)	2.13	<0.001	26 (20-33)	25 (21-28)	1.05	0.75	33 (24-41)	30 (25-35)	1.14	0.45	28 (24-32)	33 (26-40)	0.87	0.41
Gr. III-IV aGVHD (+100)	13 (8-20)	6 (3-9)	2.48	0.003	9 (6-14)	8 (6-11)	1.11	0.73	13 (8-20)	11 (8-14)	1.20	0.55	10 (7-13)	8 (4-12)	1.26	0.44
Any cGVHD (2-y)	40 (31-49)	42 (36-47)	0.83	0.25	29 (22-36)	36 (32-41)	0.67	0.011	36 (27-45)	36 (31-42)	0.83	0.29	31 (27-36)	31 (24-38)	0.90	0.52
Ext cGVHD (2-y)	21 (14-29)	19 (15-24)	0.97	0.9	14 (9-20)	15 (12-18)	0.84	0.44	17 (10-25)	17 (13-22)	0.79	0.38	12 (9-16)	14 (9-20)	0.85	0.53
CIR																
(2-years)	28 (20-37)	29 (24-34)	0.84	0.38	19 (14-26)	27 (24-31)	0.68	0.04	15 (9-23)	25 (21-30)	0.54	0.025	18 (15-22)	29 (22-36)	0.55	<0.001
Outcomes (2-years)																
Overall Survival	61 (53-71)	61 (55-67)	0.95	0.75	68 (62-76)	61 (57-65)	0.78	0.09	71 (63-79)	54 (49-60)	0.60	0.008	57 (52-62)	49 (42-58)	0.82	0.066
Relapse-Free Survival	55 (47-65)	55 (50-61)	0.88	0.39	64 (57-71)	54 (50-59)	0.77	0.07	66 (58-76)	46 (41-52)	0.56	0.001	54 (49-59)	44 (36-52)	0.75	0.008
Non-Relapse Mortality	17 (11-24)	16 (12-21)	0.95	0.84	17 (12-23)	18 (15-22)	0.9	0.62	19 (12-26)	28 (23-34)	0.58	0.018	28 (24-32)	27 (21-34)	0.96	0.8
GVDH-Free /RFS	35 (27-45)	37 (32-43)	1.02	0.88	48 (41-57)	41 (37-45)	0.85	0.15	48 (40-58)	33 (28-39)	0.70	0.015	42 (37-47)	33 (26-41)	0.86	0.13

manipulation, and GvHD prophylactic approaches. We hypothesized that more than one biological pattern of cGvHD exists, potentially explaining the divergent cGvHD biomarkers identified from different studies. To test this hypothesis, we evaluated the ABLE cohort, which included patients under 18 years of age prospectively collected from 27 centers that had taken varying approaches to haematopoietic stem cell transplantation.

Methods: The ABLE network study enrolled 241 patients and collected whole blood samples prospectively, with close adjudication of each case to ensure it met the NIH criteria for cGvHD. Some cases of atypical cGvHD were included. Excluding late aGvHD, 44 cGvHD cases were identified. Three classes of markers (75 flow cytometry markers, 10 plasma cytokines and chemokines, and 132 metabolites) were measured from the blood samples, along with 15 clinical co-factors. To divide the cGvHD cases into subgroups, we applied the Girvan-Newman algorithm to each marker type and performed consensus clustering to combine the marker types. We adopted this multimodal approach to examine cGvHD from multiple angles, to better handle heterogeneity. Due to the small number of cGvHD cases, we opted to first divide cases into 2 subgroups to test our hypothesis. To identify markers that distinguish the two subgroups, we contrasted their values using multiple regression with subgroups coded as a binary variable and 15 clinical co-factors treated as confounds. Markers that passed all three of the following criteria were considered as relevant: ROC AUC > 0.6, $p < 0.05$, and effect ratio of ≥1.3 or ≤0.75.

Results: As shown in the t-SNE plot, with cGvHD cases projected onto a 2D space, two subgroups with almost no overlap were observed. Subgroup 1 was associated with an increased transitional B cell population, CXCL10, sCD25, and the metabolites beta hydroxybutyric acid, citric acid and taurine. Subgroup 2 was associated with an increase in memory $CD8^+$ T cells, follicular Th cells, and activated and noncytolytic $CD56^{bright}$ NK cell populations that are linked to regulatory function. Subgroup 1 associated with a bone marrow donor source and F > M mismatched donor and recipient. Subgroup 2 was associated with a PBSC donor source and M > F mismatch.

Conclusions: Our analysis suggests that more than one distinctive immune profile pattern exists in cGvHD. With additional cGvHD patients, more subgroups might be identified, helping to establish more specific therapies for different patients.

Disclosure: This study was funded by a Canadian Institute of Health Research (CIHR) team grant (KRS).

We have nothing to Disclose.

12 - Graft-versus-host Disease – Clinical

P194

REDUCED BACTERIAL ABUNDANCE IS ASSOCIATED WITH DEVELOPMENT OF SKIN GRAFT-VERSUS-HOST DISEASE AFTER ALLOGENIC HEMATOPOIETIC CELL TRANSPLANTATION

Thilo Thanscheidt[1], Antonia Reimer-Taschenbrecker[2,1], Diaa Alaloh[1], Claudia Wehr[1], Ralph Wäsch[1], Reinhard Marks[1], Hartmut Bertz[1], Robert Zeiser[1], Jürgen Finke[1], Jesus Duque-Afonso[1]

[1]University of Freiburg, Freiburg, Germany, [2]Northwestern University, Chicago, United States

Background: The human microbiome is essential for human health and has been associated with human disease through its diversity and interaction with the immune system. In patients with hematological malignancies, allogeneic hematopoietic cell transplantation (allo-HCT) is established as one potential curative option. One of the main serious complications is the reaction of the transplanted immune system against the epithelial cells of the host, also known as graft-versus-host disease (GvHD), affecting several organs such as skin, gut, liver and lungs. In this project, we analyzed the composition of the human microbiome in patients prior and after allo-HCT focusing on microbiome diversity and identification of specific bacteria associated with skin GvHD.

Methods: Patient samples were collected by skin swabbing at the left forearm from November 2019 to March 2021 at the University of Freiburg Medical Center prior and after allo-HCT. Skin samples were sequenced by 16S rDNA using the DATA2 pipeline and were statistically analyzed with for associations with GvHD by using Quiime v. 1.9.1. We performed linear discriminant analysis (LDA), which identifies standard LDA Effect Size (LEfSe) taxa whose distributions are statistically different between different groups, with a p-value < 0.05 and an effect size (LDA score) greater than 2. This study was approved by the ethics committee, University of Freiburg (EK 446/18).

Results: We collected 92 samples from 73 patients (47 male; 26 females). In both groups, the mean age was 58. Grafts were from 20 related and 49 unrelated donors, 3 haplo-identical and 1 from a twin (syngenic). 71% of the patients received a GvHD prophylaxis based on in vivo T-cell depletion based on anti-thymocyte globuline (ATG). Forty-seven of the 73 patients developed GvHD during the follow-up. Of these, 37 developed skin GvHD. Eleven patients developing skin GvHD underwent a second skin analysis after allo-HCT from a GvHD-affected and a non-affected skin site. Prior allo-HCT, patients who developed skin GvHD had reduced bacterial abundance and reduced alpha diversity in a comparison to patients who did not develop GvHD. We identified a higher abundance for Staphylococcae in samples from patients who did not develop skin GvHD, for Flavobacteria in patients who developed skin GvHD of any grade after allo-HCT, for Firmicutes and Proteobacteria (Gemella sanguinis and Rhodobacteraceae) in patients with skin GvHD grade II-IV and for Streptococcaceae and Enterobacteriaceae in patients who developed skin GvHD grade III-IV GvHD. In contrast, at the time of GvHD onset, samples at the GvHD sites had a higher bacterial abundance and alpha diversity compared to samples from unaffected skin areas. Micrococcaceae were more abundant at GvHD sites.

Conclusions: In samples from patients who developed GvHD after allo-HCT, bacterial abundance and alpha diversity were lower compared to samples from patients without GvHD before allo-HCT. However, species diversity and absolute abundance was higher in samples affected by GvHD than in control unaffected skin areas in patients with GvHD after allo-HCT. Our findings might be used in the future to identify patients at risk for skin GvHD after allo-HCT depending on the microbiome composition.

Disclosure: JD-A has received speaker's honoraria from Roche, Amgen, AstraZeneca, Riemser, Lilly, Ipsen and Sobi and travel support from AstraZeneca, Gilead and Sobi.

12 - Graft-versus-host Disease – Clinical

P195

DISTINCT CLINICAL AND IMMUNOLOGICAL EFFECTS OF TWO BRANDS OF ANTI-THYMOCYTE GLOBULIN (ATG) IN THE PROPHYLAXIS OF GRAFT-VERSUS-HOST DISEASE AFTER ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Arnaud Campidelli[1], Maud D'Aveni-Piney[1,2], Stéphane Morisset[3], Laura Boulanger[2], Anne Béatrice Notarantonio[1,2], Alizée Elitcher[2], Gabrielle Roth-Guepin[1], Sylvie Tarillon[1], Charline Moulin[1], Charles Guisnel[1], Pierre Feugier[1,2], Simona Pagliuca[1,2], Marie-Thérèse Rubio[1]

[1]CHRU Nancy, Vandoeuvre les Nancy, France, [2]Lorraine University, Vandoeuvre les Nancy, France, [3]Lyon, Lyon, France

Background: Both anti-T-lymphocyte globulin (ATLG-grafalon) and anti-thymocyte globulin (ATG-thymoglobulin) can prevent acute and chronic graft-versus-host-disease (GVHD) after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Because of distinct production characteristics, ATG and ATLG display different binding affinities to T and other immune cells. Here we hypothesized that they might differentially modulate GVHD and immune responses after allo-HSCT.

Methods: This monocentric study prospectively included 114 patients transplanted between January 2017 and September 2020 for hematological malignancies with peripheral blood stem cells from matched HLA 10/10 related (MRD, n = 25) or unrelated donors (MUD, n = 89). Among those, 50 patients having received ATG (5 mg/kg) were compared to 64 patients who received ATLG (15 mg/kg for MRD and 30 mg/kg for MUD) as GVHD prophylaxis in terms of clinical outcomes and immunological parameters (recovery of T cell subsets and PD1 expression, B cells, regulatory T and invariant NKT cells, plasma cytokine levels).

Results: Patients' characteristics at transplantation were comparable between the 2 groups with the exception of more frequent reduced intensity conditioning regimen in the ATLG group (51.6% vs 46.5%, p = 0.01). Median follow-up was above 21 months in both groups. Engraftment and incidence of viral infections were similar between the two groups. In both univariate and multivariate analysis, the use of ATLG was associated with a significant reduction of the risk of grade II-IV acute GVHD (aGVHD) in comparison to ATG (HR = 0.29; 95% CI 0.14-0.62, p = 0.006). Interestingly, higher pre-conditioning lymphocyte counts was associated with higher aGVHD incidence in the ATLG group (HR = 2,42, 95% CI 1,29-5,54, p = 0,006) and was predictive of chronic GVHD in both groups (HR = 1.86, 95% CI 1.33- 2.60, p < 0.001). The type of ATG did not impact non relapse mortality, relapse incidence or overall survival, which were mainly driven by disease risk index. Immune reconstitution of total $CD3^+$, $CD4^+$, $CD8^+$, double negative and positive T cells as well as that of B cells, Tregs and iNKT cells were comparable between the two groups. By contrast, we observed a significant reduction of PD1 expression on all T cell memory subtypes at all time points analyzed during the first 6 months post-transplantation in the ATLG group, suggesting a reduced activation of T cells. Plasma levels of IL-7 in the first weeks post-HSCT were similar between the two groups, but levels of IL-15 was significantly reduced while that of IL-21 was significantly increased during the first weeks post-HSCT in the ATLG group. In line with reduced IL-15 reduction, we observed reduced percentage of CD8 TsCM cells in the first month post-HSCT in the ATLG group. Altogether, our results suggest distinctly different modulation of T cell activation by the two ATGs.

Conclusions: Our results suggest that ATLG might be better than ATG at preventing the occurrence of acute GVHD by differential effect on cytokine production and T cell activation, without increasing the incidence of relapse or viral reactivation. These results led to set up a prospective trial randomizing the two ATGs.

Clinical Trial Registry: none

Disclosure: MT Rubio received fundings from NEOVII.

12 - Graft-versus-host Disease – Clinical

P196

ENDOTHELIAL DAMAGE MEASURED USING ENDOTHELIAL ACTIVATION BIOMARKERS AND EASIX PREDICTED ACUTE GRAFT-VERSUS-HOST DISEASE IN ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Alexandra Pedraza[1], María Queralt Salas[2], Luis Gerardo Rodríguez-Lobato[2], Silvia Escribano-Serrat[3], María Suárez-Lledo[2], Nuria Martínez-Cebrian[2], María Teresa Solano[2], Jordi Arcarons[2], Laura Rosiñol[2], Gonzalo Gutiérrez-García[2], Francesc Fernández-Avilés[2], Ana Belén Moreno-Castaño[4], Patricia Molina[4], Marc Pino[4], Enric Carreras[5], Maribel Díaz-Ricart[4], Montserrat Rovira[2], Marta Palomo[4,6], Carmen Martínez[2]

[1]Hematopoietic Stem Cell Transplantation Unit, Biomedical Diagnostic Center, Banc de Sang i Teixits, Hospital Clínic Barcelona, Barcelona, Spain, [2]Hematopoietic Stem Cell Transplantation Unit, Institute of Hematology and Oncology, Hospital Clínic de Barcelona, IDIBAPS, Josep Carreras Institute, Barcelona, Spain, Hospital Clínico San Carlos, IdiSSC, Madrid, Spain, [4]Hemostasis and Erythropathology Laboratory, Hematopathology, Centre de Diagnòstic Biomèdic (CDB), Hospital Clínic de Barcelona, Barcelona, Spain, [5]Fundació i Institut de Recerca Josep Carreras contra la Leucèmia (Campus Clínic), Barcelona, Spain, [6]Haematology External Quality Assessment Laboratory, CORE Laboratory, Biomedical Diagnostic Center, Hospital Clínic Barcelona, Barcelona, Spain

Background: Early endothelial activation and dysfunction after alloHSCT measured using soluble vascular cell adhesion molecule-1 (sVCAM-1), tumor necrosis factor receptor 1 (TNFR1), and Von Willebrand factor antigen (VWF:Ag) biomarkers has been associated with an increased risk for acute GVHD (aGVHD). The Endothelial Activation and Stress Index (EASIX), a biomarker-based laboratory formula easy to calculate, is considered an indirect evaluator of endothelial activation, and higher values of EASIX have been correlated with higher risk for the post-transplant vascular endothelial complications: VOD and TA-TMA.

This study investigates whether early endothelial activation, measured using plasma biomarkers and EASIX, can predict grade II-IV aGVHD.

Methods: In 33 adults undergoing peripheral blood alloHSCT, sVCAM-1, TNFR1, and VWF:Ag plasma biomarkers were prospectively measured before alloHSCT, and on days 0, +3, +5-7, +14, and +21. EASIX (creatininexLDH/platelets) values were calculated at the same pre-defined time-points and transformed to a base-2 logarithm to perform the analysis. The association between the continuous values of sVCAM-1, TNFR1, VWF:Ag, and log2-EASIX and grade II-IV aGVHD was explored using cumulative incidence functions (CIF). Optimal cut-off values for discriminating high-risk patients were estimated, and the discriminatory ability of the most relevant biomarkers was calculated using C-Index.

Lastly, the conclusions obtained were validated in a heterogeneous cohort of 328 adults undergoing alloHSCT in the same institution.

Results: Overall, the 33 patients included underwent RIC alloHSCT from matched (70%) and mismatched (30%) donors, 64% received PTCy, and the day +100 CIF of grade II-IV aGVHD was 18.8%. Patients were classified into two groups according to the development of grade II-IV aGVHD. Patients who would develop grade II-IV aGVHD had higher values of sVCAM-1, TNFR1, VWF:Ag and log2-EASIX during the early post-transplant period and with a peak of activity on days +5-7.

As described in Table 1, higher endothelial activity, specially measured on day +5-7 and using the TNFR1 biomarker (HR 1, P < 0.001), was associated with an increased risk for grade II-IV aGVHD. Similarly, higher values of log2-EASIX (HR 2.31, P = 0.013), measured on day +5-7, were predictors for grade II-IV aGVHD. Thereafter, optimal cut-off values for TNFR1 and log2-EASIX were estimated to discriminate high-risk patients. Day +5-7 TNFR1 values ≥ 1300ng/mL (HR 7.19, P = 0.006) and log2-EASIX ≥ 3 (HR 14.7, P < 0.001) were predictors for grade II-IV aGVHD, with a predictive accuracy of 71% and 81%, respectively.

Lastly, log2-EASIX trends were calculated in 328 transplanted adults. Patients who would present grade II-IV aGVHD had higher log2-EASIX values during the early post-transplant period, and

with a maximum score on day +7. Those patients with day +7 log2-EASIX values ≥ 3 had higher risk for grade II-IV aGVHD (HR 1.6, P = 0.03).

Table 1. Predictive ability of VCAM-1, TNFR1, VWFAg and EASIX for grade II-IV aGVHD

	Pre-transplant	Day 0	Day +3	Day +5-7	Day +14	Day +21
Univariate Analysis of VCAM-1, TNFR1 and VWF:Ag at pre-defined time-points						
sVCAM-1						
HR (95% CI)	1 (0.99-1)	1 (0.99-1)	1 (0.99-1)	1 (1-1)	0.99 (0.99-1)	0.99 (0.99-1)
P value	0.9	0.92	0.54	**< 0.001**	0.27	0.44
TNFR1						
HR (95% CI)	0.99 (0.99-1)	1 (0.99-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)
P value	0.49	0.42	**0.001**	**< 0.001**	**< 0.001**	**0.002**
VWF:Ag						
HR (95% CI)	1 (0.99-1.01)	1 (0.99-1)	1 (0.99-1)	1 (0.99-1.01)	0.99 (0.99-1)	1 (0.99-1)
P value	0.62	0.89	0.31	0.15	0.75	0.99
Univariate Analysis of Log2-EASIX at pre-defined time-points						
Log2-EASIX						
HR (95% CI)	1.68 (0.96-2.98)	2.03 (1.14-3.61)	-	2.31 (1.19-4.48)	1.89 (1.16-3.07)	1.64 (1.14-2.37)
P value	0.06	**0.01**		**0.013**	**0.009**	**0.007**
Multivariate Regression Analysis of the three plasma biomarkers at day + 5-7						
sVCAM-1						
HR (95% CI)	-	-	-	0.7 (0.99-1.01)	-	-
P value				0.97		
TNFR1						
HR (95% CI)	-	-	-	1.01 (1.00-1.01)	-	-
P value				**0.002**		
VWF:Ag						
HR (95% CI)	-	-	-	1.01 (0.99-1.01)	-	-
P value				0.99		

Conclusions: In patients at risk for aGVHD, EASIX dynamics were similar to the dynamics of three known endothelial damage biomarkers during the early post-transplant period.

Higher endothelial activity measured by EASIX on day +7 predicted aGVHD in an easy and cost-effective way. Our results support the use of EASIX to early identify patients at risk for aGVHD.

Disclosure: Non disclosure.

12 - Graft-versus-host Disease – Clinical

P197

CHRONIC GRAFT-VERSUS-HOST DISEASE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION OVER 30 YEARS - A MULTICENTER RETROSPECTIVE STUDY BY TRANSPLANT COMPLICATIONS WORKING PARTY OF EBMT

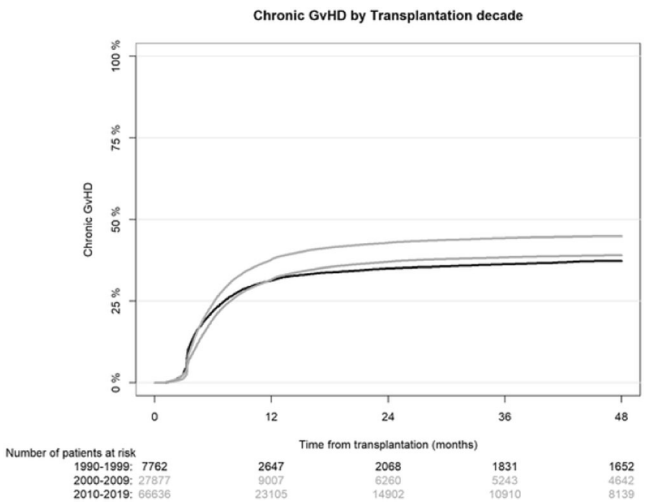
Dražen Pulanić[1], Christophe Peczynski[2], William Boreland[2], Thomas Schroeder[3], Nicolaus Kröger[4], Régis Peffault de Latour[5], Urpu Salmenniemi[6], Jürgen Finke[7], Jan Moritz Middeke[8], Edouard Forcade[9], Didier Blaise[10], Peter Dreger[11], Hélène Labussière-Wallet[12], Ivan Moiseev[13], Christian Koenecke[14], Helene Schoemans[15], Grzegorz Basak[16], Olaf Penack[17], Zinaida Peric[1]

[1]University Hospital Center Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia, [2]EBMT Paris Study Office, Saint Antoine Hospital, Sorbonne University, Paris, France, [3]University Hospital, Essen, Germany, [4]University Hospital Eppendorf, Hamburg, Germany, [5]Hospital St. Louis, Paris, France, [6]HUCH Comprehensive Cancer Center, Helsinki, Finland, [7]University of Freiburg, Freiburg, Germany, [8]University Hospital Dresden, TU Dresden, Dresden, Germany, [9]CHU Bordeaux Hôpital Haut-leveque, Pessac, France, [10]Institut Paoli Calmettes, Marseille, France, [11]University of Heidelberg, Heidelberg, Germany, [12]Hopital Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France, [13]R.M. Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany, University Hospitals Leuven, KU Leuven, Leuven, Belgium, Oncology and Internal Medicine, University Clinical Center of the Medical University of Warsaw, Warsaw, Poland, Oncology and Tumorimmunology, Charité-Universitätsmedizin Berlin, Berlin, Germany

Background: Chronic graft-*versus*-host disease (cGvHD) is a major late complication following allogeneic hematopoietic cell transplantation (alloHSCT). The aim of this retrospective study is to assess whether the incidence and outcomes of cGvHD have improved over the 30 years.

Methods: Adult patients with hematological malignancies after the first identical sibling or unrelated donor alloHSCT were studied from the large EBMT database in the following 3 decades: I) 1990-1999, II) 2000-2009, and III) 2010-2019. Patients with incomplete data were excluded.

Table 1. Patient and transplant characteristics.		I-decade (1990-1999)	II-decade (2000-2009)	III-decade (2010-2019)	Overall	p
Patient age (years), median (min-max)		37.6 (18-74.7)	46.6 (18-77)	53.4 (18-80.3)	50.1 (18-80.3)	< 0.001
Diagnosis (N (%))	Acute leukaemia	3729 (48%)	15616 (56%)	38248 (57.4%)	57593 (56.3%)	< 0.001
	Chronic leukaemia	2616 (33.7%)	3439 (12.3%)	4014 (6%)	10069 (9.8%)	
	Lymphoma	465 (6%)	3678 (13.2%)	8285 (12.4%)	12428 (12.2%)	
	Plasma cell disorders	355 (4.6%)	1949 (7%)	3265 (4.9%)	5569 (5.4%)	
	MDS/MPN	597 (7.7%)	3195 (11.5%)	12824 (19.2%)	16616 (16.2%)	
Complete remission (CR) at transplant (N (%))	CR	3138 (40.4%)	15089 (54.1%)	40424 (60.7%)	58651 (57.3%)	< 0.001
	No CR	4624 (59.6%)	12788 (45.9%)	26212 (39.3%)	43624 (42.7%)	
Cell source (N (%))	BM	6160 (79.4%)	6048 (21.7%)	5868 (8.8%)	18076 (17.7%)	< 0.001
	PB	1602 (20.6%)	21829 (78.3%)	60768 (91.2%)	84199 (82.3%)	
Type of donor (N (%))	Identical sibling	5937 (76.5%)	15019 (53.9%)	24089 (36.2%)	45045 (44%)	< 0.001
	Unrelated	1825 (23.5%)	12858 (46.1%)	42547 (63.8%)	57230 (56%)	
Intensity of conditioning (N (%))	RIC	448 (5.8%)	12116 (43.5%)	34463 (51.7%)	47027 (46%)	< 0.001
	MAC	7314 (94.2%)	15761 (56.5%)	32173 (48.3%)	55248 (54%)	
TBI (N (%))	No	2194 (28.3%)	15928 (57.1%)	50753 (76.2%)	68875 (67.3%)	< 0.001
	Yes	5568 (71.7%)	11949 (42.9%)	15883 (23.8%)	33400 (32.7%)	
In vivo T-cell depletion (N (%))	ATG / alemtuzumab	1446 (18.6%)	12614 (45.2%)	42559 (63.9%)	56619 (55.4%)	< 0.001
	No	6316 (81.4%)	15263 (54.8%)	24077 (36.1%)	45656 (44.6%)	



Results: 102,275 patients (median age 50.1 (18-80.3) years, 58.8% male) were included (I-decade N = 7,762; II-decade N = 27,877; III-decade N = 66,636). There were multiple significant differences in patient and transplant characteristics between 3 decades. Among other, over 3 decades patients were older at transplant, received more unrelated donor transplants, more peripheral blood was used as a stem cell source, more reduced intensity conditioning, less total body irradiation (TBI), and more in vivo T-cell depletion was used (Table 1). cGvHD incidence at 48 months [95% CI] changed between 3 decades (37.3% [36.2-38.4] vs 44.9% [44.3-45.5] vs 39.1% [38.7-39.5] (Figure 1), as well as extensive cGvHD at 48 months (18.1% [17.3-19] vs 22.2% [21.7-22.6] vs 19.2% [18.9-19.5]) ($p < 0.001$). Acute GvHD grade II-IV at day +100 [95% CI] decreased over time (40.4% [39.3-41.5] vs 30% [29.4-30.5] vs 26.7% [26.4-27.1], $p < 0.001$). Overall survival at 48 months improved over 3 decades (49.7% [48.6-50.8] vs 54.1% [53.5-54.7] vs 55.8% [55.4-56.2]) as well as progression free survival (41.2% [40.1-42.3] vs 43.9% [43.3-44.5] vs 46.7% [46.3-47.1]), while non-relapse mortality at 48 months decreased (28.0% [27.0-29.0] vs 19.1% [18.6-19.5] vs 18.9% [18.6-19.2]) ($p < 0.001$). 43,653 patients died with the original hematological disease as the main cause of death (47.7% of deaths), following infection (18.5%), GvHD plus infection (10.2%), and GvHD (8.3%) as the main causes of death. In multivariate analysis, II-decade (years 2000-2009), hematological disease at transplant, not in complete remission at transplant, older age at transplant, unrelated donors, peripheral blood as stem cell source, male patient, female donor, total body irradiation, without in vivo T-cell depletion were associated with both increased cGvHD and extensive cGvHD.

Conclusions: Despite better prophylaxis and improvement of supportive care over time, chronic GvHD still affects more than one third of alloHSCT recipients. This could partially be due to practice pattern changes such as older age of recipients, increased use of unrelated donors and peripheral blood as a stem cell source. This large comprehensive analysis of cGvHD outcomes over time emphasize need for future research in this field.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P198

EFFICACY AND SAFETY OF THE ADDITION OF RGI-2001 IV INFUSION TO TACROLIMUS AND METHOTREXATE FOR ACUTE GVHD PREVENTION IN MYELOABLATIVE HSCT

Yi Bin Chen[1], Shatha Farhan[2], Lazaros Lekakis[3], Gary Schiller[4], Jean Yared[5], Amer Assal[6], Dana Lee[7], Hayley Lane[7], Ted Gooley[8], Zachariah DeFilipp[1], Ayman Saad[9]

[1]Hematopoietic Cell Transplant and Cell Therapy Program, Massachusetts General Hospital, Boston, United States, [2]Henry Ford Cancer Institute, Detroit, United States, [3]University of Miami Hospital and Clinics – SCCC, Miami, United States, [4]David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, United States, [5]University of Maryland Medical Center, Baltimore, United States, [6]Columbia University Irving Medical Center, New York, United Kingdom, [7]REGiMMUNE, Marina Del Rey, United States, [8]Fred Hutchinson Cancer Center, Washington, United States, [9]The Ohio State University Comprehensive Cancer Center, Columbus, United States

Background: RGI-2001 is a liposomal glycolipid that binds the CD1d receptor of antigen-presenting cells (APC) resulting in activation of invariant natural killer (iNKT) cells. In the context of alloHCT, this interaction results in a cytokine-dependent Treg proliferation with potential modulation of the GvHD pathogenic cascade. Earlier dose-finding studies have shown that a single dose of RGI-2001 given on the day of alloHCT is safe and potentially contributed to prevention of acute GVHD (aGVHD).

Methods: RGI-2001-003 is an open-label, multi-center phase 2b study evaluating the efficacy and safety of RGI-2001 when added to a calcineurin inhibitor with methotrexate or mycophenolate mofetil (without T-cell depletion) for the prevention of aGvHD in subjects following myeloablative alloHCT. RGI-2001 was administered in a 30-minute infusion at a dose of 100 ug/kg IV weekly x 6 doses, starting on the day of transplant (Days 0, 7, 14, 21, 28, 35). The primary endpoint of the study is incidence of grades II-IV aGvHD by day 100.

Results: A total of 49 subjects treated at 7 U.S. transplant centers were enrolled. Median age was 52 (range 21-65); 27 were male. Donors were 8/8 HLA-matched unrelated (n = 32, 65%) 8/8 HLA-matched related (n = 16, 33%), or 7/8 HLA-matched unrelated (n = 1, 2%). The most common underlying diseases were AML (n = 26, 53%), ALL (n = 11, 22%), and MDS (n = 8, 16%). Graft sources were PBSC (n = 40) or BM (n = 9). Common conditioning regimens were Bu/Flu (83%) and TBI/Cy (12.2%). All subjects received standard tacrolimus/methotrexate for GvHD prophylaxis.

One infusion reaction (Grade 2) was reported. Treatment-emergent adverse events (TEAE > 5%) related to RGI-2001 were stomatitis 14%, diarrhea 12%, nausea 12%, abdominal pain 8%, increased bilirubin 8%, ALT enzyme elevation 6%, ALP elevation 6%, and rash 6%. Grade 3 or 4 related TEAE > 2% were stomatitis (6%), anemia (4%), and leukopenia (4%).

Per protocol, patients were followed for a maximum of 1 year. The median follow-up of 46 survivors was 363 days (range, 164-365), and 46 of 49 patients had complete follow-up to day 180. Through day 100, there were 10 cases of grades II-IV aGvHD [20.4% (95% CI 10.2-34.3%)], two of which were grades III-IV [(4.1% (0.5-14.0%)]. One subject died at day 102 from aGvHD due to GI bleeding, 2 subjects died without aGvHD (at days 100 and 127).

Conclusions: RGI-2001 IV infusion added to the standard-of-care tacrolimus / methotrexate GvHD prophylaxis shows promising efficacy in the prevention of aGvHD for HLA-matched donors (related or unrelated) with an acceptable safety profile. A phase III study is planned.

Disclosure: study supported by REGIMMUNE, sponsor of RGI-2001.

12 - Graft-versus-host Disease – Clinical

P199

BRONCHIOALVEOLAR LAVAGE AND BLOOD BIOMARKERS SUPPORT TH2 UPREGULATION IN BOS AFTER HCT

Muna Qayed[1], Steven Pavletic[2], Noa Holtzman[2], Fran Hakim[2], Jeffrey Switchenko[1], Jeremy Rose[2], Ronald Gress[2], Frank Flomerfelt[2], David Justus[3], Anthony Suffredini[2], Donald Farthing[2], A. Rosenberg[4], D. Kleiner[2], Joerg Halter[5], Michael Tamm[5], Spasenija Savic Prince[5], Lukas Bubendorf[5], Kirsten M. Williams[1]

[1]Emory University, Atlanta, United States, [2]National Institutes of Health, Bethesda, United States, [3]Boston Children's Hospital, Boston, United States, [4]Johns Hopkins University, Baltimore, United States, [5]Universitatsspital Basel, Basel, Switzerland

Background: Bronchiolitis obliterans syndrome (BOS) is a rare complication of allogeneic hematopoietic cell transplant (HCT) recipients with poor prognosis, in part due to late recognition of disease. Biomarkers specific for BOS could identify patients earlier in the disease process and serve as potential therapeutic targets. Having previously published increased T-helper-2 cells in the

bronchoalveolar lavage (BAL) of BOS patients, we hypothesized that the drivers of Th2 activation in the lungs would also be elevated in BOS, including systemic soluble osteopontin, and BAL cytokines: eotaxin, IL-23, IL-33, CCL15, and TRAIL.

Methods: Samples were obtained from patients on IRB approved studies with plasma from: i) chronic graft versus host disease (cGVHD) without BOS (cGVHD-BOS) (n = 38), ii) BOS (n = 39), and iii) healthy controls (HC, n = 8) and BAL from BOS (n = 16) and HC (n = 4). Plasma osteopontin was measured by protein array (Aushon Technologies) and by Luminex assay. BAL cytokines were measured via a commercial protein Discovery assay of 65-71 cytokines.

Results: Serum osteopontin levels were significantly higher in BOS vs. GVHD-BOS (median 345,955 pg/mL vs. 164,453 pg/mL, p = 0.009) by protein array, with similar results by Luminex in a subset of samples, p < 0.006. In the BAL, median levels of control and BOS were: Eotaxin were 0.9 and 6.2 (p = 0.007), GroA 281.1 and 523.7 (p = 0.03), IL-23 18.5 and 33.3 (p = 0.002), CCL15 19.5 and 254.8 (p = 0.008), TRAIL 7.7 and 27.0 (p = 0.052) for control and BOS respectively.

Conclusions: In summary, our data suggest that plasma osteopontin is increased in BOS patients compared to either those with chronic GVHD without BOS, or healthy controls, validating findings of others. We further show that Eotaxin, GroA, IL-23, CCL15, and possibly TRAIL are increased in the BAL of BOS patients compared to healthy controls. Collectively, these data support that Th2 activation and alternatively activated macrophages may be upregulated in BOS after HCT and should be validated in a larger cohort.

Disclosure: MQ: Honoraria - Vertex, Novartis. Research funding: Incyte.

12 - Graft-versus-host Disease – Clinical

P200

POST-TRANSPLANT CYCLOPHOSPHAMIDE VERSUS ANTITHYMOCYTE GLOBULIN AS GVHD PROPHYLAXIS IN PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION FROM 10/10 HLA MATCHED UNRELATED DONORS – A SINGLE CENTER ANALYSIS

Veronika Valkova[1,2], Jan Vydra[1,2], Marketa Stastna Markova[1,2], Ludmila Novakova[1], Barbora Cemusova[1], Mariana Koubova[1], Hana Bartakova[1], Michal Kolar[1], Petr Cetkovsky[1,2], Antonin Vitek[1]

[1]Institute of Hematology and Blood Transfusion, Prague, Czech Republic, Prague, Czech Republic

Background: Graf-versus-host disease (GVHD) is the leading cause of morbidity and mortality after allogeneic stem cell transplantation. The optimal prophylactic regimen for the prevention of GVHD remains elusive. Posttransplant cyclophosphamide (PTCy) is a promising approach used successfully to prevent GVHD in the HLA mismatched/haploidentical setting. The aim of our retrospective analysis was to compare GVHD prophylaxis using either PTCy/CSA + MMF or ATG/CSA + MMF in patients who underwent allo-HSCT from 10/10 HLA-matched unrelated donors.

Methods: Overall 239 patients (pts), 101 receiving PTCy (50mg/kg, D + 3 and D + 5) and 138 receiving ATG (30mg/kg), between May 2015 and April 2022 were included. Cohort's description was as follows: 126 males, median age was 53 years (range; 19-67), diagnoses were: AML, n = 113, ALL, n = 34, lymphoma, n = 20, CML, n = 8, MDS/AA, n = 43, MPN, n = 21, 225 pts received PBPC and 14 pts received BM, 169 pts were transplanted with MAC and 70 pts received RIC. The groups were comparable in terms of diagnoses distribution, age, sex, HSCT-CI, graft type, conditioning regimen and CMV patient/donor status. In the ATG group there were significantly: fewer patients transplanted in the last 2 years (p < 0,0001), longer follow-up (p < 0,0001) and fewer patients with a higher EBMT risk score (p < 0,0001).

Results: No statistical difference between the PTCy and ATG groups was observed for the two-years estimated: incidence of grade 2-4 aGVHD (21% vs 19%), 2-3 cGVHD (10% vs 18%), NRM (6% vs 9%), OS (78% vs 80%) or GFRS (52% vs 60%). We observed a borderline significantly higher two-years relapse rate in the PTCy group (34% vs 27% in the ATG group resp, p = 0,05).

Conclusions: The use of PTCy or ATG for GVHD prophylaxis may provide similar outcomes in the 10/10 HLA matched unrelated donors. In the group with PTCy, we observed a trend towards a higher incidence of relapse, which may be related to the higher number of patients with a higher EBMT risk score in this group, but the results of OS and GRFS were comparable and very good, as well as low NRM in both groups.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P201

SUBCUTANEOUS ABATACEPT FOR PROPHYLAXIS OF ACUTE GRAFT-VERSUS-HOST DISEASE AFTER HAPLOIDENTICAL DONOR HEMATOPOIETIC CELL TRANSPLANTION: EFFICACY, SAFETY AND IMMUNOLOGIC EFFECTS

Yuhua Ru[1], Jinjin Zhu[1], Yuqin Tu[1], Mimi Xu[1], Ying Wang[1], Miao Miao[1], Suning Chen[1], Huanle Gong[1], Jia Chen[1], Depei Wu[1]

[1]National Clinical Research Center for Hematologic Diseases, the First Affiliated Hospital of Soochow University, Suzhou, China

Background: Severe acute graft-versus-host disease (aGVHD) is a fatal complication particularly after haploidentical donor hematopoietic cell transplant (haplo-HCT). Abatacept is a recently approved drug for aGVHD prevention but few data have been reported in haplo-HCT with a subcutaneous form.

Methods: We performed a single-arm trial (NCT04686929) of abatacept for aGVHD prevention in haplo-HCT. Inclusion criteria were: age≥18years old; diagnosed as acute leukemia, myelodysplasia syndrome (MDS) or aggressive lymphoma; ECOG 0-2 and expected survival ≥ 3 months. Conditioning regimen was modified Bu/Cy plus ATG. All patients received 8 doses of abatacept on day -1 (250mg), days +5, +14, +21, +28, +35, +42, +49, +56 (125mg) subcutaneously in combination with cyclosporine, methotrexate and mycophenolate mofetil. The primary end point was grade 2-4 aGVHD within day +100. Meanwhile, xenogeneic aGVHD mouse model experiments were conducted. Immunologic effects were assessed in both clinical and mouse samples by flow cytometry.

Results: So far, 20 patients were enrolled into this trial, including 16 patients with acute leukemia and 4 patients with MDS. Only 1 of 20 patients developed aGVHD with Grade 4 (pt 3), and died of infection 3 months post-HCT. However, this patient ceased the injection of abatacept after the first dose due to fungemia. With a median follow-up of 233 days, 19 of 20 patients were disease-free survivors. No patient relapsed in our cohort. The most frequent adverse events were CMV reactivation (65%), febrile neutorpenia (50%), hemorrhagic cystitis (30%) and hepatic dysfunction (20%), most of them were in Grade 1-2 according to CTCAE 5.0. Lymphocyte subset analysis revealed that T cells (especially the CD4 + T cells) were significantly suppressed, while

NK cells and B cells were mildly affected. In aGVHD models, abatacept at a dose of 5mg/kg could markedly ameliorate aGVHD presentation and pathological status, and improve the survival. The count of CD4 + T cells was significantly lower in abatacept-treated mice than that in PBS-treated mice two weeks post-HCT, while the count of CD8+ cells was higher. However, both activated CD4+ and CD8 + T cells who expressing CD69, IFN-γ and TNF-α in abatacept-treated mice were lower than those in PBS-treated mice, despite of the insignificant difference in TNF-α + CD8 + T cells.

Conclusions: Our data preliminarily demonstrated that subcutaneous abatacept was a promising option to prevent aGVHD after haplo-HCT in patients with hematological malignancies. Suppression predominately on CD4 + T cells post-HCT probably increased the risk of various infections, while sparing the graft-versus-tumor effect against relapse. Randomized studies are warranted to validate our findings.

Clinical Trial Registry: NCT04686929, https://www.clinicaltrials.gov/ct2/results?cond=&term=NCT04686929&cntry=&state=&city=&dist=

Disclosure: Nothing to disclose.

12 - Graft-versus-host Disease – Clinical

P202

THE ROLE OF ANTI-THYMOCYTE GLOBULIN IN ALLOGENEIC STEM CELL TRANSPLANTATION FROM HLA MATCHED UNRELATED DONORS (MUD) FOR SECONDARY AML: A STUDY FROM THE ALWP /EBMT

Arnon Nagler[1], Myriam Labopin[2], Nicolaus Kröger[3], Thomas Schroeder[4], Tobias Gedde-Dahl[5], Matthias Eder[6], Uwe Platzbecker[7], Igor Wolfgang Blau[8], Urpu Salmenniemi[9], Régis Peffault de Latour[10], Johannes Schetelig[11], Matthias Stelljes[12], Bipin Savani[13], Fabio Ciceri[14], Mohamad Mohty[2]

[1]Sheba MC, Ramat Gan, Israel, [2]Hôpital Saint-Antoine, Paris, France, [3]University Medical Center Hamburg, Hamburg, Germany, [4]University Hospital, Essen, Germany, [5]Oslo University Hospital, Rikshospitalet Clinic for Cancer Medicine, Oslo, Norway, [6]Hannover Medical School, Hannover, Germany, [7]Medical Clinic and Policinic 1, Leipzig, Germany, [8]Charité University Medicine Berlin, Berlin, Germany, [9]HUCH Comprehensive Cancer Center, Helsinki, Finland, [10]Hopital St. Louis, Paris, France, [11]Universitaetsklinikum Dresden Medizinische Klinik und Poliklinik I, Dresden, Germany, [12]University of Muenster, Muenster, Germany, [13]Vanderbilt University Medical Center, Nashville, United States, [14]Ospedale San Raffaele s.r.l. Haematology and BMT, Milano, Italy

Background: Allogeneic hematopoietic cell transplantation (HSCT) is the only curative therapy for secondary acute myeloid leukemia (sAML). However, unrelated transplant-related mortality is still high partially due to the high incidence of graft-versus-host disease (GVHD) (Blood Cancer J. 2020). Anti-thymocyte globulin (ATG) reduces the incidence of GVHD but may increase the relapse rate, especially in high-risk diseases like sAML.

Methods: We compared outcomes of HSCT from 10/10 HLA-matched unrelated donors (MUD) in adult (≥18 years) patients (pts) with sAML receiving or not receiving ATG in addition to calcineurin inhibitor-based anti-GVHD prophylaxis. Multivariate analysis was performed using a Cox proportional-hazards model.

Results: 1609 sAML pts (ATG-1308, no ATG-301) in first complete remission (CR) that underwent HSCT from MUD from 2010-2021, were evaluated. The median age was 60.9 (range, 18.5-77.0) and 61.1 (range, 21.8-75.7) years in the ATG and no-ATG groups, respectively ($p = 0.3$). Pts in the ATG group were transplanted more recently, in 2016 vs 2014 for the no-ATG group ($p < 0.0001$). Follow-up was shorter in the ATG group at 41.6 (range, 37.3-46.3) vs 60.2 (range, 53.2-73.4) months, respectively ($p = 0.001$). In 57.3% and 58.8% of the pts in the ATG and no-ATG groups, the antecedent hematological disorder was myelodysplastic syndrome/myeloproliferative disorder (MDS/MPD). The two groups did not differ in regard to gender (male-51.5% vs 53.2%), cytogenetics risk (intermediate: 68.0 % vs 66.9% and adverse: 29.7% vs 29.6 %%), Karnofsky performance score (KPS) ≥90 (68.1% vs 75.2%), cytomegalovirus (CMV) serostatus (63.3% VS 65.1%), and time from diagnosis to transplant, median 4.6 (range 1.1-17.6) vs 4.7 (range 1.5-16.6) months for the ATG vs no ATG groups, respectively. A higher number of pts in the ATG group received peripheral blood (PB) grafts (94.8% vs 88%, $p < 0.0001$) and myeloablative conditioning (37.8% vs 28.2%, $p = 0.002$). Anti-GVHD prophylaxis was with cyclosporin-A (CSA) with methotrexate (MTX) (37.7% vs 40.5%) or mycophenolate mofetil (MMF) (43% vs 32.2%), without significant differences between the ATG and no ATG groups. Engraftment at day 60 was 98.3% in both groups. On multivariate analysis, ATG was associated with lower incidence of day 180-grade II-IV and grade III-IV acute GVHD, hazard ratio (HR) = 0.62 (95% CI 0.46-0.82, $p = 0.002$) and HR = 0.56 (95% CI 0.35-0.89, $p = 0.015$), respectively, as well as total and extensive 2-year chronic GVHD, HR = 0.7 (95% CI 0.53-0.91, $p = 0.008$) and HR = 0.45 (95% CI 0.3-0.66, $p < 0.0001$), respectively. Relapse incidence (RI) was also significantly lower in the ATG group HR = 0.76 (95% CI 0.59-0.99 $p = 0.039$), while non-relapse mortality (NRM) did not differ (HR = 0.9, 95% CI 0.65-1.23. $p = 0.51$). Leukemia-free survival (LFS), overall survival (OS), and GVHD-free, relapse-free survival (GRFS) were significantly higher in the ATG vs no ATG group, HR = 0.82 (95% CI 0.67-1, $p = 0.05$,) HR = 0.76 (95% CI 0.61-0.95, $p = 0.014$) and HR = 0.68 (95% CI 0.57-0.8, $p < 0.0001$), respectively. The main causes of death were the original disease (47.7%), infection (17.9%), and GVHD (17%).

Conclusions: ATG reduces GVHD and improves LFS, OS, and GRFS in sAML pts without increasing the relapse rate, despite sAML being a high-risk disease.

Disclosure: Kröger, Nicolaus-Martin: COI: research grant: Neovii. Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P203

CLINICAL TRIAL OF NOVEL POST-TRANSPLANT CYCLOPHOSPHAMIDE, ABATACEPT AND SHORT COURSE OF TACROLIMUS (CAST) COMBINATION FOR GRAFT-VERSUS-HOST DISEASE PREVENTION FOLLOWING HAPLOIDENTICAL PERIPHERAL BLOOD STEM CELL TRANSPLANTATION

A. Samer Al-Homsi[1], Frank Cirrone[1], Kelli Cole[1], J Andres-Suarez Londono[1], Sharon Gardner[1], Jingmei Hsu[1], Stephanie Wo[1], Judith Goldberg[2], Benjamin Levinson[2], Maher Abdul Hay[1]

[1]New York University Langone Health, New York, United States, [2]New York University Grossman School of Medicine, New York, United States

Background: Despite an incremental increase in the use of haploidentical donors in hematopoietic stem cell transplantation (HSCT), the outcomes remain inferior to matched unrelated donor transplants when post-transplant cyclophosphamide (PTCy)-based

prophylaxis is employed in both settings. Abatacept (A) impairs T-cell co-stimulation and has been shown to decrease the incidence of acute GvHD following matched and mismatched donor transplants. We hypothesized that the combination of PTCy, A and a shortened course of tacrolimus (T) (CAST) will decrease d + 120 incidence of grades II-IV acute GvHD following peripheral blood haploidentical HSCT in comparison to standard regimens.

Methods: We enrolled 46 adult patients (pts) with hematological malignancies receiving related haploidentical transplantation in a prospective single center phase Ib-II clinical trial. Following conditioning regimens of variable intensity, pts received G-CSF mobilized peripheral blood grafts and PTCy (50mg/kg on d + 3 and +4), A (10mg/kg on d + 5, +14 and +28) and T for GvHD prevention. T taper was started on d + 60 and completed by d + 90. After treating 28 pts, the study was amended to administer an additional dose of A on d + 56 based on the timing of observed cases of GvHD and the half-life of A.

Results: The median follow-up was 400.5 ds (range 126-808). Median time to neutrophil engraftment was 18 ds (13-30). One pt died prior to achieving platelet engraftment. For the remaining cohort, (n = 45) median time to platelet engraftment was 30 ds (16-125). Engraftment was confirmed by whole blood chimerism in all pts. T was tapered off as planned in all but 9 pts. D + 120 cumulative incidences of grades II-IV and III-IV acute GvHD was 17.4% (95% CI 9.2%-32.9%) and 4.4% (95% CI 1.1%-17.1%), respectively. There was no case of grade IV or steroid-refractory acute GvHD. In the last 18 pts who received 4 doses of A, there was no case of grade III-IV acute GvHD.One-y cumulative incidence of moderate to severe chronic GvHD is 11.7% (95% CI 5.1%-27%). Cumulative incidence of relapse was 13.4% (95% CI 5.6%-31.9%). KM estimated 1-y RFS, OS, and GRFS were 86.4% (95% CI 76.8%-97.2%), 90.9% (95% CI 82.7%-99.8%) and 72.4% (95% CI 60.2%-87.1%), respectively. None of the pre-defined safety stopping rules was triggered. One pt developed secondary graft failure with endogenous hematopoiesis reconstitution. There was 1 case of thrombotic microangiopathy and 2 cases of sinusoidal occlusive disease. There were 2 cases of respiratory failure, 1 due to idiopathic pneumonia syndrome and 1 to *toxoplasma gondii* and CMV. 1-y cumulative incidence of non-relapse mortality was 4.4% (95% CI 1.1%-17.1%). The incidence of CMV and EBV reactivation was 45.7% and 4.3%, respectively. Immune reconstitution results compared favorably to standard PTCy-based regimens.

Characteristic		n	Characteristic		n
Age	Median	60	**Disease Status**	CR	35
	Range	18-74		Active Disease	10
Gender	Male	25		Unknown	1
	Female	21	**Disease**	AML	16
Race	Caucasian	27		MDS	7
	Hispanic	12		ALL	16
	African American	5		Myelofibrosis	1
	Asian	2		T cell NHL	5
HCT-CI	0	17		BPDCN	1
	1-2	19	**Disease Risk Index**	Low	2
	≥3	10		Intermediate	29
CMV Status	−/−	13		High	14
(donor/ recipient)	+/+	22		Not applicable	1
	−/+	9	**Conditioning Regimen**	FluCyTBI (NMA)	16
	+/-	2		FluBuCyTBI (RI)	5
				FluBuCy (MA)	14
				FluTBI (MA)	11

Conclusions: This non-randomized study met its primary endpoint demonstrating that CAST, a novel combination for GvHD prevention following haploidentical peripheral blood stem cell transplantation is safe and effective.

Clinical Trial Registry: NCT05289167

Disclosure: A. Samer Al-Homsi, MD, MBA.

- BMS: Advisory Board
  Maher Abdul Hay, MD
- Jazz: Consultant and Speaker Bureau; Servier: Speaker Bureau; Takeda: Speaker Bureau; Kite: Ad Boards; Daiichi: Ad Boards and Rigel: Ad Boards

12 - Graft-versus-host Disease – Clinical

P204

ECP VERSUS RUXOLITINIB IN STEROID-REFRACTORY ACUTE GVHD – A RETROSPECTIVE STUDY BY THE EBMT TRANSPLANT COMPLICATIONS WORKING PARTY

Olaf Penack[1], Christophe Peczynski[2], William Boreland[2], Jessica Lemaitre[2], Ksenia Afanasyeva[3], Brian Kornblit[4], Manuel Jurado[5], Carmen Martinez[6], Annalisa Natale[7], Jose Antonio Pérez-Simón[8], Lucia Brunello[9], Daniele Avenoso[10], Stefan Klein[11], Zubeyde Ozkurt[12], Concha Herrera[13], Stina Wichert[14], Patricia Chiusolo[15], Ioanna Sakellari[16], Grzegorz Basak[17], Hélène Schoemans[18], Christian Koenecke[19], Ivan Moiseev[3], Zinaida Peric[20]

[1]Medical Clinic, Oncology and Tumorimmunology, Charité Universitätsmedizin Berlin, Berlin, Germany, [2]EBMT Transplant Complications Working Party, Paris, France, [3]First Pavlov State Medical University of St Petersburg, St Petersburg, Russian Federation, [4]Rigshospitalet, Copenhagen, Denmark, [5]FIBAO, Granada, Spain, [6]University of Barcelona, Barcelona, Spain, [7]Ospedale Civile, Pescara, Italy, [8]Hospital Universitario Virgen del Rocío, Sevilla, Spain, [9]SS. Antonio e Biagio e C. Arrigo, Alessandria, Italy, [10]King's College London, London, United Kingdom, [11]University of Heidelberg, Heidelberg, Germany, [12]Gazi University, Ankara, Turkey, [13]Servicio de Hematología Hospital Universitario Reina Sofía, IMIBIC, Cordoba, Spain, [14]Skane University Hospital, Lund, Sweden, [15]Fondazione Policlinico Universitario A. Gemelli IRCCS-Università Cattolica del Sacro Cuore-Roma, Rome, Italy, [16]Papanicolaou G. Hospital, Thessaloniki, Greece, Oncology and Internal Medicine, the Medical University of Warsaw, Warsaw, Poland, University Hospitals Leuven and KU Leuven, Leuven, Belgium, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany, University Hospital Centre Zagreb, Zagreb, Croatia

Background: Extracorporal Photophoresis (ECP) is in clinical use for steroid-refractory and steroid-dependent acute GVHD (SR-aGVHD). Based on recent Phase-III study results, Ruxolitinib has become the new standard of care for SR-aGVHD. Our aim was to collect comparative data between Ruxolitinib and ECP in SR-aGVHD in order to improve the evidence base for clinical decision making.

Methods: We identified 227 EBMT centers that use ECP and asked them if they were willing to participate in this study by completing a data form (Med-C) with very detailed information on GVHD grading, -therapy, -dosing, -response and complications for each included patient. 31 centers responded positively (14%) and we included all patients receiving alloSCT between 1/2017-7/2019

and treatment with ECP or Ruxolitinib for SR-aGVHD grades II-IV from these centers. We performed multivariate analyses adjusted on grading and type of SR-aGVHD (steroid dependent vs. refractory).

Results: We identified 51 and 38 patients with grades II-IV SR-aGVHD who were treated with ECP and Ruxolitinib, respectively. Major patient characteristics were evenly distributed between the groups (**Table 1**). At day+90 after initiation of treatment for SR-aGVHD we found an overall response rate (ORR) of 58.7% (95% CI = [43.2;73.0]) in the ECP group versus 50.0% (95% CI = [33.3;66.7]) in the Ruxolitinib group. This difference was statistically not significant in multivariate analyses (OR = 1.30, 95% CI = [0.46;3.83], p = 0.63). Non-relapse mortality (NRM) at 12 months was 40% [26.3-53.3] vs.42.9% [26.1-58.6] in the ECP and Ruxolitinib group, respectively. Overall survival (OS) at 12 months was 48.9% [36.9-64.8] vs. 55.3% [41.5-73.6] in the ECP and Ruxolitinib group, respectively. Again these differences were statistically not significant in multivariate analyses (NRM OR 0.69 [0.34-1.4] p = 0.31; OS OR 0.66 [0.37-1.18] p = 0.16. Infections, such as Bacteremia, Pneumonia, invasive fungal disease and CMV reactivation occurred frequently in this population without major differences between ECP-treated versus Ruxolitinib-treated patients.

Variable	Level	ECP only (n = 51)	Ruxo only (n = 38)	Overall (n = 89)	P
Cell source	BM	9 (17.6%)	8 (21.1%)	17 (19.1%)	0.69
	PB	42 (82.4%)	30 (78.9%)	72 (80.9%)	
Diagnosis	Acute leukaemia	29 (56.9%)	19 (50%)	48 (53.9%)	0.55
	Chronic leukaemia	4 (7.8%)	7 (18.4%)	11 (12.4%)	
	Lymphoma	4 (7.8%)	3 (7.9%)	7 (7.9%)	
	Myelodysplastic/ Myeloproliferative	14 (27.5%)	9 (23.7%)	23 (25.8%)	
Complete remission at transplant	CR	30 (60%)	19 (50%)	49 (55.7%)	0.35
	No CR	20 (40%)	19 (50%)	39 (44.3%)	
	missing	1	0	1	
Patient age (years)	median (min-max) [IQR]	54.7 (18.1-73.8) [42.3-60.9]	54.6 (20.2-69.9) [37.4-61]	54.7 (18.1-73.8) [39.8-61]	0.68
Patient sex	Male	25 (49%)	16 (42.1%)	41 (46.1%)	0.52
	Female	26 (51%)	22 (57.9%)	48 (53.9%)	
Intensity of conditioning	RIC	20 (40.8%)	19 (50%)	39 (44.8%)	0.39
	MAC	29 (59.2%)	19 (50%)	48 (55.2%)	
	missing	2	0	2	
TBI	No	44 (86.3%)	31 (81.6%)	75 (84.3%)	0.55
	Yes	7 (13.7%)	7 (18.4%)	14 (15.7%)	
In vivo T-cell depletion	ATG / Campath	18 (36.7%)	15 (39.5%)	33 (37.9%)	0.79
	No	31 (63.3%)	23 (60.5%)	54 (62.1%)	

Conclusions: Major clinical outcome parameters, such as ORR, NRM and OS were statistically not different in patients with SR-aGVHD who were treated with ECP versus Ruxolitinib. The clinical significance is limited by the retrospective study design and the current data can't replace prospective studies on ECP in SR-aGVHD. However, the present results contribute to the accumulating evidence on ECP as an effective treatment option in SR-aGVHD. The future perspective is to perform prospective clinical studies in order to define an optimal use of ECP sequentially or in combination with newer treatment options, such as Ruxolitinib and other emerging therapies.

Disclosure: The study was funded by Mallinckrodt Pharmaceuticals.

12 - Graft-versus-host Disease – Clinical

P205

FINAL SAFETY AND EFFICACY RESULTS FROM EQUATE, AN OPEN-LABEL STUDY EVALUATING ITOLIZUMAB, A NOVEL TARGETED ANTI-CD6 THERAPY, IN NEWLY DIAGNOSED ACUTE GRAFT-VERSUS-HOST DISEASE

John Koreth[1], Alison Loren[2], Ryotaro Nakamura[3], Edmund Waller[4], Joseph Pidala[5], Marco Mielcarek[6], Cherie Ng[7], Lisette Acevedo[7], Joel Rothman[7], Stephen Connelly[7], Maple Fung[7], Corey Cutler[1]

[1]Dana-Farber Cancer Institute, Boston, United States, [2]University of Pennsylvania, Philadelphia, United States, [3]City of Hope, Duarte, United States, [4]Emory University Winship Cancer Institute, Atlanta, United States, [5]H. Lee Moffitt Cancer Center and Research Institute, Tampa, United States, [6]Fred Hutchinson Cancer Center, Seattle, United States, [7]Equillium, La Jolla, United States

Background: Itolizumab is a first-in-class, non-depleting, monoclonal antibody against the co-stimulatory receptor CD6 that blocks its interaction with activated leukocyte cell adhesion molecule (ALCAM), thereby inhibiting T effector (T_{eff}) cell activity and trafficking to target organs. It is being evaluated as a treatment for immuno-inflammatory diseases where T_{eff} cells play a central role, including acute graft-versus-host disease (aGVHD). Here we present final study results, including long-term follow-up data for up to one year, from EQUATE (NCT03763318), a Phase 1b study of itolizumab in combination with corticosteroids (CS) to treat subjects with newly diagnosed severe aGVHD.

Methods: Thirty adult subjects with aGVHD Grade III-IV or Grade II with an Ann Arbor score ≥2 enrolled in EQUATE. All initiated CS treatment ≤7 days prior to the first itolizumab dose of 0.4 mg/kg (n = 4), 0.8 mg/kg (n = 17), or 1.6 mg/kg (n = 9), administered IV Q2W x up to 5 doses. Subjects were followed for up to one year. Long-term data were not available for 2 subjects who withdrew from the study. Key study objectives were safety, tolerability, efficacy, and PK/PD measurements.

Results: The median age of subjects was 61 years (range: 23-74 years); 67% were male; 3%, 70%, and 27% had Grade II, III, and IV aGVHD; 83% had lower GI involvement; and 23 (77%) subjects were treatment naïve (received itolizumab within 72 hours of initiating CS). All subjects received at least 1 itolizumab dose; 20 (67%) received ≥2 doses. Ten subjects discontinued itolizumab after the first dose, 7 due to GVHD progression.

All subjects experienced at least 1 AE. Serious AEs (SAE) occurred in 19 subjects (63%), with 11 (37%) reporting infections. Eleven subjects (37%) had SAEs leading to death (7 at 0.8 mg/kg and 4 at 1.6 mg/kg) that were deemed not related to itolizumab; 3 were due to sepsis (1 at 0.8 mg/kg and 2 at 1.6 mg/kg) and 3 (at 0.8 mg/kg) were due to worsening GVHD. Three additional deaths occurred >100 days post-last dose.

At Day 29 the highest ORR (78%) was seen with itolizumab 1.6 mg/kg, particularly in treatment naïve subjects whose ORR was 80% and CR rate was 60%. The Day 29 ORR for itolizumab 0.4 and 0.8 were 50% and 59%. Median progression free survival for itolizumab 0.4, 0.8 and 1.6 mg/kg was 3.6, 9.4 and 3.7 months, respectively. Three subjects experienced relapse of their underlying malignancy (1 at 0.8 mg/kg and 2 at 1.6 mg/kg).

Conclusions: The data from EQUATE continue to demonstrate promising outcomes in subjects with severe aGVHD. Day 29 response was consistent with progression free survival and previous PK/PD/response relationships. Based on these data, an itolizumab dosing regimen of an initial dose of 1.6 mg/kg followed by 0.8 mg/kg doses q2w x 6 is being evaluated in a Phase 3 study

(EQUATOR, NCT05263999) as initial therapy for aGVHD in combination with CS.

Clinical Trial Registry: NCT03763318 https://clinicaltrials.gov/ct2/show/NCT03763318

Disclosure: John Koreth - Advisory Board: Biolojic Design, Mallinckrodt, Cugene; Consulting to: Moderna, Amgen, EMD Serono/Merck, Gentibio Inc., Equillium; Research Support: Miltenyi Biotec, BMS, Clinigen Labs, Regeneron.

Edmund Waller / Alison Loren / Ryotaro Nakamura / Joseph Pidala / Marco Mielcerek - Nothing to declare.

Cherie Ng / Lisette Acevedo / Maple Fung / Joel Rothman - Current employment: Equillium; Current equity holder: Equillium

Stephen Connelly - Current employment: Equillium; Current equity holder: Equillium; Board of Directors: Equillium.

Corey Cutler - Consultant to: Mesoblast; Syndax; Omeros; Incyte; CareDx; Mallinckrodt; Pfizer; Kadmon (pro bono); Editas; Cimeio; Deciphera; Jazz, Equillium.

12 - Graft-versus-host Disease – Clinical

P206

ABATACEPT REDUCES ACUTE GVHD INCIDENCE IN PEDIATRIC PATIENTS TRANSPLANTED FROM HLA-MISMATCHED UNRELATED DONORS

Francesco Quagliarella[1], Pietro Merli[1], Emilia Boccieri[1], Francesca Del Bufalo[1], Marco Becilli[1], Mattia Algeri[1], Federica Galaverna[1], Chiara Rosignoli[1], Barbarella Lucarelli[1], Rita Pinto[1], Roberto Carta[1], Maria Luigia Catanoso[1], Michele Massa[1], Tiziana Corsetti[1], Arturo Maria Greco[1], Valentina Bertaina[1], Daria Pagliara[1], Franco Locatelli[1,2]

[1]Bambino Gesù Children's Hospital, Roma, Italy, [2]Catholic University of the Sacred Heart, Roma, Italy

Background: In case of lack of matched family donor, the probability of finding a fully-matched unrelated donor (MUD) ranges between 30 and 70% of cases. Patients given an allograft from a donor with antigenic/allelic disparity/ies have an increased risk of both acute GVHD (aGvHD) and TRM as compared to patients transplanted from MUD. A possible strategy to reduce risks associated with HLA-disparity is to add Abatacept to standard GvHD prophylaxis [Watkins, 2021]. Abatacept is a fusion protein that selectively inhibits T-cell co-stimulation, by binding to CD80/CD86 on antigen-presenting cells and blocking CD28-mediated signaling.

Methods: Between February/2021 and November/2022, Abatacept was administered on an off-label use basis to 30 pediatric/young adult patients (aged 3-20 years) who received an unmanipulated transplant from a mismatched (considering the loci HLA-A, -B, -C, DRB1, DQB1) unrelated donor (mMUD) (Table 1). All patients received the drug at the dose of 10 mg/kg (max 750 mg/dose) on days -1, + 5, + 14 and +28; seventeen of them received two additional infusions (every 2 weeks) until day +60 after we recorded 2 cases of late aGVHD. Abatacept was added to standard GvHD pharmacological prophylaxis [combining a calcineurin inhibitor (CNI) with short-course methotrexate (MTX) and anti-T-lymphocyte globulins (ATLG Grafalon™)]. All but SAA patients received a fully-myeloablative conditioning regimen.

Results: With a median follow-up of 7 months (range, 60-629 days), cumulative incidence of grade II-IV and grade III-IV aGVHD for the entire cohort were 35% (95% CI 18-60) and 18% (95% CI 7-43), respectively. Notably, all the episodes of aGVHD (skin, gut and liver) except one (only skin) occurred in 7 out of the 13 patients who received only four doses of abatacept; conversely, only one of the 17 patients who received abatacept until day 60 developed aGVHD. The cumulative incidence of grade II-IV aGVHD for patients receiving abatacept until day 28 (group 1) and until day 60 (group 2) were 61% (95% CI 35-87) and 8% (95% CI 1-46) ($p = 0.007$). The cumulative incidence of grade III-IV aGVHD for the same groups of patients were 26% (95% CI 9-61) and 0% ($p = 0.09$).

Only one patient, belonging to group 2, developed mild cGVHD. The cumulative incidence of infections did not significantly differ between the two groups: 75% for patients in group 1 (95% CI 47-95) and 69% in the group 2 (95% CI 45-90); most of them were viral infections, especially EBV reactivation (no PTLD was recorded). TRM was 8% (95% CI 1-23): one patient each died of TA-TMA and invasive fungal infection; both had received 4 doses of abatacept. The cumulative incidence of relapse in the malignant group was 27% (95% CI 5-57). No severe adverse events were attributable to Abatacept. Immune reconstitution is reported in Table 1.

Conclusions: Our data indicate that Abatacept, added to a standard pharmacological prophylaxis based on CNI + MTX + ATLG, is a safe and effective approach for preventing GvHD in pediatric patients undergoing mMUD HSCT for both malignant and non-malignant diseases, especially if administered up to day + 60, without apparent increased risk of relapse or TRM.

Table I. Patients and transplants characteristics

	N	% - range			
Sex (M/F)	16/14	53/47	CD3+ at 30 (mean, range)	102	11-692
Age at HSCT (years, range)	8.4	2.4-20.0	CD3+ at 90 (mean, range)	530	61-1500
Diagnosis			CD3+ at 360 (mean, range)	1000	245-2700
ALL	8	26.5	CD3 + CD4+ at 30 (mean, range)	19	3-180
AML	9	30	CD3 + CD4+ at 90 (mean, range)	109	19-338
Other malignancies	3	10	CD3 + CD4+ at 360 (mean, range)	290	15-587
SAA	7	23.5	CD3 + CD8+ at 30 (mean, range)	63	5-428
Other non-malignant diseases	3	10	CD3 + CD8+ at 90 (mean, range)	406	29-1361
Mismatch			CD3 + CD8+ at 360 (mean, range)	620	226-1950
8/10	3	10			
9/10	27	90			
Locus of MM					
Class I	23	76.5			
Class II	7	23.5			
Source of Stem Cell infused					
BM	24	80			
PBSC	6	20			

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P207

RAPAMYCIN VERSUS CYCLOSPORINE IN COMBINATION WITH PTCY FOR GVHD PROPHYLAXIS IN MATCHED RELATED AND

UNRELATED TRANSPLANTATION: A TWO-CENTRES ANALYSIS ON 213 CONSECUTIVE PATIENTS

Simona Piemontese[1], Maria Teresa Lupo-Stanghellini[1], Federica Sora[2,3], Simona Sica[2,3], Jacopo Peccatori[1], Magda Marcatti[1], Elisabetta Metafuni[2], Sabrina Giammarco[2], Raffaella Greco[1], Alessandro Bruno[1], Fabio Ciceri[1,4], Patrizia Chiusolo[2,3], Andrea Bacigalupo[2,3]

[1]Ospedale San Raffaele IRCCS, Milano, Italy, [2]Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy, [3]Università Cattolica del Sacro Cuore, Roma, Italy, [4]Vita-Salute San Raffaele University, Milano, Italy

Background: The advent of PTCy (post-transplant cyclophosphamide) as GvHD (graft versus host disease) prophylaxis strategy to overcome the HLA barrier in the setting of haploidentical SCT (stem cell transplantation) has changed the approach to transplant. Recently, PTCy/tacrolimus/mycophenolate mofetil (PTCy/Tac/MMF) proved to be superior to US standard GvHD prophylaxis with tacrolimus/methotrexate in the Phase III BMT CTN 1703 trial also in the context of MRD/MUD allogeneic HSCT paving the way as new US standard. However, PTCy platform has yet to be challenged against the EU standard based on in-vivo T-cell depletion with ATGs that emerged from two randomized trial in matched related and unrelated setting. The aim of our study was to update the impact of PTCy on GVHD/relapse or progression-free survival (GRFS) in MRD/MUD peripheral blood HSCT (PB-HSCT) in two Italian centres – Policlinico Universitario A.Gemelli (PUG) Roma and Ospedale San Raffaele (OSR) Milano.

Methods: We considered for our analysis all consecutive adults with hematologic malignancies undergoing PB-HSCT with an 8/8 MRD (N = 66) or 8/8 MUD (N = 147) between January 2018 and December 2021 with at least 100-day follow-up among survivors. At PUG patients received PTCy/CSA/MMF (N = 102) for both MRD (37) and MUD (65), while at OSR the GvHD prophylaxis was PTCy/rapamycin for MRD (N = 29) and PTCy/rapamycin/MMF for MUD (N = 82). Patients and transplant characteristics are shown in Table 1 ad did not differ in the 2 centres.

Results: The analysis for the entire population showed 2-year Overall Survival (OS), disease free survival (DFS), GRFS of 74 + /-3%, 70 + /-3%, 68 + /-3% respectively. Transplant related mortality (TRM), incidence of relapse (RI), chronic GvHD moderate/severe were as follow: 14 + /-3%, 19 + /-3%, 14 + /-3%. Day-100 acute GvHD grade 3-4 incidence was 9 + /-2%. Among the two centres, according to the univariate analysis, there was no significant difference in OS (p = 0.121), GRFS (p = 0.107), TRM (p = 0.413), cGvHD (p = 0.121). A trend for a higher incidence of acute GvHD grade 3-4 was found in OSR group (p = 0.056) while a trend for a higher RI was seen in the PUG cohort (p = 0.059). In multivariate analysis the only risk factor for a higher DSF was early disease at transplant (HR = 0.248; CI 0.126-0.428. p = 0.000054). Early disease at transplant was the only risk factor also for longer GRFR (HR = 0.225; CI 0.122-0.418. p = 0.000002).

		PUG		OSR	
Patient median age	year	55 (19-69)		58 (20-73)	
Donor median age	year	32 (20-67)		33 (16-71)	
		n	%	n	%
Patient sex	M	58	57	66	60
	F	44	43	45	40
Disease	AML	34	33	52	47
	ALL	17	17	11	10
	MDS	6	6	17	15
	MPN	31	30	11	10
	NHL	5	5	4	4
	NL	6	6	15	13
	MM/PCL	3	3	1	1
Early disease	No	10	10	15	13
	Yes	82	90	96	87
Donor	Sibling	37	36	29	26
	MUD	65	64	82	74
Female into Male	No	15	15	15	13
	Yes	87	85	96	87
Source	BM	5	5	3	3
	PBSC	97	95	108	97

PUG Policlinico Universitario A. Gemelli, *OSR* Ospedale San Raffaele, *AML* Acute Myloid Leukemia, *ALL* Acute Lymphoblastic Leukemia, *MDS* Myelodisplastic Syndrome, *MPN* Myeloproliferative Syndrome, *HD* Hodgkin Disease, *NHL* Non-Hodgking Lymphoma, *MM* Multiple Myeloma, *PCL* Plasma Cell Leukemia, *BM* bone marrow, *PBSC* peripheral blood stem cell.

Conclusions: In peripheral blood matched related and unrelated HSCT, two different PTCy package based on PTCy/CSA/MMF and PTCy/rapamycin/MMF show comparable results with 2-year GRFS of 68 + /-3% in a prospective early disease real-life adult population with hematologic malignancies. PTCy-based platforms need to be prospectively compared to ATGs-based GvHD prophylaxis in matched peripheral blood HSCT.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P208

THE IMPACT OF ADJUVANT IMMUNOSUPPRESSORS WITH POST-TRANSPLANT-CYCLOPHOSPHAMIDE FOR HLA-MATCHED ALLOGENEIC HEMATOPOIETIC TRANSPLANTATION: A MATCHED-PAIR ANALYSIS ON BEHALF OF THE ALWP OF THE EBMT

Giorgia Battipaglia[1], Myriam Labopin[2,3,4], Aleksandr Kulagin[5], Jurjen Versluis[6], Goda Choi[7], Ellen Meijer[8], Montserrat Rovira[9], Gwendolyn Van Gorkom[10], Mi Kwon[11], Yener Koc[12], Jan Vydra[13], Patrizia Chiusolo[14], Amit Patel[15], Annalisa Ruggeri[16], Arnon Nagler[2,17], Fabio Ciceri[16], Mohamad Mohty[2,3,4]

[1]Federico II University of Naples, Naples, Italy, [2]EBMT Paris Study Office, Paris, France, Hôpital Saint Antoine, Service d'Hématologie et Thérapie Cellulaire, Paris, France, [4]Sorbonne Universités, UPMC Univ Paris 06, INSERM, Centre de Recherche Saint-Antoine (CRSA), Paris, France, [5]First State Pavlov Medical University of St. Petersburg, Raisa Gorbacheva Memorial Research Institute for Paediatric Oncology, Saint Petersburg, Russian Federation, [6]Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, Netherlands, [7]University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [8]VU University Medical Center, Amsterdam, Netherlands, [9]Hospital Clinic, BMT Unit, Dept. of Haematology, Institute of Haematology & Oncology, IDIBAPS, Institut Josep Carreras, Barcelona, Spain, Division of Hematology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, Netherlands, [11]Hospital General Universitario Gregorio Marañon, Gregorio Marañon

Institute of Health Research, Madrid, Spain, [12]Medicana International Hospital Istanbul, Bone Marrow Transplant Unit, Istanbul, Turkey, [13]Institute of Haematology and Blood Transfusion, Prague, Czech Republic, [14]Universita Cattolica S. Cuore, Istituto di Ematologia, Rome, Italy, [15]Clatterbridge Cancer Centre - Liverpool, Royal Liverpool University Hospital, Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom, [16]Ospedale San Raffaele s.r.l., Haematology and BMT, Milan, Italy, [17]Chaim Sheba Medical Center, Tel Hashomer, Israel

Background: Use of single-agent post-transplant cyclophosphamide (PTCy) in HLA-matched allogeneic hematopoietic cell transplantation (allo-HCT) with peripheral blood as stem cell source (PBSC) resulted in unacceptable rates of graft-versus-host disease (GVHD), highlighting the need for adjuvant immunosuppressive therapies (IST). However, whether a calcineurin inhibitor (CNI) alone is sufficient as adjuvant IST to PTCy remains to be determined.

Methods: Included were adults (≥ 18 years) diagnosed with acute myeloid leukemia (AML) in first complete remission undergoing a first allo-HCT with PBSC from a matched related donor (MRD) or matched unrelated donor (MUD), from 2010 to 2020. GVHD prophylaxis regimens, consisting of either PTCy+CNI (n = 234) or PTCy+CNI and mycophenolate mofetil (PTCy+CNI + MMF, n = 250), were compared. To reduce or eliminate confounding effects, propensity score matching was performed using exact matching for donor type (MRD or MUD) and the nearest neighbor for other variables (i.e., age, adverse cytogenetics, Karnofsky performance status, patient and donor cytomegalovirus [CMV] serology, conditioning intensity).

Results: After pair-matching, each group comprised 146 patients, with 63% in total undergoing MUD-allo-HCT. The CNI was cyclosporin A (CsA) in 58% and 50% of PTCy+CNI and PTCy +CNI + MMF, respectively. Median age was 53 (range 18-76) and 55 (range 20-74) years for PTCy+CNI and PTCy+CNI + MMF, respectively. A female donor to male recipient was used in 17% and 19% of cases in PTCy+CNI and PTCy+CNI + MMF, respectively (p = 0.55). Conditioning regimen was mainly busulfan and fludarabine in PTCy+CNI (41%) and in PTCy+CNI + MMF (53%) and was mostly myeloablative (57% and 53%, respectively). Median follow up was longer for PTCY + CNI (36 [IQR 31-39] months versus 25 [IQR 19-30] months for PTCy+CNI + MMF, p < 0.01). Neutrophil engraftment occurred in 99% PTCy+CNI and 100% in PTCy+CNI + MMF (p = 0.50). No differences in 180-day grade II-IV (28% [95% CI 21-36] versus 20% [95% CI 14-27], p = 0.07) or grade III-IV acute GVHD (6% [95% CI 3-11] versus 9% [95% CI 5-15], p = 0.36) were observed for PTCy+CNI versus PTCy+CNI + MMF, respectively. At 2 years, PTCy+CNI was associated with a higher incidence of extensive chronic GVHD (16% [95% CI 10-22] versus 6% [95% CI 3-12] for PTCy +CNI + MMF, p < 0.03) while no differences were observed for other transplant outcomes (chronic GVHD 28% [95% CI 21-36] versus 35% [95% CI 26-44], p = 0.14; relapse incidence (RI) 30% [95% CI 23-38] versus 27% [95% CI 19-35], p = 0.86; non-relapse mortality (NRM) 8% [95% CI 4-13] versus 13% [95% CI 8-20], p = 0.14; leukemia-free survival (LFS) 62% [95% CI 53-69] versus 60% [95% CI 51-68], p = 0.53; overall survival (OS) 67% [95% CI 59-75] versus 64% [95% CI 54-72], p = 0.48; GVHD-free, relapse-free survival (GRFS) 49% [95% CI 40-57] versus 52% [95% CI 42-60], p = 0.98; for PTCy+CNI versus PTCy+CNI + MMF, respectively).

Conclusions: CNI alone appears sufficient as adjuvant IST with PTCy. However, the combination of PTCy with CNI and MMF led to a significantly lower incidence of chronic GHVD compared to PTCy +CNI alone, with no differences in other transplant oucomes for HLA-matched allo-HCT with PBSC.

Disclosure: No COI to disclose.

12 - Graft-versus-host Disease – Clinical

P209

IN VIVO DUAL T-CELL DEPLETION (TCD) IMPROVES TRANSPLANT OUTCOMES IN ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) PATIENTS ≥ 40 WHO UNDERGO ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

Ayman Sayyed[1], Carol Chen[1], Armin Gerbitz[1,2], Dennis DH. Kim[1,2], Rajat Kumar[1,2], Wilson Lam[1,2], Arjun Datt Law[1,2], Jeffrey H. Lipton[1,2], Fotios V. Michelis[1,2], Igor Novitzky-Basso[1,2], Auro Viswabandya[1,2], Jonas Mattsson[1,2], Ivan Pasic[1,2]

[1]Hans Messner Allogeneic Transplant Program, Division of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, Canada, University of Toronto, Toronto, Canada

Background: Graft-versus-leukemia effect (GVL) post allogeneic hematopoietic cell transplantation (HCT) in acute lymphoblastic leukemia (ALL) is controversial, with some studies suggesting a protective effect of graft-vs-host disease (GVHD) against disease relapse [1]. Dual T-cell depletion (TCD) is used for GVHD prophylaxis in haploidentical donor (HID) HCT [2]. Our center adopted dual TCD for GVHD prophylaxis in matched unrelated donor (MUD) transplants [3-6]. The aim of this study was to study the impact of dual TCD on rates of GVHD and outcomes of allogeneic HCT for ALL.

Methods: In a study of 137 adults who underwent allogeneic HCT for ALL at Princess Margaret Hospital, Toronto, 2010-2021 we compared transplant outcomes in individuals who received dual TCD to those who received other forms of GVHD prophylaxis. Overall survival (OS) and GVHD- and relapse-free survival (GRFS) were calculated using the Kaplan-Meier method and log-rank test. Cumulative incidences of relapse (CIR), transplant-related mortality (TRM), aGVHD and cGVHD were calculated using the Fine and Gray model.

Results: Patient characteristics are shown in **Table 1**. Median follow-up for the whole cohort was 13 months (range: 1-144). Fifty-four patients (39.0%) received dual TCD. More individuals in the dual TCD group had a HID (29.6% vs 3.6%, P < 0.001) or received reduced intensity conditioning (RIC): 57.0% vs 14.5%, P < 0.001. Total body irradiation (TBI) was more common among non-dual TCD patients: 54.2% vs 35.2%, P = 0.04.

Two-year OS, GRFS, TRM and CIR in dual TCD and non-dual TCD patients were, respectively: 50.8% vs 48.0% (P = 0.24), 34.5% vs 17.3% (P = 0.001), 24.1% vs 34.9% (P = 0.15) and 26.7% vs 20.0% (P = 0.44). Dual TCD was associated with a lower incidence of day-100 grade 2-4, 3-4 aGVHD, 2-y all-grade cGVHD and moderate-severe cGVHD: 30.7% vs 59.6% (P < 0.001), 11.1% vs 37.8% (P = 0.004), 18.7% vs 37.8% (P = 0.03), and (11.2% vs 33.3%, P = 0.004), respectively.

TBI [HR: 0.37 (95% CI: 0.18-0.76), P = 0.007] and the use of pediatric-inspired induction protocols [HR: 0.35 (95% CI: 0.14-0.89), P = 0.03] were associated with improved OS in MVA, while dual TCD was associated with higher GRFS [HR: 0.5 (95% CI: 0.3-0.9); P = 0.03].

In patients ≥40 (67 patients) dual TCD was associated with improved 2-y OS, 2-y GRFS, and lower 2-y TRM: 55.0% vs 21.4% (P < 0.001), 40.5% vs 2.6% (P < 0.001) and 23.2% vs 60.2% (P = 0.002), respectively. Similarly, patients who received dual TCD had lower rates of day-100 grade 2-4 and grade 3-4 aGVHD: 37.0% vs 68.2% (P = 0.007) and 9.6% vs 56.5% (P = 0.002), respectively. There was no difference in 2-y CIR, 2-y all-grade cGVHD or 2-y moderate-severe cGVHD: 15.8% vs 20.8% (P = 0.8), 19.7% vs 28.2% (P = 0.74) and 16.8% vs 22.5% (P = 0.61), respectively.

Table 1. Patient demographic and clinical characteristics.

Variable	Whole cohort (n = 137)	Dual TCD (n = 54)	Non-dual TCD (n = 83)	P-value
Age (median, range)	38 (18-70)	43 (18-70)	38 (19-64)	0.6
Gender (n, %)				0.8
Female	64 (46.7%)	26 (48.1%)	38 (45.8%)	
Male	73 (53.3%)	28 (51.9%)	45 (54.2%)	
Diagnosis (n, %)				0.013
Ph-B-ALL	67 (48.9%)	33 (61.1%)	34 (41.0%)	
Ph+B-ALL	50 (36.5%)	13 (24.1%)	37 (44.6%)	
T-ALL	20 (14.6%)	8 (14.8%)	12 (14.4%)	
Pediatric inspired protocol (n, %)				0.08
Yes	131 (95.6%)	54 (100.0%)	77 (92.8%)	
No	1. (4.4%)	0	6 (7.2%)	
Donor (n, %)				<0.001
MRD	43 (31.4%)	6 (11.1%)	37 (44.6%)	
MUD	58 (42.3%)	25 (46.3%)	33 (39.8%)	
MMUD	17 (12.4%)	7 (13.0%)	10 (12.0%)	
HID	19 (13.9%)	16 (29.6%)	3 (3.6%)	
Graft (n, %)				0.4
PBSC	131 (95.6%)	53 (98.1%)	78 (94.0%)	
BMSC	6 (4.4%)	1 (1.9%)	5 (6.0%)	
CMV discordance				0.38
No	85 (62.0%)	31 (57.4%)	54 (65.1%)	
Yes	52 (38.0%)	23 (42.6%)	29 (34.9%)	
HCT-CI (median, range)	1 (0-8)	2 (0-8)	1 (0-6)	0.052
KPS (median, range)	90 (60-100)	90 (60-100)	90 (70-100)	0.9
DRI (n, %)				0.2
Intermediate	89 (65.0%)	31 (57.4%)	58 (69.9%)	
High	47 (34.3%)	23 (42.6%)	24 (28.9%)	
Very high	1 (0.7%)	0	1 (1.2%)	
Conditioning (n, %)				<0.001
MAC	94 (68.6%)	23 (42.6%)	71 (85.5%)	
RIC	43 (31.4%)	31 (57.4%)	12 (14.5%)	
TBI 1200 (n, %)				0.036
Yes	64 (46.7%)	19 (35.2%)	45 (54.2%)	
No	73 (53.3%)	35 (64.8%)	38 (45.8%)	

ALL acute lymphoblastic leukemia, BMSC: bone marrow stem cells, *CMV* cytomegalovirus, *DRI* disease risk index, *HCT-CI* hematopoietic cell transplant comorbidity index, *HID* haploidentical donor, *KPS* Karnofsky performance status, *MAC* myeloablative conditioning, *MMUD* mismatched unrelated donor, *MRD* matched related donor, *MUD* matched unrelated donor, *PBSC* peripheral blood stem cells, *Ph* Philadelphia chromosome, *RIC* reduced intensity conditioning, *TBI* total body irradiation, *TCD* T-cell depletion.

Conclusions: Dual TCD improves GRFS in ALL patients who undergo allogeneic HCT. In patients ≥40, it improves OS, GRFS, and TRM without increasing relapse. This survival benefit is likely due to a reduced incidence of aGVHD. The major limitation of this study is the small number of subjects. Larger and prospective trials are needed to confirm our findings.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P210

ECP VERSUS RUXOLITINIB IN STEROID-REFRACTORY CHRONIC GVHD – A RETROSPECTIVE STUDY BY THE EBMT TRANSPLANT COMPLICATIONS WORKING PARTY

Olaf Penack[1], Christophe Peczynski[2], William Boreland[2], Jessica Lemaitre[2], Christian Reinhardt[3], Ksenia Afanasyeva[4], Daniele Avenoso[5], Tobias A.W. Holderried[6], Brian Thomas Kornblit[7], Eleni Gavriilaki[8], Carmen Martinez[9], Patrizia Chiusolo[10], Caterina Micò[11], Elisabeth Dagunet[12], Stina Wichert[13], Hakan Ozdogu[14], Agnieszka Piekarska[15], Francesca Kinsella[16], Grzegorz Basak[17], Hélène Schoemans[18], Christian Koenecke[19], Ivan Moiseev[4], Zinaida Perić[20]

Oncology and Tumorimmunology Charité Universitätsmedizin Berlin, Campus Virchow Clinic, Berin, Germany, [2]EBMT Transplant Complications Working Party, Paris, France, [3]University Hospital, Essen, Germany, [4]First Pavlov State Medical University of St Petersburg, St Petersburg, Russian Federation, [5]King's College London, London, United Kingdom, [6]University Hospital Bonn, Hematology, Immuno-Oncology and Rheumatology,, Bonn, Germany, [7]Rigshospitalet, Copenhagen, Denmark, [8]Papanicolaou G. Hospital, Thessaloniki, Greece, [9]University of Barcelona, Barcelona, Spain, [10]Fondazione Policlinico Universitario A. Gemelli IRCCS-Università Cattolica del Sacro Cuore-Roma, Rome, Italy, [11]ASST Papa Giovanni XXIII, Bergamo, Italy, [12]Institut de Cancerologie Lucien Neuwirth, Saint-Étienne, France, [13]Skane University Hospital, Lund, Sweden, [14]Baskent University, Adana, Turkey, [15]University Clinical Centrer, Medical Uiversity of Gdansk, Gdansk, Poland, [16]University Hospital Birmingham NHS Trust, Birmingham, United Kingdom, Oncology and Internal Medicine, the Medical University of Warsaw, Warsaw, Poland, University Hospitals Leuven and KU Leuven, Leuven, Belgium, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany, University Hospital Centre Zagreb, Zagreb, Croatia

Background: Extracorporal Photophoresis (ECP) is in clinical use for steroid-refractory and steroid-dependent chronic GVHD (SR-cGVHD). Based on recent Phase-III study results Ruxolitinib has become the new standard of care for SR-cGVHD. Our aim was to collect comparative data between Ruxolitinib and ECP in SR-cGVHD in order to improve the evidence base for clinical decision making.

Methods: We identified 227 EBMT centers that use ECP and asked them if they were willing to participate in this study by completing a data form (Med-C) with very detailed information on GVHD grading, -therapy, -dosing, -response and complications for each included patient. 31 centers responded positively (14%) and we included all patients receiving alloSCT between 1/2017-7/2019 and treatment with ECP or Ruxolitinib for moderate/severe SR-cGVHD from these centers. We performed multivariate analyses adjusted on grading and type of SR-cGVHD (steroid dependent vs. refractory) as well as the hematopoietic cell transplantation comorbidity index.

Results: We identified 84 and 56 patients with moderate/severe SR-cGVHD who were treated with ECP and Ruxolitinib, respectively. Major patient characteristics were evenly distributed between the groups (**Table 1**). At 180 days after treatment initiation for SR-cGVHD we found an overall response rate (ORR) of 45.7% (95% CI = [34.6-57.1]) in the ECP group versus 57.1% (95% CI = [43.2-70.2]) in the Ruxolitinib group. This difference was statistically not significant in multivariate analyses (OR = 1.45, 95% CI = [0.68;3.17], p = 0.34). Non-relapse mortality (NRM) at 24 months was 32.9% [22.6-43.7] vs. 28.6% [16.4-42] in the ECP and Ruxolitinib group, respectively. Overall survival (OS) at 24 months was 61.2% [51.5-72.8] vs. 69.3% [57.5-83.4] in the ECP and Ruxolitinib group, respectively. Again these differences were statistically not significant in multivariate analyses (NRM OR 0.72 [0.32-1.63] p = 0.43; OS OR 0.72 [0.32-1.62] p = 0.43). Infections, such as Bacteremia (25.9%), Pneumonia (15.8%), upper respiratory tract infections (12.2%) and CMV reactivation (10.1%) occurred

frequently in this population without major differences between ECP-treated versus Ruxolitinib-treated patients. Interestingly, we collected additional 62 patients with SR-cGVHD who were treated with a combination of ECP and Ruxolitinib. This population was too heterogeneous to perform comparative outcome analyses.

Variable	Level	ECP only (n = 84)	Ruxo only (n = 56)	Overall (n = 140)	P
Cell source	BM	6 (7.1%)	6 (10.7%)	12 (8.6%)	Not done
	CB	2 (2.4%)	0 (0%)	2 (1.4%)	
	PB	76 (90.5%)	50 (89.3%)	126 (90%)	
Diagnosis	Acute leukaemia	41 (48.8%)	32 (57.1%)	73 (52.1%)	Not done
	Chronic leukaemia	3 (3.6%)	3 (5.4%)	6 (4.3%)	
	Lymphoma	7 (8.3%)	5 (8.9%)	12 (8.6%)	
	Myelodysplastic/ Myeloproliferative	29 (34.5%)	15 (26.8%)	44 (31.4%)	
	Benign disorders	4 (4.8 %)	1 (1.8%)	5 (3.5%)	
Complete remission at transplant	CR	40 (50%)	33 (60%)	73 (54.1%)	0.25
	No CR	40 (50%)	22 (40%)	62 (45.9%)	
	missing	4	1	5	
Patient age (years)	median (min-max) [IQR]	55.5 (20.6-77.9) [42.3-63.3]	53 (17.7-71.3) [39.2-60.3]	55.1 (17.7-77.9) [40.9-62.2]	0.49
Patient sex	Male	48 (57.1%)	33 (58.9%)	81 (57.9%)	0.83
	Female	36 (42.9%)	23 (41.1%)	59 (42.1%)	
Intensity of conditioning	RIC	41 (49.4%)	22 (40%)	63 (45.7%)	0.28
	MAC	42 (50.6%)	33 (60%)	75 (54.3%)	
	missing	1	1	2	
In vivo T-cell depletion	ATG / Campath	47 (56%)	20 (36.4%)	67 (48.2%)	0.024
	No	37 (44%)	35 (63.6%)	72 (51.8%)	

Conclusions: Major clinical outcome parameters, such as ORR, NRM and OS were statistically not different in patients with SR-cGVHD who were treated with ECP versus Ruxolitinib. The clinical significance is limited by the retrospective study design and the current data can't replace prospective studies on ECP in SR-cGVHD. However, the present results contribute to the accumulating evidence on ECP as an effective treatment option in SR-cGVHD. The future perspective is to perform prospective clinical studies in order to define an optimal use of ECP sequentially or in combination with newer treatment options, such as Ruxolitinib and other emerging therapies.

Disclosure: The study was funded by Mallinckrodt Pharmaceuticals.

12 - Graft-versus-host Disease – Clinical

P211

ABATACEPT FOR GRAFT VERSUS HOST DISEASE PROPHYLAXIS IN PATIENTS 60 YEARS AND OLDER RECEIVING MISMATCHED UNRELATED DONOR TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCIES

Sharmila Raghunandan[1,2], Amelia Langston[1,3], Benjamin Watkins[1,2], Lev Gorfinkel[4,5], Adrianna Westbrook[1], Scott Gillespie[1], Brandi Bratrude[4], Kayla Betz[4,5], Aleksandra Petrovic[6], Yvonne Suessmuth[2,1], John Horan[4,5], Leslie Kean[4,5], Muna Qayed[2,1]

[1]Emory University, Atlanta, United States, [2]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, United States, [3]Winship Cancer Institute, Atlanta, United States, [4]Boston Children's Hospital, Boston, United States, [5]Dana-Farber Cancer Institute, Boston, United States, [6]Seattle Children's, Seattle, United States

Background: Graft versus host disease (GVHD) is a major limitation to the use of mismatched unrelated donor (MMUD) grafts for patients lacking a well-matched donor. Abatacept is FDA approved for the prevention of acute GVHD (aGVHD) based on results of ABA2, a phase II trial evaluating abatacept in addition to calcineurin inhibitor (CNI)/methotrexate (MTX). The 7/8 MMUD cohort from ABA2 showed significant reduction in grade III-IV aGVHD. Patients enrolled in that cohort ranged from 6 to 76 years old. Given the impact of recipient age on risk of transplant-related mortality (TRM), we aimed to evaluate outcomes of MMUD in patients 60 years and older undergoing hematopoietic cell transplantation (HCT) for hematologic malignancies.

Methods: We conducted a retrospective analysis including patients who received 7/8 MMUD HCT for hematologic malignancy who received GVHD prophylaxis with abatacept (days -1, +5, +14, and +28) combined with CNI/MTX between January 2015 and December 2021. Nine patients were enrolled on the ABA2 trial while others were treated per institutional standards.

Results: 22 patients were included in this analysis. Median age at HCT was 66 years (range 60-76 years). 68% of patients had MDS, and 59% had advanced disease per CIBMTR definition. 20 patients received fludarabine/melphalan reduced intensity conditioning and two received busulfan/cyclophosphamide myeloablative conditioning. 86% received peripheral blood stem cell grafts. 68% of donors were younger than 35 years. Median follow-up for survivors was 2 years.

There was one death prior to day 30, all others achieved neutrophil engraftment by day 30 and platelet engraftment by day 100. Cumulative incidence of grade II-IV aGVHD was 18.2% (95% confidence interval, CI, 5.5%-36.8%) by day +180, and grade III-IV aGVHD was 4.6% (95% CI 0.3%-19.4%). One patient developed grade II late aGVHD at day +264. Cumulative incidence of moderate-severe chronic GVHD (cGVHD)was 62.0% (95% CI 36.9%-79.6%). At 1 year, cumulative incidence of TRM and relapse were 22.7% (95% CI 8.0%-42.0%) and 4.6% (95% CI 0.3%-19.5%), resulting in disease-free survival (DFS) of 72.7% (95% CI 49.1%-86.7%), and overall survival of 77.3% (95% CI 53.7%-89.8%). 1-year Grade III-IV aGVHD-free, severe cGVHD-free, relapse-free survival (GRFS) was 59.1% (95% CI 36.1%-76.2%, **Figure 1**).

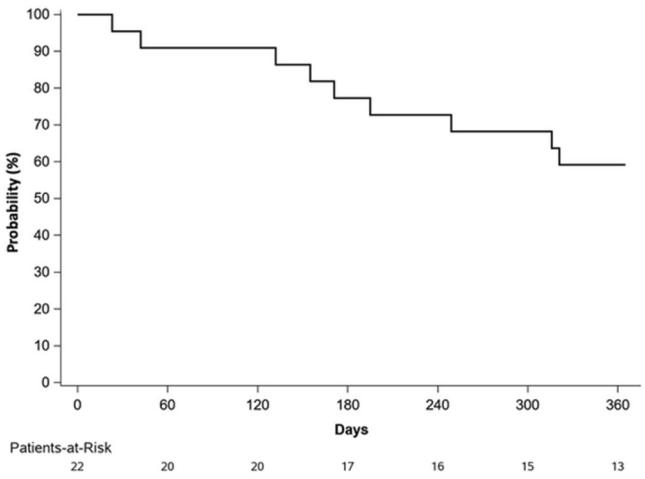


Figure 1 GRFS

Conclusions: In this analysis of older patients receiving HCT using 7/8 MMUD grafts, rates of severe acute GVHD and relapse were low and DFS encouraging. While TRM was higher than in the entire 7/8 MMUD cohort from ABA2, relapse rates and OS remained favorable relative to published data in this age group. As observed in ABA2, Abatacept was not protective against cGVHD, and is currently the focus of an ongoing randomized trial (ABA3) testing extended abatacept dosing for cGVHD prevention (NCT04380740).

Disclosure: Muna Qayed - Honoraria at Vertex and Novartis. Leslie Kean - *Novartis:* Research Funding; *Bluebird Bio:* Research Funding; *Vertex:* Consultancy; *EMD-Serono:* Research Funding; *Bristol Myers Squibb:* Patents & Royalties: clinical trial, Research Funding; *Magenta:* Research Funding; *Mammoth Biosciences:* Current equity holder in private company, Current holder of *stock options* in a privately-held company; *HiFiBio:* Consultancy.

12 - Graft-versus-host Disease – Clinical

P212

TREATMENT WITH RUXOLITINIB IN COMBINATION WITH EXTRACORPOREAL PHOTOPHERESIS IN STEROID-REFRACTORY ACUTE AND CHRONIC GRAFT VERSUS HOST DISEASE: A SINGLE-CENTRE REAL-WORLD EXPERIENCE

Verena Wais[1], Andrea Gantner[1], Conrad Weidt[1], Adela Neagoie[1], Jacqueline Schnell[1], Hartmut Döhner[1], Donald Bunjes[1], Elisa Sala[1]

[1]University Hospital of Ulm, Ulm, Germany

Background: Steroid-refractory acute/chronic graft-versus-host disease (SR-a/cGvHD) is one of the most critical complications after allogeneic stem-cell transplantation (allo-SCT). Approximately 50% of the patients after allo-SCT develop aGvHD and 30%-50% acquire cGvHD. Only 20-30% with aGvHD respond to first-line therapy, while response rates in patients with cGvHD are about 20%. With the introduction of the JAK1/2-inhibitor Ruxolitinib a significant improvement of the overall-response rate (ORR) in both entities has been achieved (Zeiser, NEJM 2020 and 2021). However, non-responder, or patients with side effects could benefit from a combination strategy with ECP to maximize the efficacy and reduce the toxicity. We here evaluated the feasibility and efficacy of Ruxolitinib in combination with ECP for the treatment of SR-a/cGvHD in a real-world setting.

Methods: We performed a retrospective, single-centre study in transplanted patients between 11/2018 and 04/2022. Included were patients receiving Ruxolitinib and/or ECP for the treatment of SR-a/cGvHD. GvHD grading was performed as previously described (Harris, BBMT 2016, Jagasia, BBMT 2015) In the inpatient setting an induction treatment with ECP up to four times/week was administered, whereas in outpatient setting, according to the severity of GvHD, a twice-weekly schema every 14 days was applied. Ruxolitinib dosage was based on published data.

Results: In the SR-aGvHD subgroup we identified 40 patients receiving Ruxolitinib and/or ECP. Patients' characteristics are listed in Table 1. Twenty-nine patients (73%) showed grade III-IV SR-aGvHD, in 28/29 patients (97%) lower GI-tract GvHD was diagnosed. Ruxolitinib was chosen as main backbone of the immunosuppressive strategy in 18/40 patients (45%), 8/40 (20%) received only ECP, while in 14/40 patients (35%) a combination with Ruxolitinib/ECP was preferred, due to progression or inadequate response in a single-agent setting. In the whole population the ORR was 75%, reaching 83% (15/18) in the Ruxolitinib-subgroup, 75% (6/8) in the ECP-subgroup, 64% (9/14) in the subgroup where Ruxolitinib/ECP was used in combination as sequential therapy. Of note, the Ruxolitinib/ECP-subgroup had the highest incidence of grade IV SR-aGvHD (43%, 6/14) versus 25% and 11% observed in the ECP and Ruxolitinib-subgroups respectively ($p = 0.004$).

In the SR-cGvHD subgroup we identified 66 patients. Fifty-eight/66 (88%) had moderate/severe SR-cGvHD, skin affection was observed most frequently (49/66, 74%). Ten/66 patients (15%) received ECP alone, 30/66 (46%) were treated with Ruxolitinib and 26/66 (39%) received the combination of Ruxolitinib/ECP. ORR overall was 76%(50/66), 70% (7/10) in the ECP-subgroup, 83% (25/30) in the Ruxolitinib-subgroup and 69% (18/26) in the Ruxolitinib/ECP-subgroup. In this subgroup we observed a trend to higher incidence of severe SR-cGvHD (36% versus 30% and 13% of the ECP- and Ruxolitinib-subgroups respectively, $p = 0.1$).

Ruxolitinib and ECP (as single agent and in combination strategy) were well tolerated, without episodes of therapy-limiting side effects.

Conclusions: Up to date Ruxolitinib is one of the most effective treatment strategies for SR-a/cGvHD. This retrospective analysis suggests a potential effective role for the combination with ECP, especially for high-risk patients with severe forms of SR a-/cGvHD not promptly responding to Ruxolitinib-strategy. These encouraging results need to be validated in further prospective studies.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P213

IMMUNE ACTIVATION AND ENDOTHELIAL DYSFUNCTION IN ACUTE GRAFT-*VERSUS*-HOST DISEASE

Nicholas Schreck[1], Aleksandar Radujkovic[2], Cryostem Consortium[3], Carsten Müller-Tidow[2], Olaf Penack[4], Ted Gooley[5], Axel Benner[1], Peter Dreger[2], Thomas Luft[2]

[1]German Cancer Research Centre, Heidelberg, Germany, [2]University Hospital Heidelberg, Medicine V, Heidelberg, Germany, [3]Cryostem, Paris, France, [4]Charité Universitätsmedizin Berlin, Hematology, Oncology and Tumorimmunology, Berlingerm, Germany, [5]Fred Hutchinson Cancer Research Center and University of Washington, Seattle, United States

Background: Acute graft-versus-host disease (aGVHD) remains a life-threatening complication and major cause of non-relapse mortality (NRM) in recipients of allogeneic stem cell transplantation (alloSCT). To test the hypothesis that the interplay of immune activation and endothelial dysfunction is fundamental for the pathophysiology of severe aGVHD, we studied the impact of a variety of inflammatory and endothelial biomarkers on aGVHD outcomes.

Methods: Four inflammatory (Reg3a, TIM3, IL18, CXCL9) and four endothelial biomarkers (ST2, Angiopoietin-2, sCD141 and CXCL8) were assessed prior to aGVHD, and two and four weeks after onset of aGVHD. Partial dependence plots were calculated to visualize the impact of combinations of one inflammatory and one endothelial marker on non-relapse mortality (NRM) and overall survival (OS) in two independent cohorts (cohort IA $n = 329$; cohort II $n = 127$). In addition, C-reactive protein (CRP) and EASIX were evaluated as surrogate inflammatory and endothelial biomarkers in a training cohort (cohort IB, $n = 535$) and a third independent validation cohort (cohort III, $n = 135$).

Results: In the training cohort (IA), partial dependence plots revealed an additive impact of high serum concentrations of all inflammatory markers in the context of high serum levels of any endothelial marker on outcome. In the independent cohort (II),

this could only be reproduced for combinations of IL18 or CXCL9 with any of the four endothelial markers measured at onset of aGVHD.

EASIX and CRP had additive impact on NRM and OS from aGVHD onset in both training (IB) and validation cohort (III).

Following escalation of immunosuppression, endothelial markers such as EASIX, ST2 and CXCL8 increased within the next 14-56 days in patients who died within one year after aGVHD. In contrast, these markers did not change significantly in aGVHD survivors. Among inflammatory biomarkers, only CXCL9 decreased during aGVHD, whereas IL18, Reg3a and TIM3 did not show significant changes independent of 1-year survival status.

The combination of high EASIX (cut-off 3.57 (1)) and increased CRP (> 5 mg/dl, upper normal range) was strongly prognostic in the training cohort (IB), and its predictive potential could be validated in the independent third cohort (III) in multivariable Cox regression.

Conclusions: The pathophysiology of NRM after aGVHD is characterized by distinct kinetics of both, endothelial and inflammatory marker serum levels, suggestive of progressive endothelial damage in non-survivors. EASIX and CRP could be validated to predict NRM and OS after aGVHD strongly and additively.

Clinical Trial Registry: None

Disclosure: Nothing to disclose.

12 - Graft-versus-host Disease – Clinical

P214

MACHINE LEARNING FOR RISK BIOMARKERS OF CHRONIC GRAFT-VERSUS-HOST DISEASE IN 936 PATIENTS FROM BMTCTN 0201 & 1202 COHORTS

Michael Martens[1], Jianqun Kou[1], Brent Logan[1], Sophie Paczesny[2]

[1]Medical College of Wisconsin, Milwaukee, United States, [2]Medical University of South Carolina, Charleston, United States

Background: We previously identified potential risk/susceptibility biomarkers that indicate the potential for developing chronic GVHD (cGVHD) in individuals without clinically apparent disease, which is a major contributor to morbidity and mortality for survivors of allogeneic hematopoietic cell transplant (HCT). In this study, we used machine learning (ML) algorithms to build a biomarker-based prediction model for development of cGVHD and nonrelapse mortality (NRM).

Methods: We assessed 9 pre-transplant factors and 7 plasma proteins at day 90 post-HCT in 936 HCT recipients from BMTCTN 0201&1202 cohorts who were randomly divided into training (80%) and validation (20%) datasets. We tested each of the markers for their association with the cause-specific hazard of cGVHD using Cox proportional hazards (PH) models. As a resource for clinicians in future clinical use, we estimated the time-varying Area Under the ROC curve (AUCt) at Days 180, 270, 360, and 540 post-HCT. A wide variety of ML approaches have been developed to address nuances of time to event data such as censoring and competing risks. We considered ML approaches within the framework of the PH model, including Boosting (XGBoost), Group SCAD, and Adaptive Group Lasso, as well as approaches which do not rely on the PH assumption, including Random Survival Forests and Bayesian Additive Regression Trees (BART).

Results: Of the 7 proteins tested, 4 (CXCL9, CXCL10, MMP3, and DKK3) were associated with risk of developing cGVHD with p-values < 0.05 using univariate Cox models (**Table 1**). We next evaluated the predictive ability of the 6 ML methods aforementioned with biomarkers effects only as well as biomarkers+clinical factors and contrasted them to a penalized regression model with clinical factors only. 4/9 clinical factors were selected by multivariate penalized regression models: age, graft type (PBSC vs BM), donor-recipient sex-mismatch, and GVHD prophylaxis, while 4/7 proteins were selected: CXCL9, CXCL10, MMP3, ST2. In the validation dataset, most ML methods with biomarkers only provided better AUCt compared to clinical factors only after Days 360, suggesting that plasma proteins measured as early as 90 days post-HCT may inform underlying cGVHD biology that has not yet manifested clinically. When biomarkers and clinical factors were incorporated in one ML model, AUCt was approximately 0.65 at all timepoints. For NRM, age, graft type, MMP3, DKK3, ST2 and CD163 were found to be prognostic. Both biomarkers only and biomarkers+ clinical models AUCt were increased as compared to clinical factors only, particularly before 360 days.

Biomarker	Effect[1]	Hazard Ratio	95% Lower CL	95% Upper CL	p-value	Overall p-value
IL17	Log IL17	1.077	0.944	1.230	0.2696	0.4614 (2 df)
	Log IL17^2	1.019	0.989	1.050	0.2185	
CXCL9	Log CXCL9	1.084	1.027	1.146	0.0038	0.0049 (2 df)
	Log CXCL9^2	1.027	1.007	1.048	0.0093	
CXCL10	Log CXCL10	1.102	1.035	1.172	0.0022	
MMP3	Log MMP3	1.224	1.129	1.329	0.0000	
DKK3	Log DKK3	1.262	1.018	1.566	0.0339	
ST2	Log ST2	1.050	0.934	1.181	0.4147	
CD163	Log CD163	0.933	0.729	1.195	0.5844	

Conclusions: Machine learning approaches using non-invasive plasma proteins can be successfully applied to identify and validate risk biomarkers of cGVHD. ML algorithms using objective and early measurements of soluble markers including CXCL9, CXCL10, MMP3, and ST2 perform better than ML with known clinical factors only. Biomarkers+clinical factors ML algorithms improved prediction of incident cGVHD after days 90. ML with MMP3, DKK3, ST2 and CD163 improved NRM prediction. Several of these proteins represent potential therapeutic targets. These data support research for further validation of these biomarkers and ML algorithms that could help identify patients at risk for developing cGVHD and NRM.

Clinical Trial Registry: NA, ancillary

Disclosure: S.P. holds a patent on "Biomarkers and assays to detect chronic graft versus host disease" (U.S. Patent #10,571,478 B2). Other authors declare no competing interests.

12 - Graft-versus-host Disease – Clinical

P215

IMPACT OF GVHD AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN YOUNG ADULTS ON SURVIVAL AND RELAPSE RATE IN GERMANY

Jochen J. Frietsch[1,2], Sarah Flossdorf[3,4], James F. Beck[5], Nicolaus Kröger[6,4], Katharina Fleischhauer[7,4], Peter Dreger[8,4], Wolfgang Bethge[9], Johanna Tischer[10], Thomas Schroeder[11], Igor-

Wolfgang Blau[12], Matthias Eder[13], Johannes Schetelig[14,4], Martin Bornhäuser[14,4], Andreas Hochhaus[2], Inken Hilgendorf[2]

[1]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany, [2]Klinik für Innere Medizin II, Hämatologie und internistische Onkologie, Universitätsklinikum Jena, Jena, Germany, [3]Institut für Medizinische Informatik, Biometrie und Epidemiologie, Universitätsklinikum Essen, Essen, Germany, [4]Deutsches Register für Stammzelltransplantationen e.V., DRST, Ulm, Germany, [5]Sektion für Hämatologie, Onkologie und Stammzelltransplantation, Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Jena, Jena, Germany, [6]Klinik für Stammzelltransplantation, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany, [7]Institut für Zelltherapeutische Forschung, Universitätsklinikum Essen, Essen, Germany, [8]Medizinische Klinik V, Universitätsklinikum Heidelberg, Heidelberg, Germany, [9]Innere Medizin II, Universitätsklinikum Tübingen, Tübingen, Germany, [10]Medizinische Klinik und Poliklinik III, Klinikum der Ludwig-Maximilians-Universität München, München, Germany, [11]Klinik für Hämatologie und Stammzelltransplantation, Universitätsklinikum Essen, Essen, Germany, [12]Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmuno-logie, Campus Virchow-Klinikum, Berlin, Germany, [13]Klinik für Hämatologie, Hämostaseologie, Onkologie und Stammzelltransplantation, Medizinische Hochschule Hannover, Hannover, Germany, [14]Medizinische Klinik I, Universitätsklinikum Carl Gustav Carus, TU Dresden, Dresden, Germany

Background: Although the outcome of young adults (YA) after allogeneic SCT (alloSCT) improved over the last two decades, the probability of 10-year OS of 47.5% is disappointing. Thereby, patients aged 18 to 39 years most likely died from relapse. Here we additionally describe the impact of acute and chronic GvHD on OS and relapse rates of YA after alloSCT.

Methods: The German Registry for Stem Cell Transplantation (DRST) was screened for YA who received alloSCT between 1998 and 2019. OS was estimated using Kaplan-Meier method and differences between the curves were evaluated by Score-test (computed by using Cox proportional hazards model, corresponds to log-rank test). Hazard Ratios were also indicated. Gray's test was applied to cumulative incidence of NRM using competing risk analysis. A p-value of < 0.05 was considered statistically significant. To prevent an immortal time bias the occurrence of GvHD was considered as a time-varying covariate in Cox Regression as well as in competing risk analysis. Patients with unknown GvHD-dates were eliminated from the analysis.

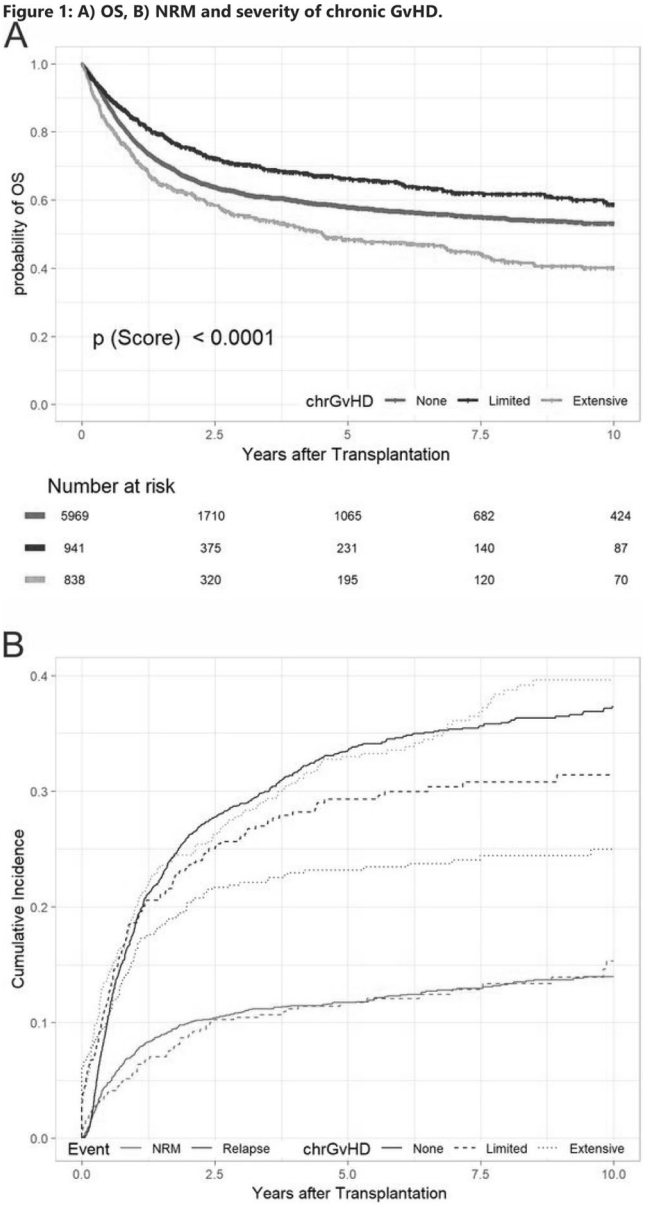
Results: Altogether information about acute GvHD (aGvHD) was provided for 5,416 of 9,299 (58.2%) SCT recipients. Of those, 1,389 (25.6%) patients developed aGvHD °I-II and 561 (10.4%) patients aGvHD °III-IV. The median 10-year OS was best after aGvHD °I-II (14.22 years; HR 0.815 [0.736, 0.902]) and worst after aGvHD °III-IV (0.85 years; HR 2.075 [1.85, 2.327]; compared to none GvHD; 11.46 years; $p < 0.0001$).

Grading of chronic GvHD (cGvHD) was available for 7,748 (83.3%) patients according to Shulman et al. The 10 year survival probability decreased as follows: limited GvHD (59%; HR 0.768 [0.672, 0.877]), extensive GvHD {40%; HR 1.348 [1.205, 1.507], compared to none GvHD (53%); $p < 0.0001$}.

Except for aGvHD °III-IV, 10-year cumulative incidence rates of relapse always topped those of NRM in the whole analysis. NRM and relapse rates significantly differed for aGvHD (none, °I-II and °III-IV: 15%, 16% and 47%; $p < 0.001$ and 38%, 34% and 20%, $p < 0.001$). Concerning cGvHD, relapse rate decreased as follows: none (37%), limited (31%) and extensive (25%; $p < 0.001$). NRM was 15% for limited and 40% for extensive cGvHD compared to 14% for patients without cGvHD ($p < 0.001$).

Although 6,128 (65,9%) patients were classified according to and to NIH-criteria, only 159 patients were allocated to mild, moderate and severe cGvHD. Therefore description of survival was not reasonably possible.

Figure 1: A) OS, B) NRM and severity of chronic GvHD.



Conclusions: This large retrospective multicenter analysis highlights, that the outcome of YA after HSCT depends on the onset of GvHD. While relapse rate is decreasing with increasing severity of GvHD, only high grade acute and chronic GvHD are associated with higher NRM. Probably the most balanced ratio between a low NRM and a low relapse rate combined with higher probabilities of survival offers low grade GvHD.

Disclosure: IH is vice chairperson of the board of trustees of the German Foundation for Young Adults with Cancer, received research funding from the H.W. and J. Hector-Foundation and honoraria from AbbVie and Novartis. JF received honoraria from Novartis. AH received institutional research support from Novartis, BMS, Pfizer and Incyte. All other authors do not declare any conflicts of interest. The Cooperative German Transplant Study group is acknowledged for project development and support.

12 - Graft-versus-host Disease – Clinical

P216

THE NEWLY DEVELOPED CORE-HCT SCORE INFORMS OUTCOME OF PATIENTS WITH ACUTE GVHD

Gunnar Weise[1], Radwan Massoud[1], Rolf Krause[1], Dietlinde Janson[1], Evgeny Klyuchnikov[1], Christine Wolschke[1], Gaby Zeck[1], Silke Heidenreich[1], Nicolaus Kröger[1], Francis Ayuk[1]

[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Acute graft-verus-host disease (aGVHD) is a key driver of treatment related morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HCT). We have developed and validated a new **C**oncise **O**bjectifiable **R**isk **E**valuation (CORE) score for non-relapse mortality after allogeneic hematopoietic stem cell transplantation. The CORE-HCT score includes 7 pre-transplant factors (serum albumin, serum creatinine, CRP, LVEF, VC, FEV1 and age).

Methods: We developed and internally validated the CORE score in patients who had undergone allo-HCT for malignant diseases between 2013 and 2020 at our center (presented at this meeting: **AS-EBMT-2023-00622**). The CORE-HCT score significantly impacted non-relapse mortality (NRM) and overall survival (OS) in the training (n = 617) and two validation sets (n = 298 and n = 205). We hypothesized, that the CORE-HCT score and aGVHD independently impacted outcome and that patients with high CORE-HCT scores would have even poorer outcomes if they developed severe aGHVD. For this analysis, we identified 1025 patients from the initial cohort who had complete data sets including maximum grade of aGVHD. Univariate analysis for cumulative incidence of NRM at 2 years was performed including all patient characteristics. Factors with $p < 0.1$ were entered into a stepwise multivariate logistic regression model with relapse and NRM as competing risk and adjusted for disease risk.

Results: The CORE-HCT score did not impact the incidence or severity of aGVHD. In univariate analysis for NRM, higher CORE-HCT score, patient age ≥ 59 years (median) and severe aGVHD (grade 3 + 4) were significantly associated with higher NRM. In multivariate analysis higher patient age had borderline significance while higher CORE-HCT score and severe aGVHD maintained significant impact (table 1a). Combination of maximum aGVHD grade and CORE score further distinguished risk groups ranging from remarkably low 2 year NRM of 6.6% for patients with no or only non-severe aGVHD (grades 1 + 2) and low CORE-HCT score, to a very high NRM rate of 67% for patients with severe aGVHD and high CORE-HCT score (figure 1, table 1b).

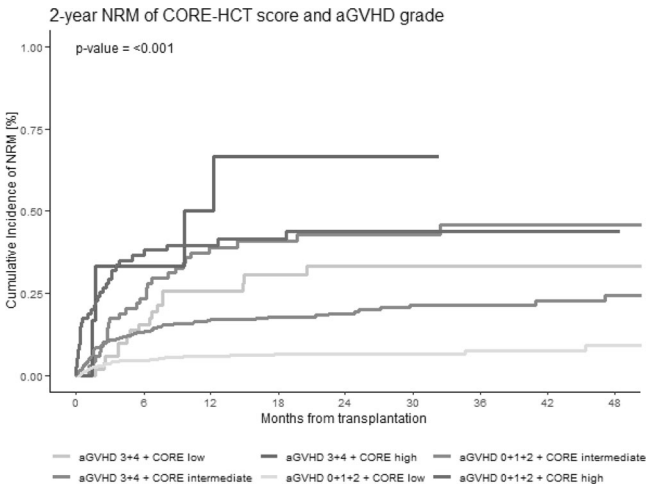
Conclusions: The CORE-HCT score is a concise and objectifiable risk evaluation tool, which may be useful in assessing the risk of death in patients with aGVHD.

Table 1a: Multivariate analysis of risk factors predictive for 2-y-NRM

Factor	HR (95% CI)	p-value
CORE-HCT low risk	reference	
CORE-HCT intermediate risk	2.15 (2-2.3)	<0.001
CORE-HCT high risk	5.47 (5.2-5.7)	<0.001
Patient age ≤59 years	reference	
Patient age >59 years	1.34 (1.2-1.5)	0.071
Grade aGVHD 0 + 1 + 2	reference	
Grade aGVHD 3 + 4	2.68 (2.5-2.8)	<0.001
Adjusted for disease risk		
For N = 1025		

Table 1b: 2-Year NRM rates according to aGVHD grade and CORE-HCT score

Factor		HR (95% CI)	p-value	
	aGVHD 3 + 4		aGVHD 0 + 1 + 2	
CORE-HCT Score	n Patients (%)	2-year NRM (%)	n Patients (%)	2-y-NRM (%)
Low risk	52 (5)	33	367 (36)	6.6
Intermediate risk	69 (7)	43	456 (44)	19
High risk	6 (0.5)	67	75 (7)	44
n = 1025 patients				



Disclosure: The authors have nothing to disclose.

12 - Graft-versus-host Disease – Clinical

P217

POST-TRANSPLANT CYCLOPHOSPHAMIDE (PTCY), ABATACEPT AND VEDOLIZUMAB IN GVHD PROPHYLAXIS IN HEMATOPOIETIC STEM CELLS TRANSPLANTATION FROM MATCHED UNRELATED AND HAPLOIDENTICAL DONORS IN PEDIATRIC ACUTE LEUKEMIA PATIENTS

Larisa Shelikhova[1], M. Perminova[1], O. Molostova[1], A. Abrosimov[1], I. Ilushina[1], M. Dunaykina[1], D. Balashov[1], I. Muzalevsky[1], S. Radygina[1], A. Livshits[1], A. Popov[1], D. Litvinov[1], G. Novichkova[1], A. Maschan[1], M. Maschan[1]

[1]Dmitry Rogachev Federal Research Centre of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: Graft-versus-host disease (GvHD) remains a key factor, which induces significant morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT). High-dose post-transplantation cyclophosphamide (PTCy) targets alloreactive donor T cells proliferating early after HSCT, promotes regulatory T cell and prevents severe GVHD. The effectiveness of PTCy-based regimens varies depending on graft source and intensity of the preparative regimen. Further improvement of GVHD control with novel targeted agents is an important clinical goal.

In this pilot trial we evaluate the safety and effects of abatacept and vedolizumab in unmanipulated haploidentical and matched unrelated transplantation (MUD) among pediatric patients with leukemia.

Methods: A total of 28 pts with acute leukemia (AML- 12, ALL-16, 18 female, 10 male, median age at the moment of HST 8,1 years (0,5-16,8), underwent unmanipulated allogeneic bone marrow (BM) (n = 26) or peripheral blood stem cell (PBSC)(n = 2) transplantation followed by PTCy between March 2022 and September 2022. Twenty-five pts received haploidentical graft, 3

a graft from matched unrelated donor. Disease status at transplant was CR1 in 14 pts, >CR1 in 12 pts and AD in 2 pts. For all patients it was the 1-st transplantation. Thirteen pts received TBI-based myeloablative preparative regimen, 15 treosulfan-based with either cyclophosphamide (n = 20) or thiotepa (n = 1) or vepesid (n = 7) as a second agent. Prophylaxis of graft-versus-host-disease (GVHD) consisted of CsA since day-1, posttransplant Cph on day +3, +4, abatacept on days +7, +14, +28, +45, +60, +90, +120 and vedolizumab on days -1, +14, +28. The median dose of CD34+ cells was 5 x10^6/kg (range 4,3-21), CD3 was 45 x10^6/kg.

Results: Primary engraftment was achieved in all pts, the median time to neutrophil and platelet recovery was 21(15-51) and 23(14-57) days, respectively. All engrafted pts had verified morphologic remission and achieved sustained complete donor chimerism by day +30. Transplant-related mortality was 4 % (95% CI: 0,06-29): one pt with ALL previously receiving inotuzumab ozogamicin, died in CR due to severe VOD on day + 60. The regimen was generally well tolerated.

Cumulative incidence of aGVHD grade II-IV was 31% (95% CI, 16 - 58), grade 3-4 was 7% (95% CI, 2 - 18) there were no cases of cGVHD. In all cases aGVHD was limited skin: grade 2 (n = 5), grade 3(n = 1), grade 4(n = 2). Neither gut nor liver aGvHD was noted. Patients with severe GVHD had a good response to immunosuppressive treatment. EFS and OS at 3,5 months was 96% (95%CI: 87-100). Median time of follow-up for survivors was 123 days (range: 53 –237).

Conclusions: Preliminary data suggest that addition of vedolizumab and abatacept to the PtCy-based GVHD prophylaxis is not associated with increased toxicity and may reduce the incidence of gut GVHD. This approach can be further tested in a prospective trial with the goal to increase the anti-leukemic efficacy of HSCT.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT05515029

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P218

ADVANTAGE OF FIRST-LINE TDM-DRIVEN USE OF INFLIXIMAB FOR TREATING ACUTE INTESTINAL AND LIVER GVHD IN CHILDREN: A PROSPECTIVE, SINGLE-CENTER STUDY

Natalia Maximova[1], Daniela Nisticò[2], Annalisa Marcuzzi[3], Erika Rimondi[3], Guglielmo Riccio[2], Egidio Barbi[2,1], Antonello Di Paolo[4]

[1]Institute for Maternal and Child Health – IRCCS Burlo Garofolo, Trieste, Italy, [2]University of Trieste, Trieste, Italy, [3]University of Ferrara, Ferrara, Italy, [4]University of Pisa, Pisa, Italy

Background: Currently, there is no commonly accepted treatment for patients with steroid-refractory (SR) acute graft-versus-host disease (aGVHD). Inhibition of TNF-α has been suggested in all phases of aGVHD treatment, as prevention, as part of primary treatment, and most commonly as a treatment for steroid-refractory or steroid-dependent aGVHD. The aim of this study was to assess the effectiveness of first-line infliximab treatment compared with infliximab use in second or further-line therapy in pediatric alloHSCT recipients. Further, the study aims to investigate whether the drop in infliximab plasma concentrations could be associated with clinical response and production of proinflammatory and anti-inflammatory cytokines.

Methods: This prospective, single-center, observational study was carried out at the pediatric Bone Marrow Transplant Center of the Institute for Maternal and Child Health – IRCCS Burlo Garofolo, Trieste, Italy, from 2018 to 2022. All patients underwent alloHSCT after myeloablative conditioning. All patients received infliximab biosimilars Inflectra® or Flixabi® at the standard dose of 10 mg/kg/dose intravenously in two hours infusions, on a weekly basis. Infliximab treatment in a second or further-line therapy for SR or steroid-dependent aGVHD was defined as standard infliximab use. Infliximab treatment started together or in the first three days of steroid treatment as part of the first-line treatment, defined as early infliximab use. All patients underwent proactive infliximab TDM with anti-drug antibodies detection. In addition, 27 pro-inflammatory and anti-inflammatory cytokines' blood levels were also measured at baseline and subsequently for every infliximab TDM.

Results: Of 28 patients, fourteen received infliximab for steroid-refractory or steroid-dependent aGVHD (Standard Group), and the remaining used infliximab as part of the first-line therapy (Early Group). Two months after the initiation of treatment, in the Standard Group, organ-specific responses were 14% (n = 1 complete response (CR), n = 1 partial response (PR)), 36% (n = 2 CR, n = 3 PR), and 86% (n = 2 CR, n = 10 PR) for skin, gastrointestinal, and liver involvement, respectively. While in the Early Group, 14 patients (100%) with gastrointestinal and liver aGVHD obtained CR and 2 patients (7%) with skin involvement obtained PR (Figure 1). Skin involvement demonstrated poor response to both early and standard administration. No adverse reactions were observed during infliximab infusions. No bacterial or fungal infections or deaths due to infections have been recorded during the follow-up period. Statistically significant differences between the two groups were found for IL-7, IL-13, MIP-1β, IP-10, MIP-1a, and IL-4 serum levels.

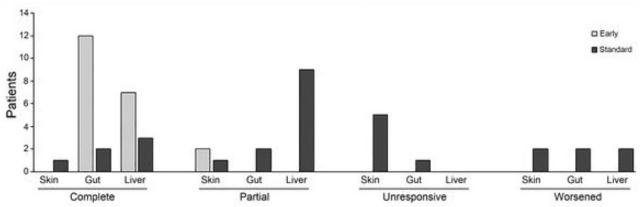


Figure 1. Organ-specific responses after two months of treatment

Figure 1. Organ-specific responses after two months of treatment

Conclusions: To the best of our knowledge, our study is the only one focusing on using infliximab as the first-line TDM-driven therapy for treating aGVHD in children. Our data suggest that the response to infliximab is organ related. The earlier the administration of infliximab, the better the clinical outcome achieved in children with intestinal and liver aGVHD. Future multi-center randomized controlled trials may verify our preliminary observation in using infliximab as part of the primary treatment for intestinal and liver aGVHD.

Clinical Trial Registry: Clinicaltrials.gov code: NCT05362630

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P219

ALPHA-1-ANTITRYPSIN EXPERIENCE FOR STEROID-RESISTANT ACUTE GRAFT-VERSUS-HOST DISEASE

Derya Koyun[1], Güldane Cengiz Seval[1], Sinem Civriz Bozdağ[1], Selami Koçak Toprak[1], Pervin Topçuoğlu[1], Muhit Özcan[1], Önder Arslan[1], Taner Demirer[1], Günhan Gürman[1], Meral Beksaç[1], Osman Ilhan[1], Meltem Kurt Yüksel[1]

[1]Ankara University School of Medicine, Ankara, Turkey

Background: Steroid-refractory acute graft-versus-host disease (SR-aGVHD) treatment has a low response rate and a high risk of infection in allogeneic hematopoietic stem cell transplantation. The standard approach to be applied in this situation is uncertain. This study aims to evaluate the effectiveness and safety of alpha-1-antitrypsin (AAT).

Methods: Between January and November 2020, five patients with SR-aGVHD at our center received off-label AAT were retrospectively evaluated. All patients were treated with 2 mg/kg/day methylprednisolone as frontline therapy. SR-aGVHD was defined as progression after >3 days of ≥1 mg/kg/day of methylprednisolone or no improvement after at least seven days of treatment. Biopsy was taken from all patients for histopathological evidence of aGVHD. Acute GVHD grading was according to the Glucksberg criteria. Patients received AAT intravenously at a dose of 60 mg/kg per day, maximum eight doses on days 1, 4, 8, 12, 16, 20, 24, 28. AAT serum levels were monitored at the time of initiation and before each dose of the treatment. Response to AAT was defined by the following standard criteria at 28 day response.

Results: After demonstrating SR-aGVHD, all patients except one recieved at least one or more line therapy before AAT administration. The median interval between aGVHD diagnosis to AAT initiation was 24 days (range, 6-43 days). All but one patients presented with grade IV SR-aGVHD. The overall response rate was 80%, including 40% with complete response and 40% with partial response. A sustained CR was observed in two patients without adding more lines of immunosuppression. One GI aGVHD patient with PR achieved CR with extracorporeal photopheresis after completing up to a maximum of eight AAT infusions. AAT administration was well tolerated, with no drug-related toxicity or infusion reactions. The most frequent infection was cytomegalovirus reactivation (viremia) and occurred in all patients. Mean serum AAT level of all patients was 1.31 gr/dl before AAT treatment initiation. However, during the treatment follow-up serum, AAT levels were in an upward trend (1.31 to 2.17 gr/dl $p = 0.006$) with stabile serum albumin levels (26.6 to 27.6 gr/dl $p = 0.48$). AAT level did not exceed upper limit in non-response patient and non-applicable in one patient due to lack of available kit.

Conclusions: On the basis of our limited experiences, AAT is an effective and well-tolerated treatment for patients with severe SR-aGVHD.

Disclosure: All authors have no conflinct of interest.

12 - Graft-versus-host Disease – Clinical

P220

MASS CYTOMETRIC IMMUNE CELL PROFILING AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLO-HSCT) IN AML IDENTIFIED AGVHD-SPECIFIC PROFILES

Pål Tore Bentsen[1,2], Reidun Kristin Kopperud[2], Luisa Bach[3], Stein-Erik Gullaksen[2], Jørn Skavland[2], Hallvard Haugen[2], Peter Brossart[3], Dominik Wolf[4], Sonia Gavasso[1], Bjørn Tore Gjertsen[1,2], Tobias A. W. Holderried[3]

[1]Haukeland University Hospital, Bergen, Norway, [2]University of Bergen, Bergen, Norway, [3]University Hospital Bonn, Bonn, Germany, [4]Medical University of Innsbruck, Innsbruck, Austria

Background: The aim of this multicenter project is to characterize single cell phenotypic and functional states in peripheral blood from patients undergoing allogeneic HSCT (allo-HSCT) at high resolution, with an emphasis on acute graft-versus-host disease (aGvHD) and corticosteroid treatment responses.

Methods: For initial explorative analysis, a pilot set of $n = 9$ samples from $n = 6$ patients with acute myeloid leukemia (AML) at days 30 and 60 after allo-HSCT was selected for mass cytometric analysis. $N = 4$ samples were from patients with active aGvHD, while $n = 5$ samples were from patients without active aGvHD. Samples were fixed and barcoded to be collectively stained with a panel of metal-conjugated antibodies against 28 cell surface markers, before acquisition on a Helios mass cytometer (Fluidigm). Intracellular staining was also done. Raw data were normalized and debarcoded, before initial analysis in Cytobank®, where single cell events were identified and chosen for downstream analysis. Resulting FCS-files were then read into R and subjected to explorative clustering, dimensionality reduction and abundance analysis.

Results: Each patient sample produced between 322818 and 466888 single cell events. Using FlowSOM unsupervised clustering and ConsensusClusterPlus metaclustering, major peripheral blood leukocyte populations could be readily identified. Of these, mature neutrophil granulocytes constituted the largest metacluster, making up nearly 50% of cells. In most of the patients with aGvHD, granulocytes with a more immature phenotype, expressing lower levels of CD11b and CD16, were more predominant than in patients without aGvHD. There was also an apparent reduction in the abundance of eosinophils and of NK cells in the aGvHD patients. UMAP dimensionality reduction confirmed the impression of a shift in the granulocyte compartment as well as for NK cells in patients with aGvHD, and also indicated an altered T cell compartment in aGvHD.

Conclusions: Multiparameter phenotyping with mass cytometry indicates distinct leukocyte population shifts in patients with aGvHD after allo-HSCT, with notable shifts in neutrophils, eosinophils and NK cell compartments in our pilot trial preceding our larger multicenter trial. This data will be further explored in larger patient cohorts including several hematologic malignancies, and serves as a basis for expanding and refining our experimental platform for single cell analysis, including intracellular signaling analysis as well as scRNAseq analyses, hopefully fueling biomarker discovery and development of targeted treatment approaches for aGvHD upon allo-HSCT.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P221

PREVALENCE AND FACTORS ASSOCIATED WITH METABOLIC SYNDROME IN PATIENTS WITH CHRONIC GRAFT-VERSUS-HOST DISEASE

Aaron Zhao[1], Filip Pirsl[1], Seth Steinberg[1], Noa Holtzman[1], Eduard Schulz[1], Alain Mina[1], Jacqueline Mays[2], Edward Cowen[3], Leora Comis[4], Galen Joe[4], Jack Yanovski[5], Steven Pavletic[1]

[1]National Cancer Institute, Bethesda, United States, [2]National Institute of Dental and Craniofacial Research, Bethesda, United States, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, United States, [4]National Institutes of Health Clinical Center, Bethesda, United States, [5]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, United States

Background: Metabolic syndrome (MetS) is a group of risk factors highly associated with the development of cardiovascular disease and type 2 diabetes mellitus. Although people with chronic graft-versus-host disease (cGVHD) are at a heightened risk for components of MetS, the prevalence and impact of MetS in the chronic graft-versus-host disease (cGVHD) patient population remain unknown.

Methods: Patients ($n = 229$) with moderate to severe cGVHD enrolled in the cross-sectional NIH cGVHD Natural History Study (NCT00092235) were evaluated for MetS based on the National Cholesterol Education Program's ATPIII classification criteria at enrollment. Components of the criteria include abdominal obesity, elevated blood pressure, elevated plasma glucose, high triglyceride levels, and low HDL levels; possessing ≥3 of these 5 components results in a positive diagnosis of MetS [Grundy et al., Circulation. 2005;112(17):e297]. Patient characteristics, cGVHD measures, and laboratory markers were assessed for association with MetS in univariate and multivariable analyses. Non-relapse mortality (NRM) and overall survival (OS) were calculated and compared by MetS status. MetS was evaluated for association with OS adjusted for previously identified prognostic factors using Cox regression, including severe lung cGVHD, Karnofsky Performance Status (KPS), and absolute eosinophil count.

Results: Approximately half of patients (54.1%, 124/229) in this cGVHD cohort met the diagnostic criteria for MetS. No significant difference in overall or organ-specific severity of cGVHD between patients with and without MetS was observed. Patients with higher BMI and lower KPS scores were more likely to have MetS ($P < 0.0001$; $P = 0.026$; respectively). In univariate analysis, two markers of inflammation, higher erythrocyte sedimentation rate (ESR) and complement component 3 (C3) levels, in addition to two markers of kidney function, lower eGFR and higher creatinine levels, were statistically associated with MetS ($P \leq 0.05$). Multivariable analysis established greater BMI (OR: 1.35; 95% CI: 1.23-1.49), greater ESR (OR: 1.02; 95% CI: 1.01-1.03), and lower KPS (OR: 0.96; 95% CI: 0.93-0.99) as factors independently associated with MetS. With a median potential follow-up of 12.1 years (IQR: 8.7-14.6), only a weak trend towards inferior OS in patients with MetS compared to patients without MetS was seen (median: 15.2 years vs. not reached; respectively; $P = 0.20$). Moreover, NRM only somewhat differed between patients with and without MetS (5-year NRM: 21.7% vs. 10.1%; respectively; $P = 0.12$). Cox proportional hazards modeling also demonstrated that MetS was not strongly associated with OS following adjustment for factors previously identified in this patient population (HR = 1.33; 95% CI: 0.88-1.99; $P = 0.17$).

Conclusions: Patients with moderate to severe cGVHD were found to have a higher prevalence of MetS (~ 54%) than the general adult population (30-40%). Although no relationship with prednisone dose was established in this analysis, chronic exposure to cGVHD medications, such as systemic steroids and calcineurin inhibitors, which have adverse effects including impaired glucose and lipid metabolism as well as renal toxicity and hypertension, may have contributed to the relatively higher prevalence of MetS. MetS places an increased burden on patients and health systems. This, coupled with its high prevalence, underscore the need to mitigate the occurrence and impact of MetS in the cGVHD patient population.

Clinical Trial Registry: NCT00092235 (www.clinicaltrials.gov)

Disclosure: The authors declare no competing interest. This research was supported [in part] by the Intramural Research Program of the NIH.

12 - Graft-versus-host Disease – Clinical

P222

TRIPLE-DRUG GVHD PROPHYLAXIS AFTER HLA-MATCHED NON-MYELOABLATIVE ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Alma Wegener[1], Niels Smedegaard Andersen[1], Lone Smidstrup Friis[1], Søren Lykke Petersen[1], Ida Schjødt[1], Brian Kornblit[1], Henrik Sengeløv[1], Lars Klingen Gjærde[1]

Rigshospitalet, Eastern Copenhagen, Denmark

Background: A randomized clinical trial found that addition of sirolimus to standard graft-versus-host disease (GVHD) prophylaxis (ciclosporin and mycophenolate mofetil (MMF)) reduced grade II-IV acute GVHD after non-myeloablative (NMA) allogenic hematopoietic stem cell transplantation (HSCT) with an HLA-matched unrelated donor. Here, we present real-world data after implementing ciclosporin, MMF and sirolimus as the standard GVHD prophylaxis in consecutive patients undergoing NMA HSCT with an HLA-matched unrelated donor at our institution.

Methods: We studied all patients (≥18 years old) who underwent NMA HSCT with an HLA-matched unrelated donor at Rigshospitalet, Denmark from 2018-2021 receiving GVHD prophylaxis with ciclosporin, MMF and sirolimus (triple-drug group). For comparison, a historical cohort (transplanted 2014-2017) who received tacrolimus and MMF as GVHD prophylaxis after NMA HSCT with HLA-matched unrelated donors was used (control group). Data were extracted from a local register. Outcomes were grade II-IV and grade III-IV acute GVHD, chronic GVHD, relapse, overall survival (OS) and non-relapse mortality (NRM).

Results: 264 patients were included (triple-drug group, n = 137; control group, n = 127). Median age in the triple-drug group was 66 years (lower quartile to upper quartile [Q1-Q3], 58 to 69 years) and 63 years (Q1-Q3, 57 to 68 years) in the control group. Myelodysplastic syndrome and acute myeloid leukemia were the most frequent indications for HSCT in both groups (triple-drug group: 38% and 33%; control group: 35% and 36%, respectively). The cumulative incidence at day +110 of grade II-IV and grade III-IV acute GVHD in the triple-drug group vs. the control group was 17% (95% confidence interval [CI] 11-23%) vs. 29% (95% CI 21-37%) (Gray's test p = 0.02) and 3% (95% CI 0-6%) vs. 5% (95% CI 1-8%) (Gray's test p = 0.4), respectively. In a Cox regression model adjusted for age, donor age and female-donor-to-male-recipient, the risk of grade II-IV acute GVHD was lower in the triple-drug group compared to the control group (HR 0.51, 95% CI 0.30-0.86, p = 0.01). 2-year OS was 77% (95% CI 70-84%) in the triple-drug group and 69% (95% CI 61-77%) in the control group (p = 0.04) and this difference remained significant after adjustment for age and Karnofsky score (HR 0.65, 95% CI 0.42-0.99, p = 0.04). The 2-year cumulative incidence of chronic GVHD, relapse and NRM were 72% (95% CI 62-83%), 21% (95% CI 13-28%) and 12% (95% CI 6-17%) in the triple-drug group and 75% (95% CI 66-84%), 27% (95% CI 19-35%) and 14% (95% CI 8-20%) in the control group, respectively. In multivariable analyses, we found no support for a difference in the risk of chronic GVHD (HR 0.91, 95% CI 0.66-1.26, p = 0.57), relapse (HR 0.70, 95% CI 0.42-1.15, p = 0.16) or NRM (HR 0.56, 95% CI 0.31-1.05, p = 0.07).

Conclusions: After changing the standard GVHD prophylaxis in patients undergoing NMA HSCT with an HLA-matched unrelated donor from tacrolimus and MMF to ciclosporin, MMF and sirolimus, we observed a reduction in the incidence of grade II-IV acute GVHD and an improved 2-year OS.

Disclosure: The authors have nothing to disclose.

12 - Graft-versus-host Disease – Clinical

P223

NOVEL MACHINE LEARNING TECHNIQUES IMPROVE THE ACCURACY OF DEMOGRAPHIC DATA-DERIVED ALGORITHMS PREDICTING ACUTE GVHD AFTER REDUCED-INTENSITY ALLOGENEIC HSCT

304

Vaish Balaji[1], Iosif Mporas[2], Fatema Mustansir Dawoodbhoy[1], Emma White[3], Delordson Kallon[3], James Aries[4], Jamie Cavenagh[4], John Gribben[5,4], Sola Adeleke[1], Jeff Davies[5,4]

[1]Curenetics Ltd, London, United Kingdom, [2]Comms and Intelligent Systems, University of Hertfordshire, Hatfield, United Kingdom, [3]Clinical Transplantation Laboratory, Barts Health NHS Trust, London, United Kingdom, [4]Haemato-Oncology, Barts Health NHS Trust, London, United Kingdom, [5]Barts Cancer Institute, Queen Mary University London, London, United Kingdom

Background: Acute graft-versus-host disease (GvHD) is a major barrier in allogeneic hematopoietic stem-cell transplantation (HSCT). Better tools to accurately predict acute GvHD could facilitate personalized strategies to improve patient outcomes. Recently, machine learning (ML) approaches utilizing donor and recipient demographic information have proved superior to parametric methodologies for predicting acute GvHD, but only achieve moderate accuracy and have not included late-onset acute GvHD that often occurs after reduced-intensity conditioning platforms that are now widely adopted. We therefore applied a novel ML pipeline to demographic data to optimize prediction models of acute GvHD after reduced-intensity allogeneic HSCT.

Methods: We scrutinized routinely available donor and recipient demographic data and clinical outcomes from a cohort of 453 patients who underwent reduced-intensity allogeneic HSCT for haematologic malignancies at our centre between 1998 and 2020. All patients received peripheral blood stem-cells from HLA-A-, B-, C- and DR-matched related or unrelated donors after uniform fludarabine-based reduced-intensity conditioning without T-cell depletion or serotherapy. Data was cleaned and pre-processed using DataWing for imputation of missing values. A bespoke artificial intelligence architecture developed by Curenetics was used to find patterns within pre-transplant demographic variables which identified patients who developed acute GvHD. Synthetic Minority Oversampling Technique (SMOTE) was implemented to address class imbalance. Various ML algorithms including logistic regression with LASSO, Perceptron, Decision Tree, XGBoost and Random Forest classifiers were used in an 80:20-weighted training and internal validation pipeline with Recursive Feature Elimination Cross Validation and hyperparameter optimization to identify the best performing models.

Results: The cumulative incidence of clinically significant classical and/or late onset acute GvHD (consensus criteria Grades 2-4) at day 180 in our cohort was 48%. The accuracy of models predicting acute GvHD in our internal validation dataset ranged between 0.65-0.71 without SMOTE or imputation, superior to Cox proportional hazards models and similar to ML models in prior published studies using demographic data from larger registry-based cohorts. The addition of SMOTE to our ML pipeline improved the accuracy of models generated from our cohort to 0.67-0.72. The addition of both SMOTE and imputation resulted in a further increase in model accuracy. The best performing model using this pipeline was generated with the Random Forest Classifier with accuracy of 0.85 resulting in sensitivity, specificity, positive and negative predictive values of 98%, 88%, 87% and 97% respectively. Using recursive selection techniques, 47 donor and/or recipient features were utilized in this model to obtain the highest cross-validation scores. Features allocated the highest predictive importance in this model included HLA-DQ- and DP-matching, donor age and recipient pre-transplant remission status. Finally, our optimized model maintained very high acute GvHD prediction accuracy when validated using a publicly available external dataset of 324 patients undergoing allogeneic HSCT with more heterogeneous stem-cell sources and conditioning regimens.

Conclusions: Our use of innovative ML techniques significantly improves the accuracy of models using demographic data to predict classical and late-onset acute GvHD after reduced-intensity allogeneic HSCT. These highly accurate models could be used to inform donor selection and underpin risk-based personalized immunosuppression strategies to improve outcomes for patients.

Disclosure: **Funding:** This study is enabled by Collaborate to Innovate: London Diagnostics, a programme managed by MedCity, the life sciences cluster organisation for London, with funding from the London Economic Action Partnership (LEAP) which is supported by the Mayor of London. The study was also received funding from Queen Mary, University of London.

Disclosures: Gribben: *Novartis:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria, Research Funding; *Morphosys AG:* Consultancy; *Gilead Sciences:* Consultancy, Honoraria; *Bristol Myers Squibb:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria; *European Hematological Association:* Membership on an entity's Board of Directors or advisory committees. Davies: *Priothera* Consultancy.

12 - Graft-versus-host Disease – Clinical

P224

RUXOLITINIB FOR TREATMENT OF ACUTE GRAFT-VERSUS-HOST DISEASE: A RETROSPECTIVE SINGLE CENTER ANALYSIS

Alexander Denk[1], Daniela Weber[1], Ernst Holler[1], Elisabeth Meedt[1], Matthias Fante[1], Cornelia Mittermaier[1], Hendrik Poeck[1,2], Wolfgang Herr[1], Matthias Edinger[1,2], Daniel Wolff[1]

[1]University Hospital Regensburg, Regensburg, Germany, [2]Leibniz Institute for Immunotherapy (LIT), Regensburg, Germany

Background: Acute graft-versus-host disease (aGvHD) represents a major complication after allogeneic hematopoietic stem cell transplantation. A considerable proportion of patients lack response to 1st line corticosteroid treatment. We conducted a monocenter study to investigate the efficacy and safety of the selective Janus kinase inhibitor ruxolitinib in treatment of steroid-refractory aGvHD.

Methods: All patients (n = 49) receiving treatment with ruxolitinib for aGvHD between 03/2016 and 08/2022 at the University Hospital Regensburg were included in the retrospective analysis. Diagnosis, organ involvement, and severity of aGvHD were assessed as part of clinical routine using criteria of Glucksberg and Thomas. Clinical response was evaluated after 1 week, 1 month, 3 months and 6 months after start of ruxolitinib therapy. To assess infectious complications and hematological toxicities, we used the common terminology criteria for adverse events version 5.0 (CTCAE 5.0).

Results: We identified 49 patients (male n = 29, female n = 20, median age 55 years) treated with ruxolitinib for aGvHD. Onset of aGvHD was at median day 20 (range 16-31). At start of ruxolitinib, aGvHD was grade I in 16%, II in 47% and ≥III in 37% with maximum severity before initiation of ruxolitinib being grade I + II in 45% and ≥III in 55% of the patients. Gut was the dominating manifestation of aGvHD (61%), followed by skin (37%) and liver (2%). Ruxolitinib was administered mainly as second treatment line (range 2nd-3rd). Steroid dependent aGvHD was present in 15 patients (31%) while 34 patients (69%) had steroid refractory aGvHD.

Overall response rate (ORR) and failure free survival (FFS, defined as absence of relapse or non-relapse mortality and no addition of further ISM) after one month was 64% and 74%, respectively. After 3 months, ORR was 53% and FFS was 56%. After

6 months, ORR was 42% and FFS 46%. Overall survival (OS) after 1 month, 3 months and 6 months was 92%, 88% and 82%, respectively. During follow-up 3 patients (6%) suffered from relapse of hematologic malignancy, 2 additional patients relapsed 7 and 12 months after stop of ruxolitinib and 7 patients (14%) died due to treatment related mortality. At start of ruxolitinib, 40 patients (82%) displayed thrombocytopenia, including 21 patients (43%) with thrombocytopenia grade ≥ III. 7 Patients (14%) had neutropenia, including 4 patients (8%) with neutropenia grade ≥ III. Within one month after onset of therapy, all but one patients (98%) demonstrated thrombocytopenia and 12 patients (24%) neutropenia. Of those, 30 patients (61%) showed thrombocytopenia grade ≥ III and 5 (10%) patients neutropenia grade ≥ III, respectively. In addition, 17 patients (35%) suffered from an infection within the first month after onset including 9 patients (18%) with an infection grade ≥ III.

Conclusions: In our cohort, ORR and FFS after one month of ruxolitinib therapy were comparable with results from the REACH-2 trial. The most frequent side effect were thrombocytopenia and infections, while neutropenia did not significantly increase after start of treatment. In conclusion, ruxolitinib is an important treatment option for patients with steroid-refractory aGvHD with thrombocytopenia and infectious complications representing the most frequent side effects.

Disclosure: D Wolff has received honoraria and research support from Novartis. All other authors declare no conflicts of interest.

12 - Graft-versus-host Disease – Clinical

P225

EFFICACY OF POSTTRANSPLANT CYCLOPHOSPHAMIDE FOR CHRONIC GRAFT-VERSUS-HOST DISEASE IN HLA-MISMATCHED TRANSPLANTS: A SINGLE-CENTER EXPERIENCE DURING 10 YEARS

Valle Gomez Garcia de Soria[1,2,3], Paula Díaz-Fernández[4,2,3], Ana María Marcos-Jiménez[4,2], Samantha Feijóo[1,2], Nuria Montes Casado[2], Isabel Iturrate Basaran[1,2], Itxaso Portero-Sainz[4,2], Beatriz Aguado Bueno[1,2], Angela Figuera Alvarez[1,2,3], Rafael de la Cámara[1,2], Cecilia Muñoz-Calleja[4,2,3]

Hospital Universitario de la Princesa, Madrid, Spain, [2]Instituto de Investigación Sanitaria Princesa, Madrid, Spain, [3]Universidad Autónoma de Madrid, Madrid, Spain, Hospital Universitario de la Princesa, Madrid, Spain

Background: Graft-versus-host disease (GvHD) continues being one of the main causes of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (alloHSCT), despite significant advances in supportive care. Prophylaxis schemes with posttransplant cyclophosphamide (PTCy) seem to offer an attractive alternative to traditional calcineurin inhibitors-based prophylaxis to reduce severe forms of acute (aGvHD) and chronic (aGvHD) in HLA-mismatched settings.

Aim: To evaluate the incidence and severity of aGvHD and cGvHD, in patients undergoing alloHSCT with different type of donors using three GvHD prophylaxis regimens, focusing on the effect of PTCy.

Methods: This is a single-institution observational study on 275 consecutive alloHSCT patients (Table 1) between January 2011 and March 2022, median follow-up of 2.5 years. Patients received grafts from either HLA-matched sibling (MSD) (n = 106), 10/10 matched unrelated (MUD) (n = 89), 9/10 mismatched unrelated (mMUD) (n = 47), or haploidentical (n = 33) donors. As GvHD prophylaxis, MSD and MUD received cyclosporine A plus methotrexate (CsA/MTX), mMUD received CsA/MTX plus Thymoglobulin (THY) (n = 30), or CsA/Mycophenolate mofetil (MMF) plus PTCy (n = 17). All haploidentical HSCTs received PTCy/CsA/MMF. GvHD and their degrees were based on EBMT criteria. aGvHD patients were classified as "No aGvHD" (No aGvHD plus grade I), global aGVHD (grade II-IV) or severe aGvHD (grades III-IV). Categories of cGvHD were defined as "No cGvHD", mild and moderate/severe.

	Matched Sibling Donor (MSD)	Matched Unrelated Donor (MUD)	Mismatched Unrelated Donor (mMUD) PTCy	Mismatched Unrelated Donor (mMUD) Thymo	Haploidentical	p-value
	(N = 106)	(N = 89)	(N = 17)	(N = 30)	(N = 33)	
Patient's gender [N (%)]						0.6920
Male	61 (57.6%)	50 (56.2%)	7 (41.2%)	17 (56.7%)	16 (48.5%)	
Female	45 (42.5%)	39 (43.8%)	10 (58.8%)	13 (43.3%)	17 (51.5%)	
Age						0.2332
median (range)	51.5 (19-72)	47 (19-71)	51 (19-65)	48 (18-67)	56 (20-70)	
Donor's gender [N (%)]						0.1814
Male	58 (54.7%)	60 (67.4%)	11 (64.7%)	16 (53.3%)	15 (45.5%)	
Female	48 (45.3%)	29 (32.6%)	6 (35.3%)	13 (43.3%)	18 (54.5%)	
Conditioning regimen [N (%)]						<0.0001
Myeloablative (MAC)	68 (64.2%)	58 (65.2%)	2 (11.8%)	19 (63.3%)	6 (18.2%)	
Non Myeloablative (RIC)	36 (34%)	31 (34.8%)	15 (88.2%)	11 (36.7%)	26 (78.8%)	
Graft Source [N (%)]						0.8462
Peripheral Blood	100 (94.3%)	83 (93.3%)	17 (100%)	29 (96.7%)	32 (97%)	
Bone marrow	5 (4.7%)	5 (5.6%)	0 (0%)	1 (3.3%)	1 (3%)	
Cells infused [mean (SD)]						
CD3 infused (106/Kg)	234.62 (98.63)	222.28 (127.1)	238.15 (107.85)	244.33 (103.73)	278.98 (173.31)	0.0003
CD34 infused (10^6/Kg)	5.13 (1.26)	5.30 (1.27)	5.49 (0.99)	5.52 (1.13)	5.72 (1.12)	<0.0001

Results: The incidence of aGvHD was similar in the 5 transplant groups, either as a whole or when divided into degrees. Nevertheless, a tendency to a higher incidence of aGvHD was observed in MUD patients, either 10/10 or 9/10. Conversely, significant differences were found for the incidence of cGvHD, with MUD showing the highest incidence of moderate/severe cGvHD (46%), followed by mMUD treated with THY and MSD (both 27%). Interestingly, no patients treated with PTCy, either mMUD or haploidentical, developed moderate/severe cGvHD. We therefore established MUD as the reference category to compare the risk of developing cGvHD among other settings. Selected variables which could influence the development of cGvHD included age, donor/receptor gender, conditioning regimen, number of infused CD34+ and CD3+ cells. Donor and recipient gender disparities was the only variable affecting the development of moderate/severe cGvHD and was included in the logistic regression model. Multivariant analysis revealed that the risk of developing global cGvHD were reduced in the mismatched settings, including mMUD-PTCy, mMUD-Thymo and haploidentical. When degrees of cGvHD were considered, compared with MUD, an important protective role of PTCy was observed with an OR = 0.1987 (p = 0.004) for mMUD-PTCy and OR = 0.076 (p = 0.000) for haploidentical transplants. Similarly, both MSD and mMUD-THY protects from moderate/severe cGvHD when compared with MUD (OR = 0.4936432 [p = 0.013] and OR = 0.3409 [p = 0.029]), respectively. Conversely, survival at five years did not differ among the different types of transplants (p = 0.124).

Conclusions: Despite the low number of patients in some transplant settings, our analysis shows that in MSD and MUD with CsA/MTX the incidence of moderate/severe cGvHD is higher than in mMUD or haploidentical with PTCy. The change in GvHD prophylaxis for MSD and MUD to PTCy could reduce the severe forms of cGvHD in these patients.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P226

GVHD ASSESSMENT IN PHASE 1 STUDY OF BRIQUILIMAB (JSP191), LOW DOSE IRRADIATION AND FLUDARABINE CONDITIONING IN OLDER ADULTS WITH MDS/AML UNDERGOING ALLOGENEIC HCT

Minyoung Youn[1], Lori Muffly[2], Andrew Artz[3], Catherine Lee[4], Arpita Gandhi[5], Ankur Varma[6], Bart Scott[7], Chikako Yanagiba[1], Rajiv Tiwari[1], Jeyakavitha Arulprakasam[1], Anne Le[1], Judith Shizuru[2], Hye-Sook Kwon[1], Wendy Pang[1]

[1]Jasper Therapeutics, Redwood City, United States, [2]Stanford University School of Medicine, Palo Alto, United States, [3]City of Hope National Medical Center, Duarte, United States, [4]University of Utah / Huntsman Cancer Institute, Salt Lake City, United States, [5]Oregon Health Sciences University, Portland, United States, [6]Rush University Medical Center / Division of Hematology, Oncology and Cellular Therapy, Chicago, United States, [7]Fred Hutchinson Cancer Research Center, Seattle, United States

Background: A phase 1 study (NCT#04429191) is currently evaluating the safety/activity of briquilimab (JSP191), an anti-CD117 monoclonal antibody, in combination with low dose total body irradiation (TBI) and fludarabine (Flu) as conditioning in older adults with AML/MDS undergoing HCT. GVHD prophylaxis was tacrolimus, sirolimus, and mycophenolate mofetil (MMF), which when given with Flu/TBI has previously resulted in grade 2-4 acute GVHD (aGVHD) of 26% by transplant day (TD) + 100 and chronic GVHD (cGVHD) of 49% (Sandmaier et al, 2019). Our objective was exploratory analyses of lymphocyte and cytokine changes that may correlate with GVHD in briquilimab/Flu/TBI for HCT.

Methods: 29 subjects (62-79 yrs) with AML in CR or MDS received 0.6 mg/kg briquilimab IV. Briquilimab serum levels determined timing of Flu (30 mg/m /day on TD-4, -3, -2), TBI 2-3 Gy (TD0), and infusion of HLA-matched related or unrelated mobilized peripheral blood (PB) (TD0; 10-14 days after JSP191). Sirolimus and tacrolimus started TD-3 and were tapered by TD + 180; MMF tapered by TD + 39. Follow up ranged from TD + 180 to TD + 360 post-HCT; 23 subjects had >TD + 180 follow up. aGVHD and cGVHD grading were based on MAGIC and NIH Consensus Criteria, respectively. T helper (Th) cell subsets in peripheral blood and cytokine profiles in bone marrow plasma were analyzed by flow cytometry and Luminex bead array.

Results: Four of 29 subjects had grade (gr) 2 aGVHD; two at TD + 90 and two subjects with late onset gr2-3 aGVHD (Table). One of gr2 aGVHD subjects developed mild cGVHD. Six had mild and four had moderate cGVHD. No severe cGVHD was observed. Nine of 10 subjects with cGVHD received unrelated grafts (Table). CD34+ and CD3+ cell doses were similar among subjects. TD + 180 donor T cell chimerism was not different between evaluable subjects regardless of GVHD (Table 1). Multiplex cytokine assays showed a trend in decreased IL-6 level in subjects without GVHD. Subjects with gr1 or gr2-4 aGVHD showed an increase trend in IL-6 level at the time of diagnosis, consistent with the previous findings of increased IL-6 level in serum of aGVHD patients. To evaluate immune repertoire associated with GVHD, Th cells from available adequate PB samples were analyzed. While the absolute numbers of regulatory T (Treg) cells (CD3 + CD4 + CD25+CD127low) were constantly increased up to TD + 360 in subjects without cGVHD, no increase of Treg cells was observed in subjects with cGVHD at TD + 360, suggesting that higher level of Treg after tapering of GVHD prophylaxis may prevent cGVHD development.

Total (= 29) aGVHD and then cGVHD (n = 1)	no GVHD (n = 16)	aGVHD gr2-4 (n = 4)	cGVHD mild (n = 6)	cGVHD moderate (n = 4)
Age (years)	69.5 ± 4.3	69.3 ± 4.1	71.8 ± 3.3	71.3 ± 6.4
Gender				
Female	6 (37.5%)	1 (25%)	1 (16.7%)	2 (50%)
Male	10 (62.5%)	3 (75%)	5 (83.3%)	2 (50%)
Donor Type				
related	5 (31.2%)	1 (25%)	1 (16.7%)	0 (0%)
unrelated	11 (68.8%)	3 (75%)	5 (83.3%)	4 (100%)
Peripheral blood stem cell dose				
Total cells x 10^8/kg	537.3 ± 489.4	359.4 ± 497.7	186.8 ± 149.5	525.5 ± 615.0
CD34+ cells x 10^6/kg	6.0 ± 2.4	6.5 ± 1.3	6.4 ± 2.3	8.6 ± 1.7
CD3+ cells x 10^8/kg	2.5 ± 1.1	2.2 ± 0.8	1.9 ± 1.5	2.6 ± 1.5
Blood CD3 T cell chimerism at TD + 180 (%, evaluable subjects)	78.0 ± 16.1 (n = 10)	87.0 ± 17.4 (n = 4)	84.5 ± 14.7 (n = 6)	92.7 ± 7.5 (n = 4)

Conclusions: To date, cumulative incidences of gr2-4 aGVHD and cGHVD are 13.8% and 34.5%, respectively. Addition of briquilimab to Flu/TBI does not appear to increase GVHD compared to previously published rates. Increased levels of IL-6 in subjects with aGVHD and decreased number of Treg population in subjects with cGVHD suggest their utility as diagnostic biomarkers for GVHD.

Clinical Trial Registry: NCT#04429191, https://clinicaltrials.gov/ct2/show/NCT04429191

Disclosure: M Youn, C Yanagiba, R Tiwari, K Arulprakasam, A Le, H-S Kwon, W Pang are current employees of Jasper Therapeutics and current holders of *stock options* in a publicly-held company. J Shizuru is a co-founder and board member of Jasper Therapeutics. C Lee receives Research Funding from Incyte and serves in Consulting, Advisory Board, Clinical Trial Steering Committee for Incyte and Advisory Board and consulting for Sanofi, and Speaker's Board and Advisory Board for Kite, Advisory Board for Bristol Myers Squibb, and Consulting for Fresenius Kabi. A Gandhi

serves on Advisory Board for Gamida Cell & Talaris Therapeutics. A Artz consults for Abbvie and Magenta.

12 - Graft-versus-host Disease – Clinical

P227

POST-TRANSPLANTATION CYCLOPHOSPHAMIDE, TACROLIMUS AND LOW-DOSE POST-ENGRAFTMENT ANTI-THYMOGLOBULIN AS GVHD PROPHYLAXIS FOR PATIENTS UNDERGOING PERIPHERAL BLOOD STEM CELL TRANSPLANTATION FROM HAPLO DONORS: A SINGLE CENTER ANALYSIS

Wenhui Gao[1], Ming Chen[1], Lining Wang[1], Ling Wang[1], Raynier Devillier[2], Jieling Jiang[1], Didier Blaise[2], Jiong Hu[1]

[1]Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, Program of Transplantation and Cell Therapy, Program of Leukemia, Centre de Recherche en Cancérologie de Marseille (CRCM), Institut Paoli-Calmettes, Aix Marseille University, Marseille, France

Background: Post-transplantation cyclophosphamide (PT-Cy) use is a recent graft-versus-host disease (GVHD) prophylaxis strategy for patients undergoing allogeneic stem cell transplantation (allo-HSCT). PT-Cy combined with two immunosuppressants is now widely used after haplo-identical (haplo) and HLA-matched peripheral blood stem cell (PBSC) transplantations with promising GVHD and relapse-free survival (GRFS) probabilities. Although appealing, these results may benefit from improvement notably outside matched sibling donor transplantation, and should be investigated in various ethnic populations.

Methods: Therefore, we report our experience of GVHD prophylaxis regimen combining PT-Cy and tacrolimus with addition of post-engraftment low-dose anti-thymocyte globulin (ATG) in allogeneic stem cell transplantation from haplo-identical donors (Haplo).

Results: Sixty-seven patients were included in the analysis. All patients received myeloablative or intensified sequential conditioning regimen. The median follow-up was 521 (range, 10 ~ 991) days. The cumulative incidences of 100-day grade II-IV acute GVHD was 14.9 ± 4.4%, and no case of grade III-IV acute GVHD was documented. The cumulative incidences of 1-year chronic GVHD and moderate-to-severe chronic GVHD were 25.4 ± 5.4% and 11.9 ± 4%,respectively. The non-relapse mortality at 1 year were 9.0 ± 3.5%, respectively. The cumulative incidence of relapse at 1 year was 4.5 ± 2.5%. The 1-year probability of DFS and OS were 85% (95%CI, 73.4 ~ 89.8%) and 89.5% (95% CI,76 ~ 92%), respectively. The 1-year GRFS was estimated as 73.1% (95% CI, 63 ~ 82.5%).

Conclusions: Our results suggested that a combination of PT-Cy, tacrolimus, and low-dose post-engraftment ATG was a promising GVHD prophylaxis with low incidence of acute GVHD in the haplo-transplantation setting.

Disclosure: Nothing to declare

12 - Graft-versus-host Disease – Clinical

P228

REAL-WORLD OUTCOMES OF GRAFT-VERSUS-HOST DISEASE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN JAPAN: RETROSPECTIVE ANALYSIS OF TRANSPLANT REGISTRY UNIFIED MANAGEMENT PROGRAM REGISTRY

Junya Kanda[1], Takaya Mitsuyoshi[1], Masatoshi Sakurai[2], Hisakazu Nishimori[3], Makoto Murata[4], Naoyuki Uchida[5], Noriko Doki[6], Yoshihiro Inamoto[7], Yukiyasu Ozawa[8], Masatsugu Tanaka[9], Yuta Katayama[10], Tetsuya Eto[11], Ken-ichi Matsuoka[3], Gyungjin Jun[12], Mio Kurata[13], Tatsuo Ichinohe[14], Takahiro Fukuda[7], Takanori Teshima[15], Yoshiko Atsuta[13], Seitaro Terakura[16]

[1]Kyoto University, Kyoto, Japan, [2]Keio University School of Medicine, Tokyo, Japan, [3]Okayama University Hospital, Okayama, Japan, [4]Shiga University of Medical Science, Otsu, Japan, [5]Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital, Tokyo, Japan, [6]Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan, [7]National Cancer Center Hospital, Tokyo, Japan, [8]Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Nagoya, Japan, [9]Kanagawa Cancer Center, Yokohama, Japan, [10]Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima, Japan, [11]Hamanomachi Hospital, Fukuoka, Japan, [12]Novartis Pharma K.K., Tokyo, Japan, [13]Japanese Data Center for Hematopoietic Cell Transplantation, Nagakute, Japan, [14]Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan, [15]Hokkaido University, Sapporo, Japan, [16]Nagoya University Hospital, Nagoya, Japan

Background: Allogenic hematopoietic stem cell transplantation (allo-HSCT) is an important therapeutic option for hematological malignancies. However, the development of graft-vs-host disease (GVHD) limits its success and is a major cause of morbidity and mortality. This retrospective study was conducted to clarify the clinical characteristics of patients who have developed acute GVHD (aGVHD) and/or chronic GVHD (cGVHD) after allo-HSCT.

Methods: Data for patients who had undergone first allo-HSCT between January 2010 and December 2019 were extracted from the Transplant Registry Unified Management Program (TRUMP®) registry. As data for second-line therapy were not available before 2014, patients with steroid-refractory aGVHD (SR-aGVHD) were only evaluated from 2014. The primary endpoint was the cumulative incidence of aGVHD and cGVHD, while the secondary endpoints included evaluation of baseline characteristics and clinical outcomes. The probability of overall survival (OS) and the cumulative incidence (CI) of non-relapse mortality (NRM) were calculated for those who developed aGVHD and/or cGVHD.

Results: Of 29,690 patients who received allo-HSCT, 2,807, 6,167, 10,556, 774, and 9,339 patients received related bone marrow (R-BM), related peripheral blood (R-PB), unrelated bone marrow (UR-BM), unrelated peripheral blood (UR-PB), and unrelated cord blood (UR-CB), respectively. Of these, 16,524 patients developed aGVHD and 8,038 patients developed cGVHD. From 2010 to 2019, 9,267 patients with aGVHD had systemic corticosteroid as first-line therapy. From 2014 to 2019, of 5,635 patients who received systemic corticosteroids, 1,399 patients developed SR-aGVHD. The CI at 100 days in Grade II-IV and Grade III-IV aGVHD was 35.8% and 11.9%, respectively, while the CI at 3 years in overall and extensive-type cGVHD was 32.8% and 17.7%, respectively. The incidence of Grade II-IV aGVHD was highest in the mismatched UR-BM group (42.7%) followed by the mismatched UR-PB group (39.6%) and lowest in the matched R-BM group (23.6%) ($P < 0.001$, Table). The CI of extensive-type cGVHD was highest in mismatched UR-PB group (28.6%) and lowest in UR-CB group (10.5%; $P < 0.001$). Patients who received first-line therapy for aGVHD reported complete response (CR) 50.0% and partial response (PR) 20.5%. Patients who received second-line therapy had CR 30.7% and PR 33.2%, which were lowest in the mismatched UR-PB group (CR/PR, 18.2%/27.3%). OS at 3 years in Grade II-IV aGVHD, SR-aGVHD, and extensive-type cGVHD was 51.0%, 34.0%, and 64.2%, respectively.

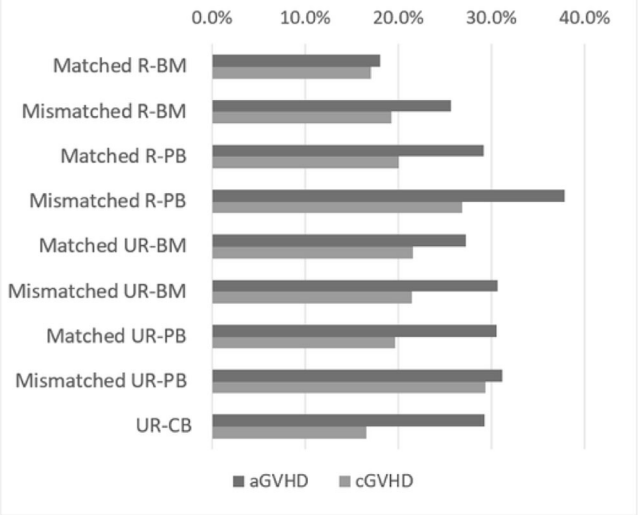
The CI of NRM at 3 years was 29.4% in aGVHD patients and 20.6% in cGVHD patients, respectively. The CI of NRM in aGVHD patients was lowest for the matched R-BM group (18.1%) and highest for the mismatched R-PB group (37.9%) and subsequently the mismatched UR-PB group (31.2%) (P < 0.001, Figure). The CI of NRM in cGVHD patients was lowest for UR-CB group (16.6%) and highest for the mismatched UR-PB group (29.4%) (P < 0.001, Figure).

Table: Cumulative incidence of Grade II-IV aGVHD (at 100 days) and extensive-type cGVHD (at 3 years)

	Grade II-IV aGVHD	Extensive-type cGVHD
Matched R-BM	23.6%	13.7%
Mismatched R-BM	36.3%	17.8%
Matched R-PB	32.8%	24.8%
Mismatched R-PB	37.1%	17.1%
Matched UR-BM	35.4%	20.1%
Mismatched UR-BM	42.7%	21.0%
Matched UR-PB	34.6%	28.6%
Mismatched UR-PB	39.6%	23.7%
UR-CB	35.9%	10.5%

Abbreviation: aGVHD, acute GVHD; cGVHD, chronic GVHD; GVHD, graft-versus-host disease; R-BM, related bone marrow; R-PB, related peripheral blood; UR-BM, unrelated bone marrow; UR-CB, unrelated cord blood; UR-PB, unrelated peripheral blood.

Figure: Cumulative incidence of NRM at 3 years



Conclusions: The incidence of aGVHD was highest in mismatched UR-BM and UR-PB groups among various stem cell source groups. Furthermore, mismatched UR-PB group showed the lowest CR/PR rate in those receiving second-line therapy for SR-aGVHD, leading to high NRM in aGVHD patients. Development of novel treatment is necessary for SR-aGVHD to improve transplant outcomes, particularly for mismatched UR-PB transplantation.

Disclosure: JK: Grants/contracts: Eisai. Consulting fee: AbbVie, SymBio, Astellas, Daiichi Sankyo, Janssen. Payment/honoraria: CSL Behring, MSD, Astellas, AbbVie, Amgen, Otsuka, Ono, Janssen, Sanofi, Kyowa Kirin, Nippon Shinyaku, Daiichi Sankyo, Sumitomo, Takeda, Chugai, Novartis, BMS, Janssen, Asahi Kasei, Asclepia, Otsuka, Nippon Kayaku.

HN: Grants/contracts: Otsuka, Chugai, Eisai, Kyowa Kirin. Consulting fees: Kyowa Kirin.

MM: Consulting fees: Asahi Kasei, JCR. Payment/honoraria: MSD, Otsuka, Kyowa Kirin, Sanofi, Sumitomo, Nippon Shinyaku, Novartis, Pfizer, Fujifilm Toyama Chemical, Janssen, AbbVie, Mallinckrodt.

NU: Payment/honoraria: Otsuka, Chugai, Alexion, Asahi Kasei, Amgen, BMS, CSL Behring, Nippon Shinyaku, AbbVie, Janssen, SymBio, Novartis, Kyowa Kirin, Astellas, Takeda, Sumitomo, Meiji Seika, Daiichi Sankyo, Sanofi, Nihon Pharmaceutical, Merck.

ND: Payment/honoraria: Novartis, Janssen.

YI: Grants/contracts: Amgen, Meiji Seika, Novartis. Honoraria: Janssen, Meiji Seika, Novartis.

MT: Grants/contracts: Chugai. Payment/honoraria: AbbVie, Daiichi Sankyo, Astellas, Otsuka, Kyowa Kirin, Sumitomo, Pfizer, MSD

TT: Payment/honoraria: Chugai, Kyowa Kirin, Fuji, Nippon Shinyaku, Asahi Kasei, Eisai, Sumitomo, Ono, Astellas, Shionogi, Priothera SAS, LUCA Science, Otsuka. Honoraria: AbbVie, Astellas, Nippon Shinyaku, Kyowa Kirin, BMS, Sumitomo, MSD, Celgene Corp, Chugai, Janssen. Adboard: Meiji Seika, Daiichi Sankyo, Asahi Kasei, Astellas, AstraZeneca, Takeda, Janssen, Roche Diagnostics, Sumitomo, Celgene Corp, Sanofi.

YA: Honoraria: Meiji Seika, JCR, Kyowa Kirin. Speaker bureaus: Novartis, AbbVie, Astellas.

ST: Payment/honoraria: Novartis.

12 - Graft-versus-host Disease – Clinical

P229

COMPARISON OF THE MODIFIED GLUCKSBERG CRITERIA VS. THE MAGIC CRITERIA FOR DIAGNOSIS OF AGVHD IN CHILDREN UNDERGOING HSCT

Sarah Weischendorff[1,2], Nakisa Kamari-Kany[1], Katrine Kielsen[1], Marianne Ifversen[1], Klaus Müller[1,2]

[1]Rigshospitalet, Copenhagen University Hospital, Copenhagen Ø, Denmark, [2]University of Copenhagen, Copenhagen, Denmark

Background: The diagnosis and grading of aGvHD is challenging, as current criteria are based solely on clinical manifestations being subject to individual interpretation and diagnostic heterogeneity. Recently, to increase consistency, the diagnostic criteria of aGvHD have been revised and the MAGIC criteria have been recommended as standard. However, few studies have performed a direct comparison between the modified Glucksberg criteria and the MAGIC criteria.

Methods: We included 117 children (median age: 8.9 years, (range: 1.1-17.9), 58% males) who underwent myeloablative allo-HSCT at Rigshospitalet, Denmark, between 2010-2020. Donor-type included either MUD (72%) or MSD (28%), and BM (96%) or PB (4%) was used as stem cell source.

The clinical manifestations of aGvHD were retrospectively re-evaluated according to the modified Glucksberg criteria and the MAGIC criteria by review of the patients' medical records for the first 100 days post-transplant by three investigators (SW, NG, KM).

The extent of a rash was determined by the Lund Browder Chart. Serum bilirubin levels were measured daily during hospitalization, and hyperbilirubinemia was only counted as liver GvHD in the absence of alternative causes (e.g., SOS or infection) and if it developed simultaneously with or after the onset of aGvHD in another target organ. For upper gastrointestinal (GI) aGvHD (as defined by the MAGIC criteria), persistent anorexia was only considered aGvHD when accompanied by ≥5% weight loss, and upper GI aGvHD was not diagnosed if an alternative cause for nausea and vomiting (e.g., mucositis and GI infections) was deemed

Table 1: Discrepancies between the modified Glucksberg criteria and the MAGIC criteria in six patients

	The modified Gluckberg criteria					The MAGIC criteria				
Patient	**Skin**	**Liver**	**Upper GI**	**Lower GI**	**Overall grade**	**Skin**	**Liver**	**Upper GI**	**Lower GI**	**Overall grade**
1	II	0	0	0	I	II	0	I	0	II
2	I	0	0	0	I	I	0	I	0	II
3	I	0	0	0	I	I	0	I	0	II
4	I	0	0	0	I	I	0	I	0	II
5	III	0	0	0	II	III	0	0	II	III
6	I	II	0	IV	III	I	II	I	IV	IV

more likely. Lower GI aGvHD was diagnosed when patients fulfilled the diagnostic criteria for at least three consecutive days.

Results: Fifty-four patients (46%) were diagnosed with aGvHD according to both the modified Glucksberg criteria and the MAGIC criteria on median day +17 (range: 5-35).

No differences in the staging of skin or liver aGvHD were found. However, the prevalence of upper GI aGvHD stage I was higher when using the MAGIC criteria (14 patients *vs*. 4 patients). Moreover, one patient fulfilled the criteria for lower GI GvHD stage II according to the MAGIC criteria but was not diagnosed with lower GI aGvHD according to the modified Glucksberg criteria. The discrepancies between the two sets of diagnostic criteria resulted in a different overall grading for six patients, all of which had increased disease severity when assessed by the MAGIC criteria (Table 1).

Conclusions: During this evaluation, we found major challenges in diagnosing GI aGvHD. Anorexia, nausea, and vomiting are extremely common symptoms after HSCT, which renders the diagnosis of upper GI aGvHD difficult, when based solely on clinical symptoms (MAGIC). We therefore suggest a more stringent definition of upper GI aGvHD, particularly since this manifestation commonly increases the overall grading, which may have significant consequences in both a clinical and research context.

Although we consider the weight-adapted measures for diarrhea volume and the implementation of diarrhea episodes for diagnosing lower GI aGvHD a significant improvement in the pediatric setting, the duration of diarrhea upon diagnosis is still not specified and may be prone to important diagnostic discrepancies.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P230

TREATMENT OF GRAFT-VERSUS-HOST DISEASE WITH EXTRACORPOREAL PHOTOPHERESIS (ECP): A LARGE MONOCENTRIC EXPERIENCE

Mattia Montanari[1], Anna Maria Raiola[2], Massimiliano Gambella[2], Stefania Bregante[2], Carmen Di Grazia[2], Alida Dominietto[2], Francesca Gualandi[2], Riccardo Varaldo[2], Anna Ghiso[2], Livia Giannoni[2], Fabio Cruciani[2], Paolo Carlier[2], Vanessa Agostini[2], Emanuele Angelucci[2]

[1]Università di Genova, Genova, Italy, [2]IRCCS Ospedale Policlinico San Martino, Genova, Italy

Background: Acute and chronic graft versus host disease (aGVHD and cGVHD) still represent the most common causes of morbidity and mortality following allogeneic stem cell transplantation. Extracorporeal photopheresis (ECP) has been demonstrated as an active therapy for GVHD with an excellent safety profile.

Methods: The aim of the study was to analyze the role and efficacy of ECP as a therapy for GVHD in a series of 86 patients transplanted in our center from January 2012 to June 2022. Thirty-six patients (42%) had aGVHD and 50 (58%) cGVHD.

Twenty cases (55%) of aGVHD were grade III – IV and 30 (52%) cases of cGVHD was severe (24/50 - 48% - with pulmonary involvement). Among aGVHD, 15 (42%) were steroid refractory.

Median duration of ECP was 6 months (1–55); the mean and the median number of ECP sessions were 20 and 19 (range 2- 99) for aGVHD and cGVHD, respectively.

ECP was the first line of treatment in 20 (23%) patients (8 acute and 12 chronic), second line in 51(59%) patients (24 acute and 27 chronic), third line in 15 (18%) patients (4 acute and 11 chronic), with a median time of ECP onset of +7, +56 and +97 days from GVHD diagnosis.

Response was defined as at least 50% reduction in organ involvement and/or steroid reduction/interruption due to clinical improvement.

Median follow-up was 64 months (95% CI: 33,9 – 94) from aGVHD and 78 months (95% CI: 59.8 – 96,1) from cGVHD diagnosis.

Results: ECP was early interrupted in 6 (7%) patients (2 aGVHD 4 cGVHD) for infections and/or cytopenia. For aGVHD 6 months overall-response-rate (ORR) was 77% and 24 months-OS was 41.8% (95% CI: 23.6 – 60). For cGVHD 6 months ORR was 66% and 48-months OS was 48.4% (95% CI: 32 – 64.4). Despite of similar rate of OS with prolonged follow up, median OS was 10 months (95% CI: ne -24.1) for aGVHD versus 47 months for cGVHD (95% CI: 38.5 – 55.4).

Clinical variables such as number of previous lines of treatment ($p = 0.8$), cGVHD ($p = 0.5$) grading, aGVHD with gastrointestinal involvement ($p = 0.1$), cGVHD with pulmonary involvement ($p = 0.2$), de-novo or progressive cGVHD ($p = 0.4$), did not show to impact OS.

OS was significantly better among patients who did at least 19 (as representing the mean number in the whole cohort) ECP sessions (OS, ECP > 19 vs ECP ≤ 19: 78% vs 24%; $p < 0.001$) Patients treated for higher grade aGVHD (III -IV) had a worse prognosis: 12 months OS was 25% (95% CI: 6 - 45) for grade III – IV vs 73% (95% CI: 52% - %94) for grade II - III ($p = 0.03$).

No response to ECP significantly worsen survival both for aGVHD and cGVHD: in a comparison between non-responders vs responders, twelve months OS was 0 vs 58,1% ($p = 0.007$) in aGVHD and 50% vs 93% ($p < 0.001$) in cGVHD.

Conclusions: ECP is confirmed as an effective treatment in aGVHD and cGVHD patients: as an immunomodulatory procedure, it shows to be safe and excellently tolerated and offers the advantage of possible associations with other immunosuppressive treatments (i.e., ruxolitinib, anti-CD26 antibodies).

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P231

HAPLOIDENTICAL VERSUS MATCHED UNRELATED HSCT WITH POST TRANSPLANT CYCLOPHOSPHAMIDE BASED GVHD PROPHYLAXIS IN CHILDREN WITH ACUTE LEUKEMIA

Anastasiia Borovkova[1], Olesia Paina[1], Zhemal Rakhmanova[1], Polina Kozhokar[1], Anastasiia Frolova[1], Luibov Tsvetkova[1], Svetlana Razumova[1], Kirill Ekushov[1], Anna Osipova[1], Olga Slesarchuk[1], Tatiana Bykova[1], Elena Semenova[1], Alexander Kulagin[1], Ivan Moiseev[1], Ludmila Zubarovskaya[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation

Background: Use of post-transplantation cyclophosphamide (PTCy) with or without additional immunosuppression has been shown to be effective GVHD prophylaxisfollowing different types of HSCT in adults with hematological malignancies. Recent reports showed lower incidence of grade II-IV, III-IV aGVHD, cGVHD with PTCy in adults following HLA-matched allo-HSCT compared to haploidentical HSCT (Gooptu et al. 2021, Bailen R. et al., 2022). However, there are no published data comparing results of MUD and haploidentical HSCT with PTCy in children. The aim of study was to compare the outcomes of allo-HSCT with PTCy between HLA-haploidentical and HLA-matched unrelated donors (MUD) in children with acute leukemia.

Methods: We retrospectively analyzed outcomes of 130 first allogeneic HSCT from MUD (n = 48) or haploidentical (n = 82) donors performed in children <18y.o. in 1st or 2nd CR of acute leukemia. All patients received triple combination of PTCY with CNI and mTOR inhibitors or MMF GVHD prophylaxis: PTCy alone was used in 2 patients (4,2%) after MUD and 2 (2,4%) patients after haploidentical HSCT. Two (2,4%) patients after MUD and 7 (8,5%) patients after Haplo received PTCY with one additional immunosuppressive agent, triple combination of PTCY with CNI and mTOR inhibitors or MMF was used in 44 (91,7%) after MUD and 73 (89,0%) patients after haploidentical HSCT. Patients, donors and graft characteristics are provided in Table 1. Bone marrow was predominant stem cell source in both groups (58,3% and 100% respectively), but 20 (41,7%) recipients of MUD received PBSC (p < 0,001)

Table 1. Patients and transplant characteristics

	MUD	Haplo	p value
Number of patients	48	82	
Age at diagnosis, years (range)	7.41 (0.10-17.00)	4.48 (0.02, 17.19)	0.128
Age at HSCT, years (range)	10.11 (0.60-18)	6,53 (0.47, 17.75)	0.068
Time to HSCT, months	13,00 (6,00-99,00)	11,00 (3,00-84,00)	0,088
Median follow-up for survivors, months (range)	54 (24-99)	23 (3-106)	**<0.001**
Year of HSCT, median (range)	2016 (2011-2019)	2019 (2012-2021)	**<0,001**
Gender, n (%)			
Male	32 (66.7)	51 (62.2)	0.747
Female	16 (33.3)	31 (37.8)	
Diagnosis, n (%)			
ALL	29 (60.4)	57 (69,5)	0.387
AML	19 (39.6)	25 (30,5)	
Disease status at HSCT, n (%)			
CR1	27 (56,2)	43 (52.4)	0.812
CR2	21 (43,8)	39 (47.6)	
Conditioning regimen, n (%)			
MAC	33 (68.8)	50 (61.0)	0.483
RIC	15 (31.2)	32 (39.0)	
Conditioning regimen, n (%)			0,192
Busulfan-based	36 (75)	51 (62,2)	
Other	12 (25)	31 (37,8)	
Stem cell source, n (%)			
BM	28 (58,3)	82 (100,0)	<0,001
PBSC	20 (41,7)	0 [A.K.1]	
Donor female for male, n (%)	13 (27,1)	13 (15,9)	<0,001
CD34 + *10_6/kgMedian (range)	4,6 (1,0-10,9)	5,8 (2,2-15,8)	0,050
GVHD prophylaxis, n (%)			0,565
PTCy alone	2 (4,2)	2 (2,4)	
PTCy+1 immunosuppressive agent	2 (4,2)	7 (8,5)	
PTCy+2 immunosuppressive agents	44 (91,7)	73 (89,0)	
Additional immunosuppression, n (%)			0,23
without CNI	3 (6,2)	8 (9,8)	
Cyclosporine A	3 (6,2)	1 (1,2)	
Tacrolimus	42 (87,5)	73 (89%)	
Sirolimus	8 (16,7)	71 (86,6)	<0,001
MMF	37 (77,1)	8 (9,8)	<0,001

Results: Cumulative incidence of 42 day engraftment, time to neutrophils and platelet engraftment were similar between groups: 97,2% (95%CI 90,4-99,8%) vs 87,8% (95% CI 79,7%-93,8%) p = 0,203; 19 (12-40) days vs 20 (13-28) days (p = 0,762); 18 (3-114) days vs 18 (7-55) days; p = 0,84, respectively. The cumulative incidence of grade II-IV, III-IV aGVHD at day 125, moderate/severe cGVHD were comparable among MUD and haplo groups: 14,6% (95%CI 6,4-25,9%) vs 13,4% (95% CI 7,1-21,8%), p = 0,87; 4,17% (95%CI 0,8-12,6%) vs 4,91% (95% CI 1,6-11,1%), p = 0,854; 15,6% (95%CI 6,8-27,6%) vs 20,9% (95%CI 12,6-30,6%), respectively. The 2-year GRFS was 52,3% (95% CI - 36,7-65,7%) in MUD and 36,9% (95% CI 36,7-54,7%) after haploidentical HSCT, p = 0.05. There was no difference in OS, 2-y LFS, 2-y NRM, 2-y relapse incidence between study cohorts: 69,8% (54,1-81,0%) vs 66,0 (95%CI 51,9-76,9), p = 0,704; 56,2% (95% CI 41,2-68,9%) vs 41,2% (95% CI 29,1-52,9%), p = 0,148; 12,5% (95% CI 5,1-23,4%) vs 7,57% (95% CI 3,1-14,8%), p = 0,358; 29,2 (95% CI 17,2-42,3%) vs 44,0 (95% CI 32,8-54,6%), p = 0,083.

Conclusions: In our analysis transplant outcomes in children, including CI of engraftment, OS, DFS, NRM, CI of aGVHD II-IV, III-IV, cGVHD, relapse rate did not differ significantly between MUD and haploidentical groups. However, MUD was associated with better 2-y GRFS compared to haploidentical HSCT. Comparable rate of acute and chronic GVHD between MUD and haplo groups can be attributed to the use of PBSC in MUD group.

Disclosure: The authors declare no conflicts of interest.

12 - Graft-versus-host Disease – Clinical

P232

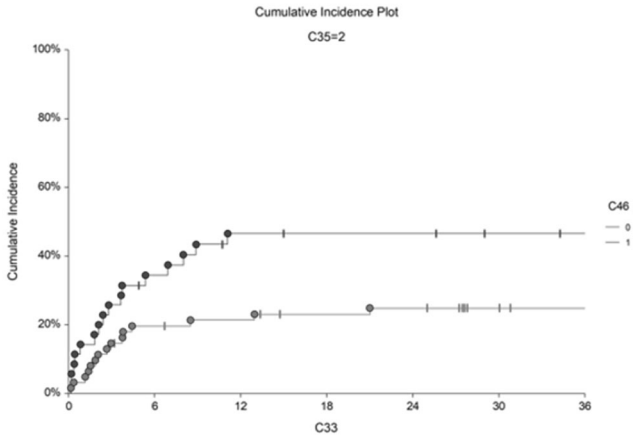
THE IMPACT OF ATG REAL-DOSE (RD) /THERORETICAL-ALC-BASED-DOSE (TD) RATIO ON OUTCOME IN ADULT PATIENTS UNDERWENT ALLOGENEIC-STEM-CELL-TRANSPLANT AFTER MYELOABLATIVE CONDITIONING FOR MYELOID MALIGNANCIES: A RETROSPECTIVE-SINGLE-CENTER ANALYSIS

Giuseppe Sapienza[1], Roberto Bono[1], Stefania Tringali[1], Emilia Gigliotta[2], Maria Giulia Butera[2], Manuela Giuseppa Ingrasci[2], Andrea Rizzuto[2], Lucia Sbriglio[1], Luca Castagna[1]

[1]Azienda Ospedaliera Ospedali Riuniti Villa Sofia Cervello, Palermo, Italy, [2]Azienda Ospedaliera Universitaria Policlinico 'Paolo Giaccone', Palermo, Italy

Background: Rabbit polyclonal anti-thymocyte globulin (ATG) is extensively used as graft versus host disease prophylaxis both after matched related (MRD) and unrelated donor (UD) allogeneic stem cell transplantation (allo-SCT). Optimal ATG dosage is crucial to obtain the higher clinical benefit. Absolute lymphocyte count (ALC)-based ATG dosing had more chance to predict the optimum exposure than fixed dose weight-based.

FIG1 (NRM of the whole cohort Legend 0= RD/TD<0,97 1 = RD/TD>0,97)



Methods: We analyzed retrospectively data from patients undergoing allo-SCT from matched UD (MUD) after MAC conditioning regimen. The principal aim of this study was to evaluate if the weight-based ATG dosing had an impact on main outcomes normalized by theoretical ALC-based dose. We calculated retrospectively a ratio between the real cumulative dose (RD) administered and theoretical (TD) ALC-based dose as proposed by Admiral et al. The hypothesis was that patients with ratio <1 (under-dosage) could have more alloreactivity, and patients with ratio>1 (over-dosage), more toxicities.

Results: 100 patients received allo-SCT from MUD after MAC regimen between 2005 and 2021 for AML (n = 60), ALL (n = 28) and MDS (n = 12). Only 3 patients with AML and 1 patient with ALL had active disease at transplant. Median age was 46 y (13.7-69). Stem cell source was PBSC in 88%. ATG was administered at day -2 and -1 before allo-SCT. Median ATG/Kg dose was 7 mg/Kg. Median ATG cumulative dose was 460 mg (212-980). Median ALC at first day of ATG infusion day was 320/microliter (1-5410). After a median follow up of 14.8 months, median OS was 30 months, the 2-y OS was 53 %, median PFS was 21 months and 2-year PFS was 50%, 1-year NRM was 31%. The cumulative incidence (CI) of grade 2-4 was 28% and 3-4 aGVHD was 10%. The RD/TD was 0.85 (0.24-1.90). We used this ratio to perform ROC analysis. For OS of the whole cohort, the best cut off was 1.08 and 1-year CI of OS above vs under cut off was 52% vs 64% respectively (p = 0.18). For NRM the best cut off was 0.97. Using this cut-off, 1-year CI of NRM above vs under cut off was 47% vs 25% respectively (p = 0.02), (Fig. 1). Using the same cut off, we showed no difference in term of grade 3-4 and 2-4 aGVHD. The analysis was restricted to AML cohort (N = 60) but we did not found difference in terms of OS (63% vs 68%), NRM (33% vs 14%, p = 0.2).

Conclusions: We found no difference in overall survival, aGVHD 2-4 and 3-4 incidence, in patients receiving allo-SCT from MUD, having lower or higher exposure to ATG. NRM was higher for patients with higher ATG/ALC ratio. This higher NRM probably due to higher incidence of infections.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P233

RUXOLITINIB IMPROVES ENDOTHELIAL SYNDROMES AND PROLONGS SURVIVAL AFTER ALLOGENEIC STEM CELL TRANSPLANTATION – UMC LJUBLJANA, SLOVENIA EXPERIENCE

Polona Novak[1], Ana Bošković[1], Nika Kraljić[1], Klara Šlajpah[1], Petra Pavlovčič[1], Samo Zver[1], Matjaž Sever[1]

[1]UMC Ljubljana, Ljubljana, Slovenia

Background: Patients with acute GvHD commonly develop signs of secondary HLH or TA-TMA that can worsen with reduction of immunosupression despite improvement of liver, gastrointestinal or skin manifestations. Effective treatment requires aggressive immunosuppression to control the hyperinflammatory state, in combination with targeted treatment against triggering factors. Prompt recognition and treatment is important and reduces mortality. Poor graft function (PGF) is common in such patients and is a consequence of more complex interactions between the immune system and the hematopoietic compartment. During GvHD, persistent IFN-γ signaling appears to have the most negative effect on hematopoietic function. Inhibition of IFN-γ signaling during GvHD with ruxolitinib may improve hematopoietic function.

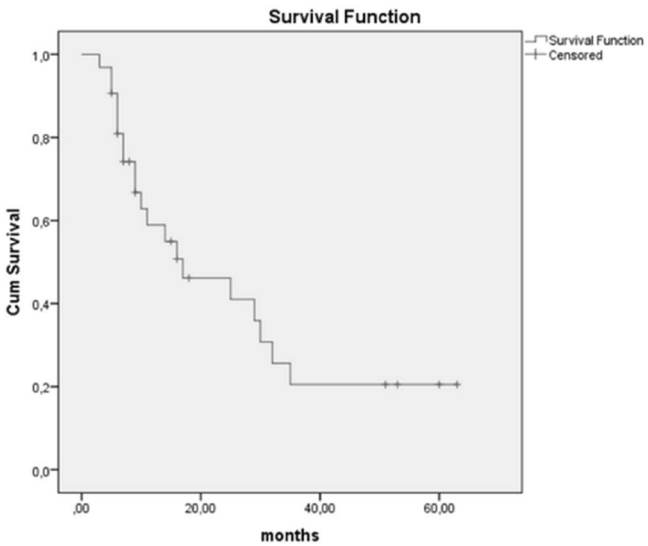
Methods: 218 patients had allogeneic stem cell transplantation performed at UMC Ljubljana, Slovenia from January 2017 to November 2022. We selected patients with either high H score or high Easix score. Medical records of these patients were retrospectively reviewed and clinical features with treatment outcomes were evaluated.

Results: We analysed 32 patients (15 %) with alloreactive state that could be defined with one of the endothelial syndromes (ES) – sHLH or TMA. Median age was 45 years (19-67). Risk factors for ES were myeloablative conditioning regimen (89 % vs 75 %) compared to patients without ES. 70 % of patients with ES were not in CR compared to 30 % of patients without ES. Additional risk factor for ES was second allogeneic SCT (19 % vs 4 %). Our standard GvHD prophylaxis was CSA/MTX or CSA/MMF with 56 % receiving additional ATG.

59 % of patients with ES had aGvHD III/IV, 50 % had severe cGvHD, 72 % had poor graft function, median peak log_2Easix score was 7,2 (r., 2,9-10,3), median H score was 210 (r., 151-271), which relates to 88-93 % propability of sHLH. 69 % of patients had ferritin above 10000 µg/L. 88 % were treated with ruxolitinib with an intent to lower the steroid dose with 70 % response. 25 % were switched from cyclosporine to sirolimus with no obvious benefit. Four patients received stem cell boost with three improving PGF. Patients with log_2Easix > 5 had significantly reduced OS (p = 0,05). After median follow up of 10,5 months (r., 3-65) median OS was 17 months (r., 2-32) and OS of 59 % at 1 year and 41 % at 2 years was observed.

Patient characteristics and results (n = 32)	N or Median (Range, %)
Age at SCT	45 (19-67)
Disease	
AML	18 (56 %)
ALL	7 (21 %)
MDS	3 (9 %)
MF	3 (9 %)
HL	1 (3 %)

Patient characteristics and results (n = 32)	N or Median (Range, %)
Conditioning regimen	
MAC	28 (88 %)
GVHD prophylaxis	
ATG	18 (56 %)
posttransplant Cy	2 (6 %)
CR status	
not in CR	23 (72 %)
CR 1	4 (12 %)
CR > 1	5 (16 %)
First allogeneic SCT	26 (81 %)
Second allogeneic SCT	6 (19 %)
Matched/mismatched donor	26/6
Related/unrelated donor	7/25
Patient sex (male/female)	16/16
H score	210 (150-271)
Ferritin	
>10000 mcg/L	22 (69 %)
Log2Easix	7,2 (2,9-10,3)
aGVHD III/IV	19 (59 %)
aGVHD IV	11 (34 %)
cGVHD III	16 (50 %)
Therapeutic interventions	
Change CSA to sirolimus	8 (25 %)
Ruxolitinib	28 (88 %)
ECP	25 (78 %)
CD 34+ selected boost	4 (13 %)
Defibrotide	2 (6 %)
Eculizumab	2 (6 %)
Mesenchymal stem cells	6 (19 %)
CMV reactivation	15 (47 %)
EBV reactivation	13 (44 %)
HHV 6 reactivation	6 (19 %)
PGF	23 (72 %)
Cause of death	
DAH	5 (16 %)
Covid 19	2 (6 %)
Sepsis	12 (38 %)
Relapse	1 (3 %)
1 year OS	59 %



Conclusions: After reviewing the most chalanging SCT patient population at our center we conclude that early recognition of endothelial syndromes using either simple easix score or H score followed by prompt treatment limits tissue injury and potentially restores hematopoetic function while damage is still reversible. Despite high ES risk of our patient cohort with most being not in remission, early introduction of ruxolitinib improved survival compared to our historical controls in which 1 year morality approached 90 %. Also, we believe that if there is poor graft function after SCT that causes vicious cycle of infections this can be reversed with a stem cell boost on condition that hyperinflamatory process is under control.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P234

THE CLINICAL BENEFIT OF ACUTE GVHD DEPENDS ON THE AGE AT TRANSPLANTATION IN PATIENTS WITH ADULT T-CELL LEUKEMIA–LYMPHOMA

Shigeo Fuji[1], Yoshitaka Inoue[2], Junya Makiyama[3], Nobuaki Nakano[4], Ayumu Ito[5], Toshiro Kawakita[6], Tetsuya Eto[7], Youko Suehiro[8], Hidehiro Itonaga[9], Yasushi Sawayama[3], Yasuo Mori[10], Naoyuki Uchida[11], Satoko Morishima[12], Makoto Onizuka[13], Kenji Ishitsuka[14], Takahiro Fukuda[5], Yoshiko Atsuta[15,16], Makoto Yoshimitsu[14]

[1]Osaka International Cancer Institute, Osaka, Japan, [2]Kumamoto University Hospital, Kumamoto, Japan, [3]Sasebo City General Hospital, Nagasaki, Japan, [4]Imamura General Hospital, Kagoshima, Japan, [5]National Cancer Center Hospital, Tokyo, Japan, [6]National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan, [7]Hamanomachi Hospital, Fukuoka, Japan, [8]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan, [9]Nagasaki University Hospital, Nagasaki, Japan, [10]Kyushu University Hospital, Fukuoka, Japan, [11]Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital, Tokyo, Japan, [12]University of the Ryukyus Hospital, Okinawa, Japan, [13]Tokai University School of Medicine, Kanagawa, Japan, [14]Kagoshima University Hospital, Kagoshima, Japan, [15]Japanese Data Center for Hematopoietic Cell Transplantation, Aichi, Japan, [16]Aichi Medical University School of Medicine, Aichi, Japan

Background: Adult T-cell leukemia–lymphoma (ATL) is a hematological malignancy caused by HTLV-1. Allogeneic hematopoietic cell transplantation (allo-HCT) is a standard of care in transplant-eligible patients with ATL. A previous study demonstrated that the development of grade 1–2 acute graft-versus-host disease (aGVHD) was associated with significantly better overall survival compared with the absence of aGVHD. The aim of this study was to clarify the clinical benefits of aGVHD according to age at allo-HCT, using a recent Japanese registry dataset of patients who underwent allo-HCT for ATL.

Methods: To assess the benefit of grade 1–2 aGVHD in a recent cohort that included more elderly patients with ATL, we performed a retrospective study using a registry dataset of ATL patients who underwent allo-HCT from 2006 to 2020. Following the inclusion criteria of the previous report by Kanda, we included patients who underwent their first allo-HCT, achieved engraftment, and survived for at least 30 days after allo-HCT. We obtained approval from the local ethics committee (Osaka International

Cancer Institute, No. 22082). This study was conducted in accordance with the Declaration of Helsinki.

Results: The median age in each group was as follows: 45.5 years (range, 20–49) in the ≤49 years group (younger group, n = 360), 55 years (range, 50–59) in the 50–59 years group (intermediate group, n = 809), and 64 years (range, 60–78) in the ≥60 years group (older group, n = 854). The most common stem cell source was HLA-matched related donors in the younger group (33.2%) and unrelated volunteer donors in the intermediate and older groups (45.8% and 41.9%, respectively). The proportion of patients who received cord blood transplantation was higher in the older group.

In comparison with the absence of aGVHD, the absolute differences in 2-year OS probabilities for grades 1, 2, and 3–4 aGVHD, respectively, were 7.0%, 19.2%, and −6.9% in the younger group; 13.9%, 1.3%, and −23.1% in the intermediate group; and 13.0%, 5.8%, and −23.6% in the older group.

In a subgroup analysis for most covariates, there was a statistically significant benefit favoring grade 1 aGVHD compared to no aGVHD. Regarding grade 2 aGVHD, we found that around one-third of patients did not receive systemic steroids as treatment for aGVHD. The absolute differences in 2-year OS probabilities between no aGVHD and grade 2 aGVHD with or without systemic steroids, respectively, were as follows: 18.7% and 20.1% in the younger group; −1.5% and 8.9% in the intermediate group; and 2.2% and 11.7% in the older group.

Conclusions: The clinical benefit of aGVHD in patients with ATL depends on the age at transplantation. The clinical impact of GVHD management should be prospectively assessed to clarify the benefits of prophylaxis and the optimal treatment strategy for GVHD in patients with ATL.

Disclosure: S.F. received honoraria from Takeda Pharmaceutical, Chugai Pharmaceutical, CSL Behring, Novartis Pharma, Otsuka Pharmaceutical, Sanofi, and Kyowa Kirin. Y.A. received honoraria from Meiji Seika Pharma, JCR Pharmaceuticals, Novartis Pharma, Kyowa Kirin, AbbVie GK, and Astellas Pharma. M.Y. received honoraria from Takeda Pharmaceutical, Chugai Pharmaceutical, CSL Behring, Novartis Pharma, Otsuka Pharmaceutical, Sanofi, and Daiichi-Sankyo.

12 - Graft-versus-host Disease – Clinical

P235

THE PROBABILITY OF BEING IN RESPONSE: A NOVEL EFFICACY ENDPOINT FOR CHRONIC GRAFT VERSUS HOST DISEASE APPLIED TO THE REACH-3 STUDY OF RUXOLITINIB VERSUS BAT

Norbert Hollaender[1], Ekkehard Glimm[1], Jennifer Gauvin[2], Tommaso Stefanelli[1], Robert Zeiser[3]

[1]Novartis Pharma AG, Basel, Switzerland, [2]Novartis Pharmaceuticals Corporation, East Hanover, United States, [3]Medical Center – University of Freiburg, Freiburg, Germany

Background: Overall response rate (ORR), defined per 2014 NIH consensus criteria (Lee et al, BBMT 2015), is a key endpoint used to assess treatment efficacy of chronic graft versus host disease (cGvHD), either as ORR at week 24 or best overall response rate (BOR) at any time point up to and including week 24. Both endpoints and duration of response (DOR) were previously reported in the REACH-3 study, a phase 3 open-label, randomized trial comparing ruxolitinib versus best available therapy (BAT) for glucocorticoid-refractory or dependent (SR/D) cGvHD. Ruxolitinib demonstrated superior efficacy compared with BAT, with a higher ORR at week 24, higher BOR at any time up to week 24 and longer DOR (Zeiser et al. NEJM 2021). The comparison between ruxolitinib and BAT was performed on ORR and BOR using all randomized patients, while DOR was derived for responders only. To further assess the "breadth and depth" of clinical benefit in cGvHD, the probability of being in response (PBR), a novel measure of efficacy is presented in this post-hoc analysis.

Methods: Here we illustrate the application of the PBR, a graphical method presenting simultaneously the time to first response and subsequent failure, i.e., combining time to first response, response rates and DOR into one measure. Considering the PBR as a function of time was suggested by Temkin (Biometrics 1978). At baseline, all patients are in State 0 (*not in response*). A patient enters State 1 (*in response*) at the time of the first documented response. Such patients may lose their response and enter State 2 (*absorbing)* or remain *in response* until statistical analysis, in which case they are censored in State 1. Patients who die, progress, change type of systemic cGvHD treatment or do not achieve response within 24 weeks switch from State 0 to State 2. Any patient who neither reached State 1 nor State 2 (i.e., drop out before week 24) is censored in State 0. PBR is estimated by applying time-to-event methodology similar to the well-known Kaplan-Meier plot.

Results: The median time to first response for all randomized patients (with non-responders censored) was 29 days (95% CI: 24–31 days) for patients receiving ruxolitinib and 50 days (95% CI: 29–57 days) for patients receiving BAT. The plot of the PBR shows ruxolitinib was associated with a higher probability of being in response at all time points. The larger area under the curve in the ruxolitinib arm also shows a longer average duration of response compared to BAT.

Conclusions: In REACH-3 ruxolitinib-treated patients had a higher probability of being in response at all time points as measured by the PBR function. This novel endpoint allows a valid comparison between randomized treatment arms and depicts long term benefit, combining response and its duration visualizing all patients, not only responders. PBR may be a useful measure that could be added to future updates of cGvHD response criteria to better describe the benefits of cGvHD therapy.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT03112603

Disclosure: N. Hollaender, E. Glimm, J. Gauvin and T. Stefanelli are employed by Novartis. Robert Zeiser has received honoraria from Incyte, Mallinckrodt, and Novartis. Domenico Russo has received honoraria from Medac and MSD, meeting/travel support from Medac, and has been a member of advisory boards for Janssen, Jazz, Medac, Sanofi and Novartis.

12 - Graft-versus-host Disease – Clinical

P236

RESULTS OF FEASIBILITY STUDY WITH SELF-LEARNING, ARTIFICIAL INTELLIGENCE BASED, MACHINE LEARNING TOOL PREDICTING THE ABSOLUTE INDIVIDUAL RISK OF ACUTE GRAFT-VERSUS-HOST-DISEASE IN A RETROSPECTIVE PEDIATRIC COHORT

Madlen Reschke[1,2], Jonathan Phillip Gross[2,1], Jonas Seiler[2], Daniel Weschke[1], David C. Higgins[2], Lena Oevermann[1,2]

[1]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, [2]Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative treatment option for about 50.000 children and adults annually (Aljurf, Weisdorf et al. 2019). However, it still holds life-threatening complications such as Graft-versus-Host disease (GvHD), relapse of a malignant disease, graft rejection, and infections. 30 to 50% of all patients undergoing HSCT will develop GvHD, causing high morbidity and mortality (grade 4 GvHD up to 90%) (Ferrara, Levine et al. 2009, Jaglowski 2014) as well as generating significantly higher treatment costs than a HSCT without GvHD occurrence (Yu 2020).

Our group is establishing an Artificial Intelligence (AI) based ML algorithm (MatchGraft.AI) - to predict the individual, absolute risk of aGvHD occurrence for every possible HSCT donor-recipient pair. By incorporating pre-transplantation clinical parameters and treatments, we are better able to predict post-transplantation outcomes. With an improved and more precise prediction, we expect the pool of possible donors to become larger as well as donor selection to become easier. Furthermore, physicians and patients will be able to better prepare and adapt conditioning and treatment plans accordingly.

Methods: A gradient boosted tree is used as ML Model. It was chosen due to its ability to handle missing data.

Analysis followed best-practices (Higgins, Paez et al. 2021). The data is split into a stratified training and validation set with a ratio of 80% / 20%. We calculated the confusion matrix statistics on the validation set. This are raw performance scores for the ability of the model to correctly distinguish outcomes (e.g. aGvHD occurrence). Derived performance scores include AUC, F1-score and Accuracy, which convert the confusion matrix scores into single metrics.

Results: The model was trained at the Charité University against a retrospective, single center data set of 232 patient/donor sets. 53 cases were excluded due to insufficient data. The following analyzation focuses on the 179 included patient/donor sets (143 in training set and 36 in validation set) pediatric stem cell transplants. Transplantations were performed between January 2013 – December 2019. M:F = 104:75; age 0 – 21 (median: 8 years). Indications for transplantation were malignant diseases (hematological neoplasms, lymphomas, solid tumors) in 98 patients and benign (hemoglobinopathies, immune deficiencies, bone marrow failure) in 81 cases. Input parameters are listed in table 1. Initial model performance of predicting absolute individual risk for GvHD was good. It was estimated at 0.69 AUC. This is comparable with model performance outcomes, published in the literature (Sorror, Martin et al. 2014).

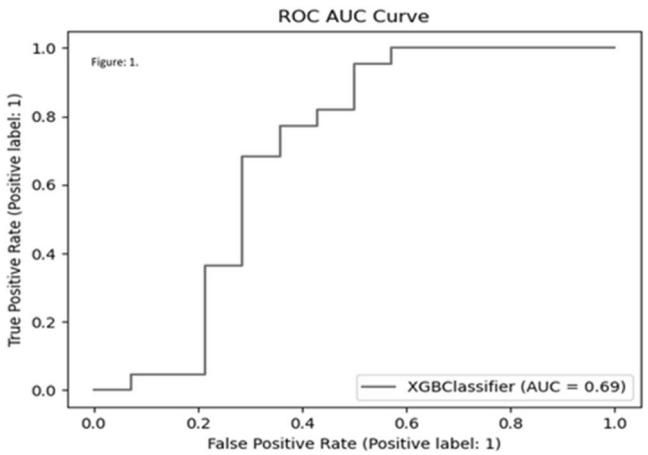


Table 1.

Included parameters (not complete for all cases)	
Graft	donor type, source, manipulation
Recipient/ Donor	Age, Sex, blood group, CMV-, EBV-, HHV6 - status, KIR – and HLA typing
Recipient, before HSCT	Stem cell transplantation date, diagnosis, remission, relapses, creatinine, LDH and thrombocyte levels before conditioning, conditioning regimen, planned GvHD prophylaxis, Karnofsky / Lansky / ECOG score before, HCT-CI (comorbidity index) / Sorror Score
Recipient, after HSCT (minimal follow up one year)	Acute GvHD grade, skin/liver/gut. Death, cause of death, relapse, graft loss / graft failure / secondary rejection, chronic GvHD affected organ, bacterial, viral, fungal infections, veno occlusive disease, transplant-associated autoimmune phenomena, Karnofsky / Lansky / ECOG score at day 100

Conclusions: The prediction of individual acute GvHD risk, using this AI ML model, is feasible. Continous training, testing and adapting on retrospective and prospective as well as international, multicenter data is being analyzed to further improve its performance. Once established, the tool will aid physicians in donor selection and treatment planning.

Outlook: We are currently collecting international data sets of HSCT donor – recipient sets in order to train and test the algorithm. We are further planning on experimenting with linear models and ensemble methods in order to identify a best model for the use-case.

Disclosure: No conflicts o interest for this study.

12 - Graft-versus-host Disease – Clinical

P237

RENAL CHRONIC GRAFT-VERSUS-HOST DISEASE AS A RARE POSTRANSPLANT COMPLICATION: A RETROSPECTIVE STUDY FROM A SINGLE CENTER EXPERIENCE

Pablo García Jaén[1,2], Carlos Puerta Vázquez[1], Evelyn Zapata Tapia[1], Celia Nicolás Boluda[1], Manuel Heras[3], Ana África Martín[1], Estefanía Pérez López[1], Ana García Bacelar[1], Almudena Cabero[1], Alejandro Avendaño[1], Mónica Baile[1], Fermín Sánchez-Guijo[1], Lourdes Vázquez[1], Pilar Fraile[3], Lucía López Corral[1], Mónica Cabrero[1]

Salamanca University Hospital, Salamanca, Spain, [2]University of Salamanca, Salamanca, Spain, Salamanca University Hospital, Salamanca, Spain

Background: Renal complications are a relatively common condition after **allogeneic stem cell transplantation** (Allo-SCT) due to several causes: conditioning regimen toxicity, veno-occlusive disease, thrombotic microangiopathy, etc. However, direct kidney damage due to graft versus host disease (GVHD) remains as a controversial diagnosis with no defined clinical criteria or pathological findings. Cases reported in the literature identifies renal GVHD as a pattern based on nephrotic syndrome that appears in the **late post-Allo-SCT** after tapering immunosuppressive treatment (IST),

but with diversity of pathological findings, concurrence or not with other GVHD manifestations or therapy used.

Here we present a **single-center series of 8 cases** of nephrotic syndrome diagnosed as **renal chronic GVHD** (rGVHD) in our center after **more than 1.000 Allo-SCT** carried out in our center from 2002.

Methods: We retrospectively review all patients diagnosed with rGVHD in our center from January 2002 to August 2022.

Results: Patients and Allo-SCT characteristics are detailed in **table 1**.

Patients developed **rGVHD** after a median of 26.5 months (28 ± 11.2) after Allo-SCT. Seven out of 8 patients had finished IST a median of 10 months before (24 ± 8.1). Five patients had developed previous acute GVHD and five had other chronic GVHD manifestations at diagnosis of nephrotic syndrome. Kidney was the only organ chronically affected in three patients. Median proteinuria at diagnosis was 13.78 g/24h (24.4 ± 7.2). **Renal biopsy** was performed in all but one patient with a solitary kidney. Pathological diagnosis was **membranous nephropathy** in four cases, glomerulonephritis similar to lupus nephropathy III, focal segmental glomerulonephritis and mesangiocapillary glomerulonephritis in one patient each.

Treatment consisted of **high dose steroids** (1 mg/kg of prednisone or equivalent dose of metil-prednisolone) in 100% of patients and **reintroduction of IST** in all but one (tacrolimus 6, ciclosporine 1). 7 patients (87.5%) achieved **complete remission (CR)** after a median of 8 months (2.2 ± 7) and 1 achieved partial response (PR) after a median follow up of 3 months. In 6 patients (**75%**) there was a **recurrence** of nephrotic syndrome after a median of 38 months (94 ± 39.4). Treatment of recurrence was similar to first episody, achieving a **2nd CR in 100%**.

After a **median follow-up of 10.5 years** (16 ± 5.9), all patients are alive, 87.5% of them with rGVHD in CR. Prevalence of chronic kidney damage in these patients is 62.5%, with a median of glomerular filtration rate of 76.5 mL/min. 3 patients still maintain IST and 5 had finished it without recurrence of nephrotic syndrome.

Conclusions: Chronic rGVHD is a rare condition after Allo-SCT, affecting **less than 1% of patients**; it usually occurs after withdrawal of IST and it can be independent of other GVHD manifestation. **Steroids plus reintroduction of IST** is a highly effective therapy with **87.5% of CR**, but recurrences were observed in 75% of cases after a new attempt of IST tapering. The most common histological diagnosis was **membranous glomerulonephritis**, but there are not patognomonic data in the biopsy, with different patterns observed.

Disclosure: Nothing to declare.

Table 1

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Recipient sex and age	Female, 33	Male, 44	Female, 57	Female, 38	Male, 57	Male, 37	Male, 65	Female, 61
Diagnosis	Transformed MALT non-Hodgkin's gastric B-cell lymphoma	Acute myeloblastic leukemia	Chronic lymphocytic leukemia Binet stage C	Acute myeloblastic leukemia M5b	Acute myeloblastic leukemia M5	Chronic myelogenous leukemia	Acute myeloblastic leukemia	Acute lymphoblastic leukemia Ph+
Donor/recipient CMV	IgG + / IgG +	IgG + / IgG +	IgG + / IgG +	IgG - / IgG +	IgG - / IgG -	IgG + / IgG +	IgG +/ IgG -	IgG + / IgG +
Conditioning regime	Myeloablative	Myeloablative	Reduced intensity	Myeloablative	Reduced intensity	Myeloablative	Reduced intensity	Reduced intensity
Prophylaxis for GVHD	Cyclosporin /Tacrolimus Methotrexate	Cyclosporin Methotrexate	Cyclosporin Methotrexate	Cyclosporin Methotrexate	Tacrolimus Rapamycin	Cyclosporin Methotrexate / Rapamycyn/ Tacrolimus	Tacrolimus Rapamycin Mycophenolate mofetil	Tacrolimus Methotrexate
Acute / Chronic GVHD history	Yes / Yes	Yes / Yes	Yes / Yes	Yes / Yes	No / No	No / Yes	Yes / No	No / No
Cutaneous / Gastrointestinal / Liver GVHD	No / Acute grade II / No	Acute grade I / Chronic / Chronic	Acute grade I / No / No	No / Acute grade II / No	No / No / No	Chronic grade II / Chronic / Chronic grade III	No / Acute grade III / No	No / No / No
Diagnosis of Renal cGVHD	Glomerulonephritis similar to lupus nephropathy III C	Focal segmental glomerulonephritis	Membranous nephropathy I	Membranous nephropathy	Membranous nephropathy I	Membranous nephropathy I	No possibility of biopsy	Mesangiocapillary glomerolunephritis
Time until appearance of renal GVHD (months)	37	45	17	26	27	45	21	20
Time until appearance of renal GVHD after removal of the prophylaxis (months)	29	5	6	15	10	0	10	13
Proteinuria at diagnosis (g/24h)	2.64	15.46	12.3	6.77	14.2	27	13.35	16.84
Treatment of Renal cGVHD	Steroids	Steroids Tacrolimus	Steroids Cyclosporin	Steroids Tacrolimus	Steroids Tacrolimus	Steroids Tacrolimus	Steroids Tacrolimus	Steroids Tacrolimus
Complete/partial remission	CR	CR	CR	CR	CR	CR	PR (currently)	CR
Time until RC (months)	8	5	12	7	7	8	-	9
Recurrence	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Time until recurrence (months)	11	2	12	96	72	64	-	-
Proteinuria in recurrence	0.9	14.5	4.03	4.4	2.52	1.9	-	-
Last renal function (mL/min)	87	59	51	79	74	>90	89	46
IST at last follow up	No	No	No	Yes	No	Yes	Yes	No

12 - Graft-versus-host Disease – Clinical

P238

PILOT STUDY OF USING LOW DOSE PTCY FOR GVHD PREVENTION AFTER MATCHED SIBLING AND UNRELATED ALLOGENIC TRANSPLANTATION

Alex Juarez Cusirimay[1], María Queralt Salas[1], María Suárez-Lledó[1,2], Nuria Martínez-Cibrian[1], Andrea Rivero[1], Jordi Arcarons[1], María Teresa Solano[1], Laura Rosiñol[1,2], Álvaro Urbano-Ispízua[1,2], Francesc Fernández-Avilés[1,2], Montserrat Rovira[1,2], Carmen Martínez[1,2]

[1]*Institute of Hematology and Oncology, Hospital Clínic of Barcelona, Barcelona, Spain,* [2]*IDIBAPS, Institute Josep Carreras, Barcelona, Spain*

Background: Using high-dose post-transplant cyclophosphamide (PTCY) for GVHD prevention is becoming prevalent in allo-HSCT performed from different donor types. PTCY is generally administered at a dose of 50mg/kg on d + 3 and d + 4 and combined with one or two additional immunosuppressive agents. Nevertheless, a standard dose and drug combination have not been established. PTCY-based prophylaxis is being used at our institution for all allo-HSCT independently of the selected donor type since 2019. The experience gained from using this prophylaxis is that provides appropriate GVHD prevention with acceptable infectious complications and relapse rates (Pedraza A, TCTJ 2021; Salas MQ, TCTJ 2022). Based on the hypothesis that lower doses of PTCY, would provide sufficient immunosuppression to permit engraftment and prevent GVHD, the dose of PTCY was lowered to 40mg/kg on d + 3 and d + 4 in matched sibling and unrelated donors (MSD and MUD) allo-HSCT in September 2021. We present the preliminary results of this pilot study.

Methods: Between September 2021 and September 2022, 10 adults underwent allo-HSCT from MSD and MUD and received GVHD prophylaxis composed of 40mg/kg of PTCY (d + 3, d + 4) and tacrolimus. All patients were prospectively included. This analysis evaluated the probability of engraftment, the incidence of acute GVHD, early infectious complications, and early post-transplant mortality. For that reason, the post-transplant follow-up was censored at 6 months. All patients received T-cell repleted PBSC grafts G-CSF was administered from day +7 until neutrophil engraftment, and all patients at risk of CMV reactivation received letermovir.

Results: Overall, the median age was 61 (range 32 - 70), all patients were diagnosed with hematological malignancies (AML 50%, MDS 30%, and MPN 20%), 20% received MAC regimens, and 70% adults received grafts from MSD and 30% from MUD. All patients engrafted. The median of days to neutrophil and platelet engraftment were 16 (IQR 15-18) and 20 (IQR: 13-31), respectively. No patient had hepatic sinusoidal obstruction syndrome or thrombotic microangiopathy. The cumulative incidence of grade II-IV aGVHD at day +100 was 21.3%, and no patient had grade III or IV. Skin was the only organ affected in patients with aGVHD, and all were successfully treated with high-dose corticosteroids. Two patients had BK-virus-associated hemorrhagic cystitis (G1 N = 1, G4 n = 1), and two had HHV6 reactivation. Six patients had viral infections: 4 COVID-19, 2 rhinovirus. No CMV reactivation was observed. Four patients had bacterial bloodstream infections and no fungal invasive infections were reported. During the first six months after allo-HSCT, only one (10%) patient died (due to diabetic ketoacidosis). At 6 months, the estimated overall survival, relapse-free survival, non-relapse survival, and cumulative incidence of relapse were 88.9%, 76.2%, 12.7%, and 12.7%, respectively.

Conclusions: Double PTCy-based prophylaxis composed of 40 mg/kg/day of PTCy and a standard dose of tacrolimus provides sufficient immunosuppressive effect to allow stem cell engraftment without increasing rates of aGVHD in MSD and MUD allo-HSCT. Further analysis will be conducted on a larger sample size of patients to confirm these results.

Disclosure: Nothing to disclose.

12 - Graft-versus-host Disease – Clinical

P239

EXERCISE PHYSIOLOGY APPLIED TO THE CLINICAL SETTING OF PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Francesca Limido[1], Francesca Lanfranconi[1], William Zardo[1], Monica Barbieri[1], Valeria Valdata[1], Adriana Balduzzi[1]

[1]*University of Milano-Bicocca, MBBM Foundation, Monza, Italy*

Background: Exercise intolerance is one of the clinical hallmarks of the transplanted patients, it deeply affects their quality of life and have a negative prognostic value. Adapted precision exercise (PEx), tailored to the specific needs of each patient, recently added to modern therapeutic interventions and focus on the main determinants of quality of life such as pain and exercise tolerance. Accordingly, the availability of non-invasive tools, able to objectively identify and quantify functional impairments first and the effects of training interventions on transplanted patients, has become crucial.

Methods: All patients undergoing transplant in our HSCT Unit were eligible for a prospective PEx and osteopathy study. The effectiveness of the intervention was evaluated longitudinally before, during and after PEx plus osteopathic treatments. Assessments included district mobility of: spine (sacral, dorsal, lumbar, and cervical extension), hips and knees (intra- and extra-rotation), ankle (flexion) and chest and abdomen. Goal attainment scaling (GAS) was used to identify the accomplishment of a desired clinical result.

Results: From January 2019 to November 2022 109 patients (age 4-19 years) of the 127 transplanted were enrolled. Among them, 34 patients (31.1%) were evaluated longitudinally at two time points, i.e. the baseline evaluation (T0) and after the intervention (T1). Of those patients 26 were trasplanted for a malignant disease, which was acute leukemia for 16 of them, and 8 for a non-malignant disease. This subgroup of transplanted patients was trained and treated for 7,1 ± 4,7 months and received, besides a 2-3 weekly PEx sessions, 13,5 ± 8,5 osteopathic treatments. PEx plus osteopathy reached positive GAS scores by improving sacral and cervical extension (94,5% and 90,9%, respectively), lower limb joints' range of motion (ROM, 87,9%) and abdomen mobility (90%). A characteristic point of structural impairment was seen at dorsal extension, lumbar extension and chest mobility: better mobility was set as a goal, and at least half of the patients ameliorated theirs impairment (56,5%, 66,6% and 63,6%, respectively). The more relevant impairment at both T0 and T1 was the reduced extension of the dorsal spine and in 13% of the cases dorsal extension even worsened at T1 compared with T0. Twenty % of the patients showed no improvement in more than 1/3 of the evaluated parameters combined to a lower adherence to PEx and osteopathic treatments. In the 10 patients with chronic graft-versus-host disease (cGVHD), PEx plus

osteopathy contributed to improve the reduced range of motion (ROM) of upper and lower limbs, besides allowing to monitor the effective response to immunosuppressive treatment.

Conclusions: PEx plus osteopathy could be a support in the clinical management of patients after HSCT. Non-invasive assessments of PEx and osteopathy efficacy facilitated patient management and follow-up. Osteopathic evaluations were crucial tools for patients with cGVHD.

Clinical Trial Registry: ClinicalTrials.gov PRS (n. NCT04090268)

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P240

THYMIC STROMAL LYMPHOPOIETIN LEVELS ARE ASSOCIATED WITH INFLAMMATION AND ACUTE GVHD IN PEDIATRIC HSCT

Kristine Bohn Sørensen[1], Maria Ebbesen Sørum[1], Dina Leth Møller[1], Marianne Rosenkrantz Segelcke Ifversen[1], Claus Henrik Nielsen[1,2], Lars Peter Ryder[1], Anders Elm Pedersen[1], Katrine Kielsen[1], Klaus Müller[1,2]

[1]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, [2]University of Copenhagen, Copenhagen, Denmark

Background: Thymic stromal lymphopoietin (TSLP) is an immunoregulatory cytokine that is produced at the epithelial surfaces and maintains homeostasis in the interplay between the microbiota and mucosal immune cells by promoting type 2 inflammation in response to epithelial damage. In HSCT, plasma levels of TSLP have been associated with development of GvHD in adults, and single nucleotide polymorphisms in the IL-7Rα-chain of the TSLP-receptor of the donor are associated with increased risk of both aGvHD and cGvHD. In this prospective study, we explored the role of plasma levels of TSLP in relation to development of GvHD and epithelial damage after pediatric HSCT.

Methods: 68 children with a median age of 7.7 years (range: 1.1-16.6) undergoing allogeneic HSCT in Denmark were prospectively included from 2010-2017. Diagnoses were hematological malignancies (n = 38) or benign disorders (n = 30). Donors were either MSD (n = 19) or MUD (n = 49), and patients received BM (n = 65) or PBSC grafts (n = 3). All patients underwent a myeloablative conditioning regimen based on either TBI (n = 20), cyclophosphamide combined with busulfan (n = 16) or other chemotherapy-based regimens (n = 32). ATG was applied in 51 patients. We measured plasma TSLP at day -7, 0, +7, +14, +21, +28, +60, +90 and +180 using ELISA. To assess the degree of early post-transplant gastrointestinal damage, circulating plasma citrulline levels were measured as a marker of enterocyte integrity.

Results: TSLP levels before start of conditioning were comparable in patients and healthy controls although with a large variability in both groups. TSLP levels increased significantly from pre-conditioning levels to day 0 ($p = 0.003$), highly variable with an interpatient variability of 22-32.000 pg/ml, and then gradually declined. As expected, a higher degree of damage to the intestinal mucosa was associated with increased levels of TSLP, as reduced levels of citrulline at day +7 after HSCT correlated with a subsequent increase TSLP at day +21 ($B = -0.16$, $p = 0.013$). In line with this, TBI-based conditioning was associated with significantly increased levels of TSLP from day 0 to +28 compared with non-TBI conditioning regimens ($p < 0.05$). Furthermore, increased TSLP levels were associated with the use of ATG at day +7, +21, and +28 (all $p < 0.05$). A total of 30 patients (44%) developed aGvHD at median day +18 (9 to 74), of these 6 had aGvHD grade III-IV. Low plasma levels of TSLP were associated with an increased risk of severe aGvHD that reached significance at day +21, comparing aGvHD grade III-IV with no or grade I-II aGvHD ($p = 0.037$). TSLP levels were not significantly associated with cGvHD.

Conclusions: This study demonstrates significantly changed dynamics of TSLP levels in relation to increased gastrointestinal toxicity and severe aGvHD. Overall, the data suggest that insufficient release of TSLP in response to epithelial damage in the gastrointestinal tract is associated with an increased risk of severe aGvHD.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P241

SURVIVAL DIFFERENCES BETWEEN ADULTS AND CHILDREN IN TREATMENT WITH ETANERCEPT FOR GRADE III-IV SD/SR-AGVHD: A RETROSPECTIVE SINGLE-CENTER COHORT STUDY

Or Gilad[1], Shlomo Elias[2], Irina Zaidman[2], Ehud Even-Or[2], Eran Zimran[2], Adir Shaulov[2], Sigal Grisaru‡[2], Batia Avni ‡[2], Hebrew University of Jerusalem, Jerusalem, Israel, Hadassah - Hebrew University Medical Center, Jerusalem, Israel

***Background**: Severity of acute Graft-versus-Host-Disease (aGvHD) is correlated with significant morbidity and mortality, particularly among patients who are dependent on or refractory to high-dose systemic steroids (SD/SR-aGvHD). To date, there is no consensus standard-of-care for SD/SR-aGvHD, and outcomes remains poor*

Etanercept, a tumor necrosis factor-α (TNF- α) inhibitor, is a recombinant DNA-derived soluble fusion protein composed of two identical chains of the human TNF receptor 2 (TNFR-2) fused with the Fc domain of human IgG1. The pivotal role of TNF-α in the pathogenesis of aGvHD has led to off-label use of Etanercept for the treatment of SD/SR-aGvHD. Review of literature has demonstrated significant differences in outcomes between adults and children who were treated with Etanercept for SD/SR-aGvHD. To the best of our knowledge, no single-center experience with Etanercept for SD/SR-aGvHD in adults and children has been reported to date. Therefore, age-related comparison of treatment with and without Etanercept for SD/SR-aGvHD is needed.

Methods: A retrospective single-center cohort study designed to assess the overall survival (OS) differences between adults and children with grade III-IV SD/SR-aGvHD who were treated with Etanercept (treatment) vs. best available therapies (control) at the Hadassah Medical Center Combined Adult and Pediatric Program.

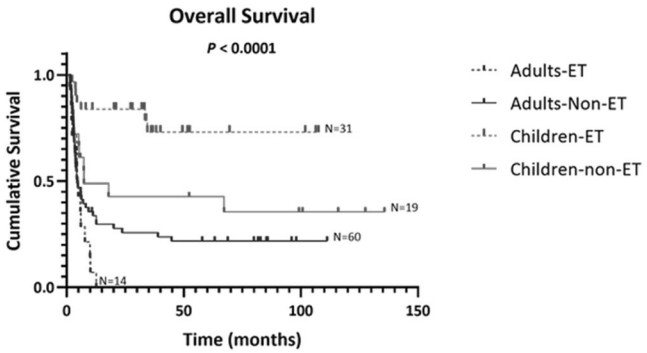
Results: A total of 123 patients, 74 adults and 49 children have undergone alloHSCT and developed grade III-IV SR-aGvHD between January 2010 to June 2019, constitute the study population. Altogether, 45 patients, 14 adults and 31 children, have been treated with Etanercept (4 mg/kg, maximum 25 mg/dose).

Adults were mainly diagnosed with malignant diseases (85.71% vs. 96.67%, treatment vs. control, p = 0.1027), whereas children who were treated with Etanercept were mainly diagnosed with non-malignant diseases (70.97% vs. 33.33, treatment vs. control, p < 0.05).

Mean time to onset of aGvHD was similar among same age subgroups (42 vs. 53 days, treatment vs. control in adults, p = 0.6533; 79 vs. 25 days, treatment vs. control in children, p = 0.3744). Organ involvement was similar among all groups and included GI, skin and liver involvement, from most to least

common. Overall, adults were treated with greater number of treatment lines and achieved poorer responses. No adults who were treated with Etanercept achieved CR compared with CR rate of 18.52% among adults in the control group, whereas 74.04% of the children who were treated with Etanercept acheived CR compared with only 35.29% among children in the control group ($p < 0.05$).

Cumulative survival is presented in Figure 1. Dramatically, all the adults who were treated with Etanercept deceased compared with OS rate of 26.67% among adults in the control group ($p < 0.0001$). On the contrary, children who were treated with Etanercept have had OS rate of 77.42% compared with 38.89% among children in the control group ($p < 0.0001$).



Conclusions: Treatment with Etanercept for SD/SR-aGvHD is associated with dismal prognosis in adults and favorable prognosis in children, compared to their control subgroups. Further studies are needed to truly understand the difference in SD/SR-aGvHD response to Etanercept between adults and children.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P242

PRE-TRANSPLANTATION DIABETES MELLITUS AND OBESITY AND ACUTE GRAFT-VERSUS-HOST DISEASE AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION: A STUDY FROM THE EBMT TRANSPLANT COMPLICATIONS WORKING PARTY

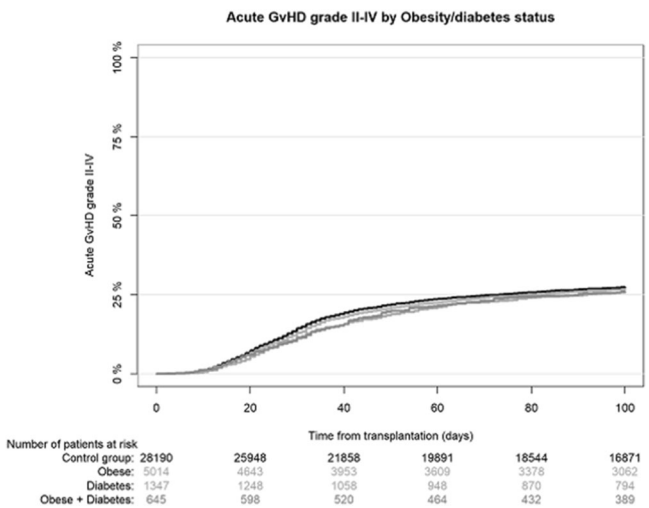
Lars Klingen Gjærde[1], Tapani Ruutu[2], Christophe Peczynski[3], William Boreland[3], Nicolaus Kröger[4], Didier Blaise[5], Thomas Schroeder[6], Régis Peffault de Latour[7], Tobias Gedde-Dahl[8], Aleksandr Kulagin[9], Henrik Sengeløv[1], Ibrahim Yakoub-Agha[10], Jürgen Finke[11], Matthias Eder[12], Grzegorz Basak[13], Ivan Moiseev[9], Hélène Schoemans[14], Christian Koenecke[12], Olaf Penack[15], Zinaida Perić[16,17]

[1]Rigshospitalet, Copenhagen, Denmark, [2]Helsinki University Hospital, Helsinki, Finland, [3]EBMT Paris Study Office, Paris, France, [4]University Hospital Eppendorf, Hamburg, Germany, [5]Institut Paoli Calmettes, Marseille, France, [6]University Hospital, Essen, Germany, [7]Saint-Louis Hospital, Paris, France, [8]Oslo University Hospital, Oslo, Norway, [9]Pavlov University, St. Petersburg, Russian Federation, [10]CHU de Lille, Lille, France, [11]University of Freiburg, Freiburg, Germany, [12]Hannover Medical School, Hannover, Germany, [13]University Clinical Center of the Medical University of Warsaw, Warsaw, Poland, [14]KU Leuven-University of Leuven, Leuven, Belgium, [15]Charité-Universitätsmedizin Berlin, Berlin, Germany, [16]University of Zagreb, Zagreb, Croatia, [17]University Hospital Centre Zagreb, Zagreb, Croatia

Background: Obese mice develop more severe acute graft-versus-host disease (GvHD) after allogeneic hematopoietic cell transplantation (HCT), possibly due to an increased pro-inflammatory cytokine production and a dysregulation of the gut microbiome; likewise, hyperglycemia and new-onset post-transplantation diabetes have been linked to a higher incidence of acute GvHD in patients. However, the impact of pre-existing obesity and diabetes on the risk of acute GvHD and mortality after acute GvHD in patients undergoing allogeneic HCT is unclear.

Methods: From the EBMT registry, we included all adult (≥ 18 years) patients who underwent a first bone marrow or peripheral blood stem cell allogeneic HCT for a hematological malignancy between 2016–2020. We defined obesity as having a body mass index ≥30 kg/m^2, calculated from the pre-transplantation height and weight. Pre-transplantation diabetes was defined as having diabetes requiring treatment with insulin or oral hypoglycemics, but not diet alone. Patients with obesity, diabetes, and obesity +diabetes, respectively, were compared with patients without obesity and diabetes (control group). The primary objective was to compare the incidence of grade II–IV acute GvHD; secondary objectives included comparing the incidence of grade III–IV acute GvHD and chronic GvHD, non-relapse mortality (NRM), and overall survival (OS) after acute GvHD. Multivariable Cox proportional hazards models were used to estimate associations adjusted for patient-, donor-, disease-, and treatment-related variables.

Results: A total of 36 539 patients were included, of which 5228 (14%) had obesity (without co-existing diabetes), 1415 (4%) had diabetes (without co-existing obesity), and 688 (2%) had obesity +diabetes prior to transplant. Patients with diabetes and obesity +diabetes were generally older (median age 61.5 and 59.5 years, respectively) and more likely to be male and have a Karnofsky performance score <90, compared with patients with obesity and the control group (median age 53.8 and 54.3 years, respectively). The cumulative incidence of grade II–IV acute GvHD did not differ according to pre-transplantation obesity or diabetes (Figure). The hazard ratio (HR) of grade II–IV acute GvHD was 1.00 (95% confidence interval [CI] 0.94–1.06, $p = 0.89$) for patients with obesity, 0.95 (95% CI 0.85–1.07, $p = 0.43$) for patients with diabetes, and 0.96 (95% CI 0.82–1.13, $p = 0.63$) for patients with obesity+diabetes. We also did not find support for any difference in the risk of grade III–IV acute GvHD and chronic GvHD, but NRM was higher in patients with obesity (HR 1.08, 95% CI 1.00–1.17, $p = 0.047$), diabetes (HR 1.40, 95% CI 1.24–1.57, $p < 0.001$), and obesity+diabetes (HR 1.38, 95% CI 1.16–1.64, $p < 0.001$). In patients who experienced grade II–IV acute GvHD, the OS from the diagnosis of GvHD was lower in patients with diabetes (HR 1.46, 95% CI 1.25–1.70, $p < 0.001$).



Conclusions: Our findings suggest that the presence of obesity or diabetes prior to allogeneic HCT does not influence the risk of developing grade II–IV acute GvHD. However, having diabetes prior to transplant was associated with an increased risk of death after being diagnosed with grade II–IV acute GvHD.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P243

COMPARISON OF EFFICACY AND TOLERABILITY OF A RUXOLITINIB-BASED THERAPY VERSUS OTHER TREATMENT OPTIONS FOR STEROID REFRACTORY ACUTE GVHD IN A REAL LIFE EXPERIENCE

Marta Lisa Battista[1], Gabriele Facchin[1], Michela Cerno[1], Antonella Geromin[1], Chiara Savignano[1], Giuseppe Petruzzellis[1], Giulia Battaglia[1], Umberto Pizzano[1], Giampaolo Vianello[1], Martina Pucillo[1], Maria De Martino[2], Miriam Isola[2], Renato Fanin[1], Francesca Patriarca[1]

[1]Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy, [2]University of Udine, Udine, Italy

Background: Although the REACH 2 study recently demonstrated higher efficacy of ruxolitinib in comparison with best available treatments for steroid refractory acute GvHD (SR-aGvHD), the impact of this new standard in the real life has still to be determined.

The aim of this retrospective single center study was to compare a ruxolitinib-based therapy versus other treatments used for SR-aGvHD in terms of response rate at day 28, infections and oucome.

Methods: From 2015 to 2021, 159 out of 412 (39%) adult patients undergoing allogeneic stem cell transplantation in our center developed grade II-IV aGvHD and started standard high dose sistemic steroids. Forty-nine out of 159 patients (31%) started a second-line (2L) therapy because of steroid refractoriness and 12 (24%) had a subsequent third-line (3L) therapy.

Median age was 57 years (range 22-73), the underlying diseases were mainly acute leukemias (47%), 55% received a myeloablative conditioning regimen and 94% peripheral blood stem cells; overall, stem cells came from mismatched unrelated donors (47%), matched unrelated or sibling donors (39%) and haploidentical donors (14%).

The 2L and 3L therapies used were: ruxolitinib monotherapy (13 patients), ruxolitinib in association with extracorporeal photopheresis (ECP) (11 patients), ECP (10 patients), ECP in combination with etanercept (6 patients), etanercept monotherapy (17 patients), pentostatin (4 patients) (see table below).

Results: Overall response (OR) at day 28 was significantly higher after ruxolitinib-based treatment corresponding to groups 1-2 (19 out of 24 patients, 79%) in comparison with other therapies (19 out of 37 patients, 51%) ($p = 0.028$), with no significant difference in the rate of complete responses ($p = 0.174$). It's worth remarking that ruxolitinib-based therapy was administered more frequently as 3L option in comparison with other treatments [9/24 (38%) versus 3/37 (8%); $p = 0.004$], while grade III-IV aGVHD was similarly distributed in groups 1-2 versus groups 3-6 ($p = 0.392$).

Among the most commonly observed infectious events, bacteremias occurred in 10 patients (42%) during ruxolitinib-based therapy and in 16 patients (43%) during other therapies ($p = 0.903$); clinically relevant CMV reactivations (CR-CMV) occurred in 12 patients (50%) during ruxolitinib-based therapy and in 13 patients (35%) during other therapies ($p = 0.249$). Among CMV positive patients undergoing letermovir prophylaxis, a late CR-CMV occurring after day 100 was detected in 7 out of 10 patients (70%) during ruxolitinib-based treatment and in 2 out of 11 (18%) during other therapies ($p = 0.016$).

At a median follow-up of 19 months (range 4-84) after the start of 2L treatment, cumulative incidence of mortality at day 100 was 28% after ruxolitinib-based treatment and 31% after other therapies ($p = 0.551$).

One-year overall survival was 43%, without significant difference between ruxolitinib-based treatment and other therapies.

Conclusions: In our experience, a ruxolitinib-based therapy for SR-aGVHD resulted in a significantly higher OR rate at day 28 in comparison with other treatment options, while infectious complications and outcome didn't significantly differ according to the administered treatment, suggesting that infections management and failure to maintain initial GVHD response are still problems that need to be addressed in the real life setting.

Disclosure: Nothing to declare.

Group	Treatment type	N. patient	N. patients for therapy line (%)		aGvHD at refractoriness (%)		Involved organ (%)				OR (%)	CR (%)	PR (%)	NR/ Prog (%)
			2L	3L	gr II	gr III-IV	skin	liver	GI tract	multi organ				
1	**Ruxolitinib**	13	7 (54)	6 (46)	6 (46)	7 (54)	2 (16)	0	6 (46)	5 (38)	8 (62)	6 (46)	2 (16)	5 (38)
2	**ECP+ Ruxolitinib**	11	8 (73)	3 (27)	3 (27)	8 (73)	2 (18)	0	0	9 (82)	11 (100)	8 (73)	3 (27)	0
3	**ECP**	10	9 (90)	1 (10)	9 (90)	1 (10)	8 (80)	0	1 (10)	1 (10)	8 (80)	6 (60)	2 (20)	2 (20)
4	**ECP+ Etanercept**	6	6 (100)	0	2 (34)	4 (66)	1 (17)	0	1 (17)	4 (66)	2 (34)	1 (17)	1 (17)	4 (66)
5	**Etanercept**	17	16 (94)	1 (6)	6 (35)	11 (65)	2 (12)	1 (6)	2 (12)	12 (70)	8 (47)	7 (41)	1 (6)	9 (53)
6	**Pentostatin**	4	3 (75)	1 (25)	1 (25)	3 (75)	0	0	2 (50)	2 (50)	1 (25)	1 (25)	0	3 (75)
Total		**61**	**49**	**12**	**27**	**34**	**15**	**1**	**12**	**33**	**38**	**29**	**9**	**23**

12 - Graft-versus-host Disease – Clinical

P244

FEASIBILITY AND EFFICACY OF PARTIAL OR COMPLETE REPLACEMENT OF POST-TRANSPLANTATION CYCLOPHOSPHAMIDE WITH BENDAMUSTINE IN PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION

Manthan Kathrotiya[1], Ankit Jitani[1], Hemant Menghani[1], Vijay Shirure[1], Shruti Bhise[1], Mayur Mundhe[1], Wajid Kazi[1], Sandip Kheni[1], Jayani Patel[1], Velu Nair[1]

[1]Apollo CBCC Hospital, Gandhinagar, India

Background: With Post-transplantation cyclophosphamide (PT-CY) use, frequency of viral reactivations (BK and CMV) is high leading to increase in transplant related morbidity, mortality and total cost of allogenic stem cell transplant (alloSCT) which is a major concern in developing countries. Katsanis et.al. published results of a phase I trial where they compared outcomes of

combination of PT-CY (Day+3) and Post-transplantation bendamustine (PT-BEN) (Day+4) with only PT-CY on both days. Based on their encouraging outcomes we did a pilot study to replace PT-CY with PT-BEN either partially or completely.

Methods: To prospectively compare outcomes of alloSCT in benign hematological disease and hematologic malignancies between 14 patients who received either PT-BEN on Day +3, +4 or PT-CY on Day +3 and PT-BEN on Day +4 against 17 contemporaneous recipients treated with only PT-CY (Day+3 and +4).

Results: We found that complete or partial replacement of PT-CY with PT-BEN was associated with significantly earlier trilineage engraftment. The median time to an ANC of 0.5 x 10^9/L was 11 days (9-17 days) in PT-BEN/PT-CY-BEN group, compared with 15.5 days(12-28 days) in PT-CY group (P = 0.0039). Trilineage engraftment was seen in 85.7% of patients in PT-BEN/PT-CY-BEN group, with all demonstrating complete donor chimerism in peripheral blood studies on days +30, +60, and +90 while two patients (14.3%) with haplo-identical donors developed primary graft failure due to high Donor Specific Antibodies (DSA). The cumulative incidence of CMV was 71.4% in PT-BEN/PT-CY-BEN group, compared with 58.8% in PT-CY group (P = 0.46). BK hemorrhagic cystitis was detected in 4 PT-CY patients (23.5%), compared with 1 patient (7.14%) in PT-BEN/PT-CY-BEN group (P = 0.21). One patient (5.8%) each in PT-CY group had EBV reactivation and HHV6 encephalitis. The incidence of gram-negative bacteremia in the PT-CY and PT-CY-BEN groups in the first 6 months post-transplant was 35.29% and 21.4%, respectively (P = 0.39). The cumulative incidence of grade II-IV and grade III-IV acute graft versus host disease (aGVHD) was 21.4% and 7.1%, respectively, in the PT-BEN/PT-CY-BEN group, while in the PT-CY group, two patient (11.7%) had grade I aGVHD but no patients had grade II-IV aGVHD. One patient (7.1%) had limited oral cGVHD following PT-CY-BEN with no patients developing severe cGVHD, while in PT-CY group, incidence of cGVHD was 11.7% with 5.8% patients developing severe cGVHD (P = 0.66). With a median follow-up of 11 months (3-19 months) Non Relapse Mortality (NRM) was seen in only one patient (7.1%) receiving PT-BEN/PT-CY-BEN due to complication of post-transplant HLH while it was 23.5% in PT-CY group at median follow up of 12 months (1-41 months) (P = 0.21). Total cost (INR) of transplant was 31% lesser in PT-BEN/PT-CY-BEN group (INR 1760532) compared to PT-CY group (INR 2489528)(P = 0.0002).

Characteristic	PT-BEN/ PT-CY-BEN (N = 14)	PT-CY (N = 17)
Age, yr, median (range)	8 (6-48)	41 (7-56)
Male sex, n (%)	7 (50)	13 (76)
Diagnosis, n (%)		
Hematologic malignancies	10 (71)	14 (82)
Benign hematologic diseases	4 (29)	3 (18)
Pretransplantation status, n (%)		
CR1	5 (36)	6 (36)
CR2	7 (50)	4 (23)
>CR2	-	3 (18)
Other	2 (14)	4 (23)
HCT Comorbidity Index, n (%)		
≤2	14 (100)	15 (88)
≥3	-	2 (12)
Conditioning, n (%)		
MAC	8 (57)	13 (77)
RIC	6 (43	4 (23)
MSD, n (%)	4 (29)	5 (29)
HAPLO, n (%)	9 (64)	12 (71)
MUD, n (%)	1 (7)	-

Conclusions: We confirm that partial or complete substitution of PT-CY with PT-BEN enhances engraftment which helps reducing total transplant cost significantly. A trend towards lower BK viruria in PT-BEN/PT-CY-BEN group was observed with comparable CMV reactivations in both groups. Incidence of aGVHD and primary graft failure was more in PT-BEN/PT-CY-BEN group but numbers are limited to confirm the findings. PT-BEN/PT-CY-BEN is a promising treatment option but requires further evaluation.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P245

A PHASE 1B STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF AN INVESTIGATIONAL MICROBIOME THERAPEUTIC, SER-155, IN ADULTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION

Bina Tejura[1], Satyajit Kosuri[2], Nandita Khera[3], M. Zachariah DeFilipp[4], Mary-Jane Lombardo[1], Christopher Ford[1], Jonathan U Peled[5], Marcel R.M. van den Brink[5], Lisa von Moltke[1], Doris M. Ponce[5]

[1]Seres Therapeutics, Cambridge, United States, [2]University of Chicago Medicine, Chicago, United States, [3]Mayo Clinic, Phoenix, United States, [4]Massachusetts General Hospital, Boston, United States, [5]Memorial Sloan Kettering Cancer Center, New York, United States

Background: In patients undergoing allogeneic hematopoietic cell transplantation (HCT), loss of gastrointestinal microbial diversity is associated with risk of bloodstream infections (BSI), acute graft-versus-host disease (aGvHD), and death. SER-155 is an investigational cultivated microbiome therapeutic rationally designed to improve clinical outcomes in HCT by restoring colonization resistance to potential pathogens, promoting epithelial barrier integrity, and reducing colonic inflammation. SER-155-001 is a Phase 1b study to evaluate the efficacy, safety, and pharmacokinetics (PK) of SER-155 in adults undergoing HCT that is currently ongoing at 4 sites.

Methods: This study will enroll approximately 75 subjects ≥18 years in an open-label Cohort 1 (n = 15) followed by a double-blind, placebo-controlled Cohort 2 (n = 60) randomized 1:1 to SER-155 or placebo. Exclusion criteria include history of severe colitis or active inflammatory bowel disease or total colectomy, umbilical cord blood or ex vivo T-cell depletion, exposure to fecal microbiota transplant or any live microbial therapeutic within 3 months prior to screening, and evidence of relapse or progression of hematologic malignancy (minimal residual disease is allowed).

Following screening, subjects in both cohorts will receive 2 treatment courses (one before and one after HCT), each comprised of microbiome conditioning with oral vancomycin or placebo followed by SER-155 or placebo, and a conditional 3rd treatment course if the subject receives antibiotics (Table 1). Safety outcomes will be followed through 52 weeks post HCT.

The primary endpoint is the incidence and severity of adverse events, serious adverse events, and adverse events of special interest. Secondary endpoints include rates of BSI, gastrointestinal infections, aGvHD, febrile neutropenia and overall survival in placebo vs SER-155 arms. Microbiome related endpoints include engraftment of SER-155 bacterial strains in the gastrointestinal tract (PK endpoint) and fecal microbiome diversity, composition and metabolites.

Table 1.	Microbiome conditioning regimen (4 days)	Treatment course* (10 days)
Cohort 1	Oral vancomycin (125 mg)	2 capsules of SER-155 once daily
Cohort 2	Oral vancomycin (125 mg)	2 capsules of SER-155 once daily
Cohort 2	Placebo	2 capsules of placebo once daily

*A 3rd course of SER-155 will be administered without microbiome conditioning following completion of antibiotics for subjects who receive 3 days of systemic antibiotics following HCT.

Results: In April 2022, the SER-155 Data and Safety Monitoring Committee met as part of a planned review of available safety data from Cohort 1 and supported continuation of Cohort 1 enrollment. Cohort 1 enrollment is complete and data analysis is ongoing.

Previously presented at ASH 2022 (Blood (2022) 140 (Supplement 1): 10532–10533. https://doi.org/10.1182/blood-2022-162386) and ASCO 2022 (DOI: 10.1200/JCO.2022.40.16_suppl.TPS7074 Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022) TPS7074-TPS7074. Published online June 02, 2022.)

Conclusions: In this Phase 1b study, the feasibility, safety, and clinical efficacy of SER-155 is being assessed in the setting of allogeneic HCT. This trial will add to the expanding clinical experience of microbiome- directed interventions in allogeneic HCT recipients.

Clinical Trial Registry: NCT04995653

Disclosure: **Doris M. Ponce** has received funding from Incyte, and Takeda, and has declared financial interests in Incyte, Sanofi, CareDx, Ceramedix.

Satyajit Kosuri - Nothing to declare

Nandita Khera – Nothing to declare

M. Zachariah DeFilipp reports research support from Incyte, Corp., Regimmune, Corp and Taiho Oncology, Inc. and receiving consulting fees from Kadmon Corp., Omeros Corp., Incyte, Corp., MorphoSys AG, and Inhibrx.

Mary-Jane Lombardo is an employee and shareholder of Seres Therapeutics

Christopher Ford is an employee and shareholder of Seres Therapeutics

Jonathan U. Peled reports funding from NHLBI NIH Award K08HL143189, the MSKCC Grant NCI P30 CA008748. He has research funding, intellectual property fees, and travel reimbursement from Seres Therapeutics, and consulting fees from DaVolterra, CSL Behring, and from MaaT Pharma. He serves on an Advisory board of and holds equity in Postbiotics Plus Research, has filed IP applications related to the microbiome (reference numbers #62/843,849, #62/977,908, and #15/756,845). MSK has financial interests relative to Seres Therapeutics.

Marcel R.M. van den Brink reports funding from NCI, R01-CA228358, R01-CA228308, P30 CA008748 MSKCC Support Grant/Core Grant and P01-CA023766; NHLBI award R01-HL123340 and R01-HL147584; NIA award P01-AG052359, and Tri-Institutional Stem Cell Initiative; research support and stock options from Seres Therapeutics and stock options from Notch Therapeutics and Pluto Therapeutics; he has received royalties from Wolters Kluwer; has consulted, received honorarium from or participated in advisory boards for Seres Therapeutics, Vor Biopharma, Rheos Medicines, Frazier Healthcare Partners, Nektar Therapeutics, Notch Therapeutics, Ceramedix, Lygenesis, Pluto Therapeutics, GlaskoSmithKline, Da Volterra, Thymofox, Garuda, Novartis (Spouse), Synthekine (Spouse), Beigene (Spouse), Kite (Spouse); he has IP Licensing with Seres Therapeutics and Juno Therapeutics; and holds a fiduciary role on the Foundation Board of DKMS. MSK has institutional financial interests relative to Seres Therapeutics.

Lisa von Moltke is an employee and shareholder of Seres Therapeutics

12 - Graft-versus-host Disease – Clinical

P246

BELUMOSUDIL AND RUXOLITINIB COMBINATION THERAPY FOR TREATMENT OF STEROID-REFRACTORY CHRONIC GRAFT-VERSUS-HOST DISEASE

Iskra Pusic[1], Chelsea Minor[1], Catherine Lee[2], Muthu Veeraputhiran[3], John F DiPersio[1]

[1]Washington University School of Medicine, Siteman Cancer Center, St. Louis, United States, [2]The University of Utah Transplant and Cellular Therapy Program at Huntsman Cancer Institute, Salt Lake City, United States, [3]University of Arkansas for Medical Sciences, Winthrop P Rockefeller Cancer Institute, Little Rock, United States

Background: Belumosudil and ruxolitinib are FDA-approved agents for steroid-refractory chronic graft-versus-host disease (cGVHD) in the USA and combination therapy may lead to increased treatment response due to their different mechanisms of action.

Methods: We conducted a multi-institutional retrospective study of real-world practice adding the ROCK2-inhibitor belumosudil in patients already receiving the JAK-inhibitor ruxolitinib (B + R) for steroid-refractory cGVHD from June 2021 to October 2022. Treatment response was determined according to the investigator's opinion. Results are reported descriptively.

Results: A cohort of 14 patients was evaluated (Table 1). Patients received a median of 3 (range, 2-5) lines of therapy (LOTs) before initiating ruxolitinib. Four patients had additional LOTs prior to starting belumosudil. The median time from cGVHD diagnosis to B + R was 58 months (range, 6-200). The median number of organs affected by cGVHD at the time of B + R was 4 (range, 1-6), and the most commonly affected organs were skin (n = 10), eyes (n = 10), mouth (n = 9), joint/fascia (n = 7) and lung (n = 5). Sclerotic features occurred in 7 of 10 patients with skin involvement. At initiation of B + R, patients were on a median of 1.5 (range, 0-3) additional immunosuppressive therapies, including prednisone (n = 9), sirolimus (n = 5), tacrolimus (n = 3), mycophenolate mofetil (n = 4), and ECP (n = 1).

Belumosudil was initiated at 200 mg QD (n = 8) and 200 mg BID (n = 6) for patients on a proton pump inhibitor. At belumosudil initiation, the ruxolitinib dose was 10 mg BID in 8 patients, 5mg BID in 5 patients, and 5 mg QD in 1 patient. Ruxolitinib dose was reduced by 50% in 8 patients, and eventually discontinued in 4 patients. Belumosudil was dose-reduced in 4 patients for worsening renal function, fatigue and rash. Prednisone dose was successfully reduced in 4 of 9 patients.

At a median follow up of 10.7 months (range, 1-13) after starting B + R, 6 patients had partial response, 7 had stable disease, and 1 progressed. In patients who had partial response, responding organs were skin (n = 3), mouth (n = 3), joint/fascia (n = 2), eyes (n = 2), and lungs (n = 1). Of the 7 patients with stable disease, 4

were on prednisone, and 2 of these 4 patients had their prednisone dose reduced.

Overall, B + R was well tolerated. Grade 3 anemia (n = 2) resolved with ruxolitinib dose reduction. There were no grade 3 thrombocytopenia, neutropenia or transaminitis. One patient had grade 3 elevation in creatinine that resolved after stopping sirolimus, and reducing mycophenolate and ruxolitinib doses. Documented bacterial infections (n = 6) occurred in 3 patients; respiratory viral infections (n = 9) and disseminated zoster (n = 1) occurred in 5 patients. There were no cases of CMV reactivation or fungal infection. Other grade 3 adverse events included nausea, fatigue, skin blisters and pulmonary embolism. There was no malignancy relapse. One patient with partial response died at home from an unclear cause.

Table 1.

Variable	N = 14
Median age at B + R, years	48 (34-78)
Median number of LOT for cGVHD prior to initiating ruxolitinib	3 (2-5)
Median time from cGVHD diagnosis to B + R initiation, months	58 (6-200)
Median number of organs involved with cGVHD at the start of B + R	4 (1-6)
Skin [skin sclerosis]	10 [7/10]
Eyes	10
Mouth	9
Joint/fascia	7
Lung	5
Median additional IST at the start of B + R	1.5 (0-3)
cGVHD response (%)	
Partial response	6 (43)
Stable disease	7 (50)
Progression	1 (7)
Median follow up on B + R, months	10.7 (1-13)
Median time to PR from B + R initiation for 6 PR patients, months	2.6 (1-4.3)
Median number of organs responding for 6 PR patients	2 (1-2)
Number of patients with prednisone dose reduction (%)	4 (44)
Number of patients alive at last follow-up (%)	13 (93)

Conclusions: This retrospective analysis demonstrates that treatment of steroid-refractory cGVHD with B + R is feasible, safe and tolerable. B + R led to a clinical response in approximately 43% of patients and stabilized disease in 50% of patients while also allowing prednisone dose-reduction in several patients.

Clinical Trial Registry: N/A

Disclosure: **Iskra, Pusic:**
Incyte: Advisory Board, Research Funding
Syndax: Advisory Board
Chelsea, Minor:
Nothing to declare
Catherine, Lee:
Incyte: Research Funding; Consulting; Advisory Board; Clinical Trial Steering Committee
Sanofi: Advisory Board; Consulting
Muthu, Veeraputhiran:
KITE: Speaker Bureau,
KITE: Advisory Board, Consulting
ADC therapeutics: Advisory Board, Consulting
Sanofi: Advisory Board, Consulting
John F. DiPersio:
Incyte: Research Funding
Mallinckrodt Pharmaceuticals: Research funding
Magenta Therapeutics: Scientific Advisory Board

12 - Graft-versus-host Disease – Clinical

P247

CYCLOSPORINE AND METHOTREXATE VERSUS CYCLOSPORINE FOR PROPHYLAXIS OF GRAFT-VERSUS-HOST DISEASE IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM AN HLA-IDENTICAL SIBLING FOR PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

Sabrine Mekni[1], Nour Ben Abdeljelil[1], Saloua Ladeb[1], Rimmel Yosra Kanoun[1], Insaf Ben Yaiche[1], Rihab Ouerghi[1], Lamia Torjemane[1], Ines Turki[1], Dorra Belloumi[1], Tarek Ben Othman[1]

[1]Centre National de de Greffe de Moelle Osseuse, Tunis, Tunisia

Background: It is still controversial whether the combination of cyclosporine and methotrexate (CsA/MTX) is superior to CsA alone in the prevention of graft-versus-host disease (GVHD) in allogeneic hematopoietic stem cell transplantation (allo-HSCT) for pediatric acute lymphoblastic leukemia (ALL).

The objective of this study was to Compare the outcomes of CsA/MTX to CsA alone for prophylaxis of GVHD in allo-HSCT from an HLA-identical sibling for high-risk pediatric ALL.

Methods: Retrospective observational study conducted on patients < 18 years who underwent allo-HSCT from an HLA-identical sibling for ALL between February 2007 and September 2021. GVHD prophylaxis consisted of CsA/MTX or CsA alone. CsA was initiated on day-1 before allo-HSCT (3 mg/kg/day). Optimal target CsA concentration was 150–300 ng/mL. CsA administration was continued until 3 months after allo-HSCT and then tapered off in the absence of GVHD. MTX was administrated intravenously 24 hours after infusion of the graft (15 mg/m^2 on day 1 and 10 mg/m^2 on days 3 and 6).

Results: Seventy-one patients were included (53.5% B-ALL and 46.5% T-ALL): CsA/MTX (n = 21) and CsA (n = 50). Patient's characteristics of the 2 groups were comparable. Median age was 10 years (range, 4-17 years). At transplant, 68% patients were in first complete remission. Conditioning was TBI or chemotherapy based in 68% and 32% of patients, respectively. The source of graft was bone marrow in 86% of patients (92% in CsA/MTX and 62% in CsA group). The median time for neutrophil engraftment was significantly longer in CsA/MTX group: 16 days (range, 11-27 days) vs 13 days (range, 6-31days), respectively (p = 0.005), but no difference in documented infections rate (p = 0.58). There was a trend toward a lower cumulative incidence (CI) of acute GVHD ≥ grade II in CsA/ MTX (20% vs 48%, respectively, p = 0.08). CI of chronic GVHD was 8% and 27% in the CSA/MTX and CsA group, respectively (p = 0.2). Ten patients (1CsA/MTX and 9 CsA) had extensive GVHD. One patient died of GVHD in the CsA group. CI of relapse and NRM were not significantly different between the two groups (27% vs 38%, p = 0,6 and 9.5% vs 11%, p = 0.7, respectively). After a median follow-up of 29 months (range, 1-179), the estimated 3-year overall survival and event-free survival were 77% vs 59% (p = 0.4) and 77% vs 54% (p = 0.27), in CsA/MTX and CsA group, respectively.

Conclusions: In our experience, ALL pediatric patients receiving Geno-identical allo-HSCT and CsA alone as GVHD prophylaxis have fast granulocyte reconstitution and comparable outcome to CsA/MTX combination.

Disclosure: Nothing to declare

12 - Graft-versus-host Disease – Clinical

P248

OUTCOMES OF PATIENTS DIAGNOSED WITH STEROID-REFRACTORY CHRONIC GRAFT-VERSUS-HOST DISEASE RESISTANT OR INTOLERANT TO SECOND-LINE RUXOLITINIB

Maria Sola[1,2], Sara Redondo[3], Sara Garrido[1,2], Laura Fox[1,2], Sonia García-García[1], Carla Alonso-Martínez[1], Ana Pérez-González[1,2], Olga Salamero[1,2], Antonieta Molero[1,2], Rodrigo Martino[3], Francesc Bosch[1,2], David Valcárcel[1,2], Irene García-Cadenas[3], Guillermo Ortí[1,2]

[1]University Hospital Vall d'Hebron, Barcelona, Spain, [2]Experimental Hematology Unit, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [3]University Hospital Sant Pau, Barcelona, Spain

Background: Chronic graft-versus-host disease (cGvHD) represents a major cause of mortality and morbidity after allogeneic hematopoietic cell transplant (Allo-HCT). After steroid failure, the dual JAK1/2 inhibitor, ruxolitinib, represents a standard of care in steroid refractory chronic GvHD (SR-cGvHD). However, the prognosis and clinical management of SR-cGvHD patients resistant or intolerant to second-line (2L) ruxolitinib is uncertain.

Methods: This retrospective and collaborative study included patients from two EBMT centers. The study was approved by the Vall d'Hebron University Hospital, Barcelona, ethics committee. Inclusion criteria were: 1)patients undergoing allo-HCT; 2)diagnosed with SR-cGvHD, 3)resistant or intolerant to 2L ruxolitinib. The primary endpoint was the overall response rate (ORR) after third-line (3L) treatment. Secondary endpoints were overall survival (OS) and non-relapse mortality (NRM).

Results: A total of 17 patients treated with ruxolitinib 2L were included between July 2016 and November 2021. The median follow-up from cGvHD diagnosis was 42 months (range 4-119). Eleven patients (65%) were diagnosed with moderate cGvHD and 6 (35%) with severe. Skin (14 patients; 82%), liver (7 patients; 41%) and ocular (7 patients; 41%) were the most frequently affected organs at cGvHD diagnosis. Ruxolitinib led to a 25-75% decrease in steroid dose in 12 patients (70%). The most common cause to discontinue ruxolitinb was suboptimal response in 12 patients (71%). Out of the 5 patients who discontinued ruxolitinib due to intolerance, 2 patients discontinued due to infection, 2 due to haematolological toxicity and one patient due to liver toxicity. The 3L therapeutical approach consisted on extracorporeal photopheresis (ECP) in six patients (35%), calcineurin inhibitors in 3 patients (18%), mTOR inhibitor (3; 18%), etanercept (1; 6%), mesenchymal stem cells (1; 6%), alpha 1-antitrypsin (1; 6%), PUVA (1; 6%) and Rituximab plus plasmapheresis (1; 6%). The 6-month overall response rate (ORR) after 3L was 82%, including 2 patients (12%) with CR and 12 patients (70%) with PR. The 6-month ORR of patients treated with 3L ECP was 66%. Out of the 15 patients receiving steroid at the time of 3L onset, 12 patients (80%) achieved a steroid dose reduction. At last follow-up, 7 patients (42%) were free of immunosuppression therapy. The median OS was 53.4 months (range, 7.1 – 175). The estimated 2- and 5-year OS and were 94% and 66%, respectively; and the 2- and 5-year NRM was 0%, and 14%, respectively. Four patients died during the study period. The cause of death was infection in 2 patients, CNS-related in 1 patient and disease relapse in 1 patient.

Conclusions: In this cohort, the 6-month ORR after 3L treatment for SR-cGvHD exceeded 80%. Additionally, 3L after ruxolitinib failure allowed a steroid dose reduction in a remarkable proportion of patients. Interestingly, a third of patients were treated with ECP as 3L and nearly half of the patients were free of immunosuppression therapy at last follow-up. These data should encourage the exploration of an optimal 3L therapeutic approach after 2L ruxolitinib failure in SR-cGvHD. A study on this subject including a larger number of patients is warranted.

Disclosure: Nothing to declare

12 - Graft-versus-host Disease – Clinical

P249

CD52 EXPRESSION ON T CELLS PREDICT DEVELOPMENT OF ACUTE GVHD IN PATIENTS AFTER ALEMTUZUMAB BASED CONDITIONING

Pascal Woelfinger[1], Saskia Hendriks[1], Diana Wolff[1], Matthias Theobald[1], Tobias Bopp[2], Eva-Maria Wagner-Drouet[1]

Oncology and Pneumology, University Cancer Center Mainz (UCT), Mainz, Germany, [2]Institute for Immunology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

Background: Reduced intensity conditioning regimen (RIC) followed by allogeneic hematopoietic stem cell transplantation (alloHSCT) is an effective therapy to cure hematological malignancies. Acute and chronic Graft versus Host Disease (a/cGVHD) are common and life-threatening complications for patients after alloHSCT. Alemtuzumab, a humanized monoclonal antibody against CD52, is an effective way to prevent GVHD.

In 2020, we could proof in a retrospective patient cohort that reconstitution of $CD52^{neg}$ T cells and $CD52^{neg}$ Treg correlated with onset, severity and clinical course of aGVHD. Patients with aGVHD showed significant lower levels of $CD52^{pos}$ T cells compared to patients with cGVHD or without GVHD ($p < 0.001$). Former results from our last restrospective study indicated a rate of <40% $CD52^{pos}CD4^{pos}$ T cells and $CD52^{pos}$ Treg at day + 50 may be used as a predictive treshhold for the development of aGVHD. In this study, we focus on prospective analysis of $CD4^{pos}$ and $CD8^{pos}$ T cells as well as Treg within the first 100 days after TCD with Alemtuzumab to serve a cut-off value of $CD52^{pos}$ T cells to predict development of aGVHD.

Methods: Peripheral blood samples were collected weekly from 30 patients who underwent alloHSCT (d + 30 up to d + 200). Patients were treated with RIC: fludarabine (30 mg/m^2 days -7 to -3), melphalan (140 mg/m^2 day 2) and alemtuzumab (20 mg days -8 to -4). Phenotypic analyses were performed by flow cytometry (CD3, CD4, CD8, CD25, CD52, Foxp3). To assess each cell population, discrimination was analyzed by obtaining the area under the receiver operating characteristic curve (AUC, Youden-Index to asses sensitivity and specificy).

Results: We tested CD52 expression at different time points after alloHSCT. The optimal cut off values for the CD52 expression of each T cell subset was established day + 50 after alloHSCT to predict aGVHD: 9.2% for $CD4^{pos}$ T cells (sensitivity: 0.88; 1-specificity: 0.19), 68.7% for $CD8^{pos}$ T cells (sensitivity: 0.77; 1-specificity: 0.14) and 48.4% for Treg (sensitivity: 1; 1- specificity: 0.09). Therefore, for all three T cell subgroups CD52 expression at day + 50 have at least excellent discrimination power and are a useful and easy to analyze marker for the prediction of aGVHD. For chronic GVHD no cutt of could be defined.

Conclusions: For all three T cell subgroups, CD52 expression at day + 50 has at least excellent predicitive value. CD52 expression could be useful and an easy to analyze marker for the prediction of aGVHD after alemtuzumab. CD52 expression may lead to a more indiviualized strategy in tapering of immunosuppressive drugs.

Clinical Trial Registry: -
Disclosure: No conflict of interest

12 - Graft-versus-host Disease – Clinical

P250

CHRONIC GRAFT-VERSUS-HOST DISEASE IN CHILDREN AFTER ALLOGENEIC HSCT- SINGLE-CENTER RETROSPECTIVE ANALYSIS OF INCIDENCE, SEVERITY, RISK FACTORS AND IMPACT ON OUTCOME

Jaroslava Adamcakova[1], Miroslava Makohusova[1], Julia Horakova[1], Ivana Bodova[1], Tomas Sykora[1], Dominika Doczyova[1], Miroslava Pozdechová[1], Maria Fussiova[1], Peter Svec[1], Alexandra Kolenova[1]

[1]National Institute of Children's Diseases, Bratislava, Slovakia

Background: Chronic graft-versus-host disease (cGvHD) is a non-infectious complication after allogeneic HSCT with an incidence of 6 – 63%, depending on transplant modalities and risk factors. It can result in serious damage to individual organs, in children it can lead to unfavorable motor development, disability and, ultimately, to a poor overall quality of life. In particular, the severe form of cGvHD represents the major cause of late morbidity and worsens overall survival after HSCT, requiring long-term immunosuppressive therapy. On the other hand, in patients with a malignant diagnosis, a mild form of GvHD is desirable, as a lower risk of relapse is expected due tu the GvL effect.

Methods: A single-center retrospective analysis of the incidence, organ specificity, and overall severity of chronic GvHD according to NIH 2014 and evaluation of the relationship of chronic GvHD to selected risk factors (age, malignant / non-malignant diagnosis, bone marrow / PBSC, acute GvHD, conditioning regimen, HLA disparity, female to male mismatch). The impact of chronic GvHD and its severity on overall survival (OS) and the impact of chronic GvHD on survival in children with malignant and benign disease in our cohort were also evaluated.

Results: We retrospectively analyzed 270 children who underwent allogeneic HSCT at the Bone Marrow Transplantation Unit in Bratislava in the period 1995-2020 for malignant (n = 188) or nonmalignant (n = 82) diseases. The donor was an HLA-matched family donor in 114 cases and an alternative donor in 153. Bone marrow was the stem cell source in 131 cases, peripheral blood stem cells (PBSC) in 136, and cord blood (CB) in 3 cases. Chronic GVHD developed in 92 children (34%). According to the NIH 2014 criteria, we diagnosed a mild form of GvHD in 11 %, moderate in 19% and severe form in 4,4% of patients with cGvHD. Skin involvement dominated (80%). In statistical analysis, variables predicting cGVHD were grade III to IV of acute GVHD ($p = 0{,}002$) and diagnosis of malignancy ($p = 0{,}040$). On the contrary, the incidence of cGvHD was significantly lower in children after HSCT from a matched family donor ($p = 0{,}002$) or if BM was used as the source of HSC ($p = 0{,}015$). When comparing the probability of 5-year overall survival in terms of the overall severity of cGvHD, patients with mild (96%) and moderate forms of cGvHD (92%) had a significantly better 5 year-overall survival than children without cGvHD (80%), because our cohort was dominated by patients with malignant disease, and they benefited from the GvL effect. On the contrary, in patients with a severe form of cGvHD, the 5-ys OS was significantly worse (50%).

Conclusions: The incidence of GvHD in our cohort is comparable to published data. We confirmed also the GvL effect in a subgroup of children with a malignant diagnosis and mild or moderate cGvHD. The goal is to completely avoid cGvHD for non-malignant diagnoses, to maintain the best possible graft versus leukemia effect for malignant ones, while maintaining the best possible quality of life and to prevent a severe form of chronic GvHD.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P251

CHRONIC GRAFT-VERSUS-HOST DISEASE ASSOCIATED POLYMYOSITIS: A SINGLE-CENTER CASE SERIES, DIAGNOSTIC AND MANAGEMENT APPROACH

Jing Yuan Tan[1], Ming Lee[1], Lai Peng Chan[1], Jeffrey Quek[1], Francesca Lim[1], Tertius Tuy[1], Yeh Ching Linn[1], William Hwang[1], Aloysius Ho[1], Jordan Hwang[1], Jing Jing Lee[1], Yeow Tee Goh[1], Hein Than[1]

[1]Singapore General Hospital, Singapore, Singapore

Background: Graft-versus-host disease (GvHD) remains a major cause of morbidity and mortality following allogenic haematopoietic stem cell transplantation (HCT). GvHD-associated myositis is an uncommon presentation with significant sequalae, and thus highlights the importance of early recognition and prompt treatment. We present 3 cases of GvHD-associated polymyositis at our institution.

Methods: A retrospective chart review was performed with our institutional review board's approval. Three cases of GvHD-associated polymyositis were identified among 708 allogenic HCT performed in Singapore General Hospital from 2005 to 2021.

Results: Three male patients, ages 23 to 44 were identified with diagnosis of acute myeloid leukaemia (n = 1), acute lymphoblastic leukaemia (n = 1) and blast-phase chronic myeloid leukaemia (n = 1). All 3 patients had myeloablative conditioning followed by HLA full-matched sibling stem cell transplant and, received calcineurin inhibitor and methotrexate as GvHD prophylaxis. Table 1 summarizes the patient and transplant characteristics. All 3 patients had a history of either acute or chronic GvHD prior to presentation of GvHD-associated myositis. Common main presenting complaints were fatigue, proximal myopathy and upper limb/lower limb pain, and Case-3 also had dyspnoea from respiratory muscle involvement. Laboratory testing showed high serum creatine kinase (CK) and aldolase levels in all cases with unyielding infective and autoimmune myositis panels. Improvement in myopathy and serum CK levels after initiating corticosteroids in Case-1 led to a clinical diagnosis of GvHD-associated myositis; while Cases-2 and 3 were diagnosed histopathologically. In Case-3 where karyotype of female donor origin and 100% donor chimerism were detected, we utilized fluorescence in situ hybridization (FISH) analysis to further support the diagnosis of GvHD-associated polymyositis. FISH using CEP X and CEP Y probe set on immunohistochemistry stained muscle tissue specimen visualized that 30% of nuclei scored were in the muscle fibres of recipient XY origin and 70% were of T-lymphocytes of donor XX origin. All the patients achieved initial clinical and biochemical response with intravenous methylprednisolone 1-2 mg/kg/day and subsequently required low-dose corticosteroids and/or immunosuppressants for recurrent flares of myositis. Case-3 at the time of leukaemic relapse was maintained on extracorporeal photopheresis (ECP) while corticosteroids were rapidly tapered off. Two patients were alive more than 10 years post-transplant at

their last follow-up, whereas Case-3 succumbed to the relapsed leukaemia at 11 months post-transplant.

Table 1. Patient and Transplant Characteristics

	Case-1	Case-2	Case-3
Age (years)/ Gender	33/Male	44/Male	23/Male
Diagnosis	Acute myeloid leukaemia	Acute lymphoblastic leukaemia	Chronic myeloid leukaemia
Disease status at transplant	Complete remission	Complete remission	Complete cytogenetic remission
Donor type	HLA full-matched brother	HLA full-matched brother	HLA full-matched sister
Conditioning regimen	Busulphan, cyclophosphamide	Cyclophosphamide, TBI	Busulphan, cyclophosphamide
GvHD prophylaxis	Tacrolimus, methotrexate	Ciclosporin	Tacrolimus, methotrexate
Neutrophil engraftment	Day 14	Day 14	Day 19
History of acute/ chronic GvHD: Day from transplant/organ involvement	Day 17/Liver and gut	Day 141/Liver	Day 120/Skin and liver
Time of onset of GvHD-associated myositis (months)	14	20	6
Serum creatine kinase (U/L)	4028	3219	5105

Conclusions: GvHD-associated polymyositis is an uncommon manifestation of chronic GvHD following allogeneic HCT in our institution. With its variable presentation and significant risks of morbidity and mortality, a comprehensive approach incorporating knowledge of donor chimerism, karyotype/FISH analysis and immunohistochemistry is necessary to aid in the prompt diagnosis and management.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare

12 - Graft-versus-host Disease – Clinical

P252

SAFETY AND EFFICACY OF DOSE-ADJUSTED IBRUTINIB FOR STEROID-REFRACTORY AGVHD AND CGVHD IN PATIENTS TAKING ORAL ANTIFUNGAL AZOLES

Rong Xie[1], Wenlan Chen[1], Yaogong Wu[1], Ping Zou[1], Yong You[1], Zhaodong Zhong[1]

[1]Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Graft-versus-host-disease (GVHD), especially steroid-refractory GVHD (SR-GVHD), is a worrisome challenge after allogenic hematopoietic stem cell transplantation (allo-HSCT)[1-4][Mohty, M. et al, *Blood* 2020; Toubai, T. et al, *Blood* 2020; Shapiro, R. M. et al, *Expert Rev Hematol* 2020; Yalniz, F. F. et al, *Biol Blood Marrow Transplant* 2018]. Given the outstanding effectiveness of ibrutinib, it has been authorized for chronic GVHD (cGVHD) patients who have not responded to prior therapies[5, 6][Miklos D. et al, *Blood* 2017; Waller E. et al, *Biol Blood Marrow Transplant* 2019], but relevant clinical studies are still needed. This clinical exploration, we attempted to determine whether ibrutinib is safe and effective in treating SR-aGVHD for first time, and we further tested the efficacy of dose-adjusted ibrutinib against SR-cGVHD in patients receiving oral antifungal azoles.

Methods: We conducted a retrospective single-center study of 23 patients with SR-aGVHD (6/23) or SR-cGVHD (17/23) who received dose-adjusted ibrutinib while prophylactically taking antifungal agents between December 2017 and June 2019 at the Institute of Hematology, Union Hospital of Tongji Medical College, Huazhong University of Science and Technology (Table 1). We evaluated the severity of SR-aGVHD and SR-cGVHD and involved organ, the dose of steroid reduced or discontinued, treatment-related side effects, infections, relapse of primary disease, and survival after treatment with dose-adjusted ibrutinib. The initial dosage of ibrutinib was established at 140mg daily or every 3 days according to the patient's condition and adjusted in accordance with the tolerance and therapeutic response of the patient.

Results: After a median follow-up of 143.5 days and 280 days, the overall response rate (ORR) was 82.35% (14/17, 95% CI: 55.80%-95.33%) for SR-cGVHD and 83.33% (5/6, 95% CI: 36.48%-99.12%) for SR-aGVHD. Among the evaluable cases in the SR-cGVHD and SR-aGVHD groups, the median treatment response times were 15 days (range 4-60) days and 9 (range 6-31) days respectively. The steroid dose was reduced or discontinued in 76.74% (13/17) of SR-cGVHD patients and 66.7% (4/6) of SR-aGVHD patients. The most common adverse effect was thrombocytopenia with moderate skin and mucous membrane bleeding (8.70%, 2/23), and the incidence of other adverse effects was not significant. At the end of follow-up, the overall survival rate (OS) was 70% (12/17) among the SR-cGVHD patients and 50% (3/6) among the SR-aGVHD patients.

Table 1. Basic information of the SR-aGVHD and SR-cGVHD patients

Characteristic	SR-aGVHD (N = 6)	SR-cGVHD (N = 17)
Median age (range), y	26.50 (22.25-43)	31(18-55)
Gender (M/F)	3/3	7/10
Underlying Diagnosis		
AML	1(16.67)	8(47.06)
ALL	5(83.33)	4(23.53)
MDS	0	3(17.65)
CML	0	1(5.88)
PNH-AA	0	1(5.88)
Stem cell source		
PB	5(83.33)	15(88.24)
PB + BM	1(16.67)	2(11.76)
Donor type		
Matched related donor	0	8(47.06)
Mismatched related donor	6(100.00)	8(47.06)
Matched unrelated donor	0	1(5.88)
Kinds of treatments before ibrutinib (Except corticosteroids)		
≤3	5(83.33)	3(17.65)
å 3	1(16.67)	14(82.35)
Number of involved organs		
1	3(50.00)	3(17.65)
2	1(16.67)	5(29.41)
3	2(33.33)	7(41.18)
≥4	-	2(11.76)
Involved organ		
Skin	6(100.00)	8(47.06)
Liver	3(50.00)	6(35.29)
GI tract	2(33.33)	1(5.88)

Characteristic	SR-aGVHD (N = 6)	SR-cGVHD (N = 17)
Hematological system	-	2(11.76)
Joints and fascia	-	5(29.41)
Kidney	-	2(11.76)
Central nervous system	-	1(5.88)
Eyes	-	5(29.41)
Lung	-	9(52.94)
Mouth	-	2(11.76)
Steroid dependence of GVHD		
Steroid-dependent GVHD	3(50.00)	5(29.42)
Steroid-refractory GVHD	2(33.33)	6(35.29)
Both	1(16.67)	6(35.29)

Conclusions: The results demonstrate that dose-adjusted ibrutinib is an effective treatment for SR-cGVHD in patients receiving oral antifungal azoles. Furthermore, this pilot study of ibrutinib application shows its potential for the treatment of SR-aGVHD.

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P253

STUDY DESIGN AND RATIONALE OF STARGAZE – A PHASE 2 CLINICAL TRIAL EVALUATING APRAGLUTIDE IN PATIENTS WITH STEROID-REFRACTORY GASTROINTESTINAL (GI) ACUTE GRAFT-VERSUS-HOST DISEASE (AGVHD)

Robert Zeiser[1], Miguel-Angel Perales[2], Holger Adelman[3], Federico Bolognani[3], David Hockenbery[4]

[1]University Medical Center Freiburg, Freiburg, Germany, [2]Memorial Sloan Kettering Cancer Center, New York, United States, [3]VectivBio AG, Basel, Switzerland, [4]Fred Hutchinson Cancer Center, Seattle, United States

Background: GI aGvHD is a life-threatening condition and one of the leading causes of morbidity and mortality following allogeneic hematopoietic stem cell transplant (alloHSCT), and there is an urgent need for more effective, non-immunosuppressive therapies, to ensure greater success of alloHSCT. The GI tract is a primary target of aGvHD. Its inflammation and destruction lead to a compromised mucosal barrier, mucosal protein loss and nutrient/fluid absorption failure, which are the main drivers of morbidity and mortality in aGvHD. Glucagon-like peptide-2 (GLP-2), an essential endocrine peptide naturally secreted in the intestine, has shown intestinal regenerative, protective and microbiome-preserving effects in animal models. Preclinical and clinical data have shown that GLP-2 improved intestinal absorption and clinical signs of GI aGvHD. Apraglutide is a potent and selective next-generation, long-acting synthetic GLP-2 analogue rationally designed to present a unique pharmacokinetic (PK) profile to achieve enhanced intestinotrophic effects with once-weekly (QW) dosing.

Methods: STARGAZE (NCT05415410) is an ongoing Phase 2, randomised, single-blind proof-of-concept trial. The primary objective is to evaluate the safety and tolerability of apraglutide dosed QW in patients with steroid-refractory (SR) aGvHD of the lower-GI tract who are receiving best available therapy (defined as systemic steroids [SS] and ruxolitinib [RUX]). Secondary objectives include PK, response rate, duration of response and survival-related outcomes at various time points throughout the trial, as well as quality of life changes. Thirty-four patients aged ≥12 years (≥ 18 years in Germany) who have undergone alloHSCT from any donor source with confirmed myeloid and platelet engraftment will be included. Patients must have clinically diagnosed Grade II to IV SR GI aGvHD and Stage 1 to 4 lower-GI aGvHD based on the Mount Sinai Acute GVHD International Consortium (MAGIC) scoring system. Suitable diagnostic procedures must be conducted to exclude alternative reasons for diarrhoea. Patients receiving any systemic GvHD therapy (other than SS, calcineurin inhibitor and RUX) or Janus kinase inhibitor are excluded from this trial. Patients who have failed alloHSCT are also excluded. Eligible patients who have been receiving RUX for up to 5 days at 10 mg twice daily and SS, will receive apraglutide QW subcutaneous injections for up to 13 weeks. For the complete list of objectives and outcome measures, please see the full study protocol or visit ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT05415410).

Safety and efficacy follow-up assessments will continue to be performed for 2 years after the first dose of apraglutide. An independent Safety Review Committee (iSRC) will provide intensive review of the safety data. These data will be compared with historical control.

Results: N/A (note that this is a trial in progress [TiP]).

Conclusions: Despite recent improvements, SR aGvHD is still associated with unfavourable outcomes. Preclinical and clinical data provide a strong rationale for the use of GLP-2 as a potential tissue regenerative approach that promotes repair of aGvHD-related tissue damage when combined with immunosuppressive therapy, a concept that will be tested in the STARGAZE trial.

Clinical Trial Registry: https://clinicaltrials.gov/ct2/show/NCT05415410

Disclosure: Robert Zeiser – Consultancy fees from VectivBio.

Miguel-Angel Perales – Support and study funding from VectivBio.

Holger Adelman – Consultancy fees from VectivBio.

Federico Bolognani – Employee of VectivBio.

David Hockenbery – Support and study funding from VectivBio.

12 - Graft-versus-host Disease – Clinical

P254

SAFETY AND EFFICACY OF COMBINATION DOSE-ADJUSTED ATG AND ANTI-CD25 ANTIBODY IN PATIENTS WITH HAPLO-HSCT

Lidan Zhu[1], Jia Liu[1], Shichun Gao[1], Lu Wang[1], Huanfeng Liu[1], Peiyan Kong[1], Ting Chen[1], Yimei Feng[1], Han Yao[1], Lu Zhao[1], Lei Gao[1], Xi Zhang[1]

[1]Xinqiao Hospital, Army Medical University, Chongqing, China

Background: Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is the most effective method for curing a variety of hematologic malignancies, haploidentical donors have been increasingly considered for transplantation in patients without HLA matched donors. However, graft-versus-host disease (GVHD) is one of the most common complications after allo-HSCT, especially severe in haploidentical HSCT (haplo-HSCT), therefore, exploring an optimal GVHD prevention strategy is unmet need. Antithymocyte globulin (ATG) has been used as part of the conditioning regimen in haplo-HSCT to reduce the incidence of acute and chronic GVHD, to date, the optimal dose of ATG is still unclear. Recently, anti-CD25 antibody has been demonstrated to play an important role in preventing and treating GVHD, whether combination dose-adjusted ATG and anti-CD25 antibody have a synergy effect is worthy to figure out.

Methods: From December 2020 to November 2022, 35 patients in our center who underwent haplo-HSCT for a variety of

hematologic diseases were enrolled in this study. Sixteen pts were diagnosed as AML, 13 pts were ALL, 5 pts were MDS-EB, and 1 pts was CMML. All patients received combination dose-adjusted ATG and anti-CD25 antibody as follows: 29 patients received conditioning regimen with Me-CCNU+Ara-C + BU + CY + ATG + CD25, and 6 cases were given G-CSF+decitabine+Me-CCNU +Ara-C + BU + CY + ATG + CD25 regimen. The short-course tacrolimus (FK506) + methotrexate (MTX) + mycophenolate mofetil (MMF) regimen was administered to prevent GVHD.

Results: Among the 35 patients. The median time of neutrophil recovery was 17 (11-27) days, and the time for platelet reconstitution was 18 (11-33) days. All patients were 100% complete donor engraftment, and 5 patients occurred secondary implantation dysfunction, when treated with umbilical cord MSCs and TPO-RA, the 5 patients had complete engraftment. During the follow up, 20 patients occurred fever with only 6 patients had been found evidence of etiology, and the remaining 14 cases were agranulocytosis with fever. 15 patients (42.8%) had cytomegalovirus (CMV) infections, which was obvious lower than previous report of our center, the median time was 41 (20-66) days, only 2 patients were diagnosed as retinitis and retinal necrosis, with antivirus treatment, the patients were recovery. Among the 35 patients, 12 patients (34.2) developed acute GVHD with grade I-II aGVHD, no grade III-IV aGVHD was observed in our cohort, the medium time of aGVHD occurred was 48.5 (21-91) days, which was significantly lower compared with our previous results (53.5%). 9 patients (25.7%) developed chronic GVHD (cGVHD), the medium time was 117.5 (104-188) days, no significantly difference was observed compared with our previous results (23.2%). Medium followed up was 294(32-499) days, only 1 patient died with uncontrolled infection, and 1 patient died with intracranial hemorrhage and TMA. Three relapsed patients received system therapy strategy with CART, DLI, demethylating drugs and immunomodulators achieved complete remission again.

Conclusions: Combination of dose-adjusted ATG (7.5mg/kg) and anti-CD25 antibody strategy could decrease the occurrence of GVHD, without increase of severe infection and risk of disease relapse. Limited to the retrospective and small scale, future prospective and controlled studies are needed to further investigate the efficacy of this treatment on haplo-HSCT.

Disclosure: The authors declare non conflict of interest.

12 - Graft-versus-host Disease – Clinical

P255

RUXOLITINIB FOR TREATMENT OF CHRONIC GRAFT-VERSUS-HOST DISEASE: A SINGLE CENTER RETROSPECTIVE ANALYSIS

Alexander Denk[1], Daniela Weber[1], Ernst Holler[1], Elisabeth Meedt[1], Matthias Fante[1], Cornelia Mittermaier[1], Hendrik Poeck[1,2], Wolfgang Herr[1], Matthias Edinger[1,2], Daniel Wolff[1]

[1]University Hospital Regensburg, Regensburg, Germany, [2]Leibniz Institute for Immunotherapy (LIT), Regensburg, Germany

Background: Chronic graft-versus-host disease (cGvHD) displays a major complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). A considerable proportion of patients lack response to first line glucocorticoid treatment. We conducted a single center retrospective analysis to investigate the efficacy and safety of ruxolitinib in 2nd line treatment of cGvHD.

Methods: All patients treated with ruxolitinib for cGvHD at the transplant center of the University Hospital Regensburg between 07/2015 and 12/2022 were included in the analysis. Diagnosis and response assessment was performed according to the criteria of the National Institute of Health (NIH) consensus criteria. Response was assessed at 1, 3, 6, and 12 months after first administration. For assessment of infectious complications the common terminology criteria for adverse events version 5.0 (CTCAE 5.0) were applied.

Results: 46 patients with a median age of 50 years (range 42-58; male n = 27, female n = 19) treated with ruxolitinib for cGvHD were identified. At start of ruxolitinib, 20 patients (44%) suffered from severe cGvHD, while moderate cGvHD was present in 19 patients (41%) and residual mild cGvHD in 7 patients (15%). 34 patients had steroid-refractory cGvHD (74%), while 12 patients had steroid-dependent disease (26%). The most dominating manifestations of cGvHD were skin (n = 30, 65%), eyes (n = 26, 57%) and oral cavity (n = 23, 50%) while the lung was involved in 9 (20%) patients. Onset of cGvHD was median on day 202 (range 137-275) and start of ruxolitinib median on day 599 (362-878) after allo-HSCT with a median of 2 (range 1-3) prior treatment lines. Overall response rate (ORR) and failure free survival (FFS) after one month was 37% and 93%, respectively. Three months after onset, ORR was 27% and FFS 69% with one patient dying of COVID 19 pneumonia. After 6 months, ORR was 33% and FFS was 53%. After 12 months, ORR was 26% and FFS 34% and another patient died due to pneumonia. During follow-up, 2 patients died due to TRM and 3 patients suffered from relapse of underlying hematologic malignancy. In addition, 20 patients (43%) suffered from an infection within the first six months of treatment including 2 patients (4%) with an infection grade ≥ III. At start of ruxolitinib, 22 patients (47%) displayed thrombocytopenia, including 3 patients (7%) with thrombocytopenia grade ≥ III. Within the first 6 months of therapy, 25 patients (54%) demonstrated thrombocytopenia including 4 patients (9%) with thrombocytopenia grade ≥ III.

Conclusions: In our study, ORR after 6 months was 33%, which is lower compared to the REACH-3 trial (ORR after 6 months: 62%), which might be due to the use in advanced treatment lines and unselected patients. Still, the ORR was better than the reported ORR for patients with best available therapy from REACH-3-trial (ORR after 6 months: 25.6 %). Moreover, the reported FFS after 6 months was higher in the REACH-3-trial (75% vs. 53%). The results indicate that ruxolitinib displays an important treatment option for patients with cGvHD in clinical routine.

Disclosure:

D Wolff has received honoraria and research support from Novartis. All other authors declare no conflicts of interest.

12 - Graft-versus-host Disease – Clinical

P256

EXPERIENCE IN REDUCED DOSE OF POST-TRANSPLANTATION CYCLOPHOSPHAMIDE AS GRAFT-VERSUS-HOST DISEASE PROPHYLAXIS IN PATIENTS RECEIVING HLA-IDENTICAL RELATED DONOR TRANSPLANTS

Adolfo Jesús Sáez Marín[1], José María Sánchez Pina[1], Rafael Gil Colmenares[1], Rodrigo Gil Manso[1], Daniel Gil Alos[1], Ana Jiménez Ubieto[1], Pilar Martínez Sánchez[1], Tycho Baumann[1], Magdalena Corona de la Puerta[1], Paula Lázaro del Campo[1], Joaquín Martínez López[1], María Calbacho Robles[1]

[1]Hospital Universitario 12 Octubre, Madrid, Spain

Background: The use of post-transplantation cyclophosphamide (PTCy) for graft-versus-host disease (GVHD) prophylaxis is

increasing in patients undergoing allogeneic hematopoietic cell transplantation (HCT) and it is even becoming the standard for GVHD prophylaxis beyond the haploidentical-donor transplant setting. PTCy is associated with significant toxicity however strategies to lower toxicity are still lacking. The objective of our study is to evaluate the safety and efficacy of reduced doses of PTCy compared to the standard PTCy dose in patients receiving HLA-identical related donor transplants.

Methods: Single-center prospective study in which 11 patients with HST related donor 10/10 were included from December 2021 to July 2022. GVHD prophylaxis consisted of cyclophosphamide 50 mg/kg on day +3 and 25/mg/kg on day +4 and cyclosporine, and mycophenolate from day 5. The latter began to be withdrawn from day 35. Results were compared with a retrospective cohort of 15 patients, treated with standard PTCy dose (50 mg/kg on days +3 and +4.) from January 2018 to November 2021. We have compared the engraftment quality, the toxicity, and incidence and severity of aGVHD.

Table 1. Characteristics of the patients.

Variables	Reduced PTCy	PTCy
Age, median (min-max)	45,6 (19-67,1)	56,9 (33,3-67)
Sex M/V	4/7	10/5
HCT-CI, n (%)		
>2	3 (27,3%)	3 (27,3%)
CMV D/R, n (%)		
+ +	7 (63,3%)	12 (80%)
+-	2 (18,2%)	1 (6,67%)
-+	0 (0%)	2 (13,3%)
--	2 (18,2%)	0 (0%)
Disease, n(%)		
AML	3 (27,3 %)	4 (26,7 %)
ALL	3 (27,3 %)	1 (6,67%)
MDS, MPC, Aplasia	5 (45, 4%)	6 (40%)
LNH and MM	0	4 (26,7 %)
Conditioning regimen, n		
MAC/RIC	4/7	7/8
Donant		
Age, median (min-max)	45,5 (20,5-70,5)	50,5 (34,5-61,5)
Sex M/V	7/4	8/7

Results: The median follow-up was 21,3 months (0,5-120,2).

Neutrophil and platelet engraftment dates were similar in both groups. However, the mean number of neutrophils on day +30 was 2,35 x10^3/uL in the reduced PCTy group and 1,2 x10^3/uL in the conventional group ($p = 0.04$); and platelets on day 30 was 168x10^9/uL in the reduced PCTy group and 95,9x10^9/uL in the standard group ($p = 0,02$). The results

No patient in the reduced PTCy group presented aGVHD, instead there was only one episode of aGVHD in the conventional PCTY group (cumulative incidence=0,083, IC95 = 0,012-0,46).

Gatrointestinal toxicity was lower in the reduced PTCy Group although without statistical significance ($p = 0,19$). 1 patient had cardiotoxicicy in the reduced group which consisted in hypotension and changes in the electrocardiogram (infero-lateral ST elevation).

Conclusions: Dose reduction of cyclophosphamide seems safe in terms of aGVHD, with early engraftment. It is also impressive that hospital admission is shorter. The main limitation of our study is the small size and the short follow-up.

Disclosure: Not disclosures.

12 - Graft-versus-host Disease – Clinical

P257

COULD USTEKINUMAB BE AN ALTERNATIVE IN PATIENTS WITH REFRACTORY CUTANEOUS GRAFT-VERSUS-HOST DISEASE? A SINGLE CENTER EXPERIENCE

María Casado Sánchez[1], Pablo Garcia Jaen[2], Carlos Puerta Vázquez[2], Evelyn Zapata[2], Monica Baile[2], Almudena Cabero[2], Alejandro Avendaño[2], Ana Garcia Bacelar[2], Ana África Martín[2], Estefania Pérez López[2], Fermín Sánchez-Guijo[2], Lourdes Vazquez[2], Monica Cabrero[2], Lucia Lopez Corral[2]

[1]Hospital Universitario de Cruces, Barakaldo, Spain, [2]Hospital Universitario Salamanca, Salamanca, Spain

Background: Steroid-refractory cutaneous graft versus host disease (SR-cGVHD) remains as an unmet need. Ruxolitinib or extracorporeal photopheresis (ECP) had demonstrated to be effective in this setting, although some cases are still relapsing or refractory to these options. Ustekinumab, a monoclonal IgG1κ anti-interleukin (IL)-12/23 antibody could be an alternative given its activity in immune-mediated disorders such as moderate-severe psoriasis.

Methods: Hereby we describe our single-center experience with Ustekinumab in steroid-refractory cutaneous GVHD.

Results: **Patient 1**: He developed grade 1 acute skin GVHD on day +22, resolved with topical steroid. On day + 69, skin lesion reappeared involving >50% BSA (grade 3), so he received 1 mg/kg/d prednisone. Biopsy showed chronic features. He achieved partial response (PR) at day +7, hence we administered mesenchymal stem cells, maintaining PR after 4 doses. On day +169 he presented with skin progression and S. aureus sepsis. New skin biopsy showed psoriatic dermatitis. Then he received 2 mg/kg/d prednisone and ECP without response, thus we started Ustekinumab 130mg and we observed complete response (CR) in 72 hours. On day +202 skin lesions reappeared and progressed to generalized erythroderma, so he received 2 doses of Ustekinumab, added to Ruxolitinib and ECP, achieving new CR. On day +385 he relapsed with 10% BSA, so we decided Ustekinumab maintenance (90mg/12 weeks), maintaining long-term CR after 2 years follow-up.

Patient 2: He was diagnosed with lichenoid grade 2 skin GVHD and achieved CR with 1mg/kg/d prednisone. While tapering steroids, GVHD relapse with 25-50% BSA, so we initiated ECP with initial clinical improvement but later progression at day +14. He showed maculo-papular lesions suggesting psoriatic dermatitis through >80% BSA. Considering diagnosis of psoriasis-like SR-cGVHD, we added Ustekinumab 130mg and patient achieved PR with clear skin improvement at day +3. Unfortunately, patients showed disease progression and finally died.

Patient 3: On day +114 she developed grade 1 chronic cutaneous GVHD. He started topical corticosteroid with progression to grade 3 psoriasis-like GVHD. She received 1 mg/kg/d prednisone without response, so we increased dose to 2mg/kg and started 2nd line with Ruxolitinib, reaching PR. Due to suboptimal response, we started 3rd line with biweekly ECP and 4th line with phototherapy, but the patient was refractory. Facing with SR-cGVHD with psoriasis features, we started Ustekinumab on day +226. After two doses of Ustekinumab, Ruxolitinib was increased to 10 mg/12 h. After 4 doses of Ustekinumab and Ruxolitinib at 10mg bid, she achieved a very good PR that maintained after 6 months.

Conclusions: Our data suggest that Ustekinumab could be effective in SR-cGVHD, specially in those showing psoriasis-like features that do not respond to approved 2nd line therapy. Larger controlled studies are needed to confirm our results and asses what patients could benefit from this treatment.

Disclosure: Nothing to declare.

ID	Diagnosis	Transplant characteristics	Time to GVHD diagnosis	Treatments before Ustekinumab	Lines of therapy before Ustekinumab	Best response achieved with Ustekinumab
1	MDS-EB2	Myeloablative, unrelated 10/10	Day +69	HD steroids Mesenchymal stem cellsECP	3	Complete response
2	CMML-2	Reduced-intensity conditioning, unrelated 10/10	Day +93	HD steroidsECP	2	Partial response
3	CMML-2	Reduced-intensity conditioning, unrelated 10/10	Day +114	HD steroids RuxolitinibECP	4	Complete response

*ID patients identification; *MDS-ER2* myelodysplastic syndrome with exceed blast type2; *CMML* chronic myelomonocytic leukemia, *HD* high dose; *ECP* extracorporal photopheresis.

12 - Graft-versus-host Disease – Clinical

P258

REAL-LIFE EXPERIENCE WITH RUXOLITINIB AS A SECOND-LINE TREATMENT IN ACUTE AND CHRONIC GRAFT-VERSUS-HOST DISEASE

Belén Olivares Pérez[1], Francisco José Jiménez Najar[1], Ana Camila González Teomiro[1], Noelia Romero Mata[1], Estefanía García Torres[1], Carmen Martín Calvo[1]

[1]Reina Sofía University Hospital, Córdoba, Spain

Background: Allogeneic haematopoietic cell transplantation (HSCT) is a potentially curative treatment for haematological malignancies, but isn't without complications. The major cause of transplant-associated mortality is graft-versus-host disease (GVHD). The standard of care for both acute and chronic forms is corticosteroids. Unfortunately, up to 50% of cases become resistant to corticosteroids. Ruxolitinib is a selective inhibitor of JAK-kinases, which play a key role in the regulation of the immune system, and has shown efficacy in the treatment of corticosteroid-dependent or resistant GVHD.

Methods: We conducted an observational and retrospective study of 40 patients undergoing HSCT at our centre from April 2016 to September 2022 treated with second-line Ruxolitinib. We analysed transplant-related variables, acute and chronic GVHD (aGVHD and cGVHD), infections during treatment, as well as toxicity and progression-free survival (PFS) and overall survival (OS).

Results: A total of 40 patients received Ruxolitinib as 2nd line treatment of GVHD initially in addition to corticosteroid therapy, for aGVHD (17 patients, 42.5%) or cGVHD (23 patients, 57.8%). The median follow-up of the series is 35 months (4.7-120).

The characteristics of HSCT are shown in table 1.

In the aGVHD group, 47% of patients were treated with Ruxolitinib for corticodependence. 47% of patients had GVHD grade 3 at the time of treatment initiation. The median duration of treatment was 2 months (0,26-14); 35% of patients were concomitantly treated with photopheresis. 11(65%) patients achieved complete response. CMV reactivation occurred in 5 patients (29%) and there was no fungal infection. 4 (23.5%) patients relapsed. 5 patients (29%) died, most frequently due to aGVHD (60%). The median PFS is 27 months (8-46.5), with an estimated 2-year probability of 50% (± 15.2). For OS, the median wasn't reached and the estimated 2-year probability is 54% (± 15.8). Among patients with cGVHD, ruxolitinib was added in 44% of cases due to lack of improvement with corticosteroid therapy (no criteria for steroid-refractory) and in 30% due to corticodependence. The median duration of treatment was 7 months (0.8-58). 84% of patients had moderate or severe cGVHD; the response rate was 74% (57% partial response). Unlike aGVHD cases, the infection rate was higher in this group (52%), with fungal infections ocurring in 26% of cases. CMV was reactivated in only 2 cases. 3 (13%) patients relapsed and 8 patients died (35%), with bacterial and fungal infections being the most frequent cause of exitus.

The median PFS is 102 months (56-149.5), with an estimated 2-year probability of 78% (± 8.6). Median OS is 102 months (75-131), with an estimated 2-year probability of 87% (± 7).

TABLE 1.

	Acute GVHD (n = 17)	Chronic GVHD (n = 23)
Men n (%)	10 (59)	16 (70)
Median age (range), y	52 (22-74)	44 (3-64)
Underlying malignancy, n (%)		
- Lymphoma	6 (53)	4 (18)
- Acute myeloid leukaemia	4 (24)	9 (39)
- Acute lymphoblastic leukaemia	1 (6%)	4 (18)
- Myelodysplastic syndrome	3 (18)	1 (4)
- Chronic lymphocytic leukaemia	1 (6%)	1 (4)
- Myeloproliferative neoplasm	2 (12)	1(4)
- Other	0	3 (13)
Donor type, n (%)		
- Matched	6 (35)	16 (70)
- Mismatched	11(65)	7 (30)
Graft type, n (%)		
- Peripheral blood stem cells	16 (94)	20 (87)
- Bone marrow	1 (6)	3 (13)
Conditioning regimen, n (%)		
- Myeloablative	4 (23.5)	7 (32)
- Reduced intensity conditioning	13 (76.5)	15 (68)
CMV serostatus, n (%)		
+/+	10 (62.5)	12 (57)
−/−	0 (0)	4 (19)
+/−	2 (12.5)	4 (19)
-/+	4 (25)	1 (5)
Previous HSCT, n		
- Autologous HSCT	2	1
- Allogeneic HSCT	0	4

Conclusions: GVHD remains the leading cause of non-relapse mortality, so it's necessary to initiate early treatment and to have alternatives when first-line treatment fails.

In our series, Ruxolitinib is an effective and well-tolerated drug for second-line treatment of aGVHD and cGVHD, and its effectiveness allows a faster withdrawal of corticosteroid therapy. Also, Ruxolitinib in cGVHD is mostly started in severe cases, perhaps too late. More studies are needed to assess the efficacy of the drug with an earlier use.

Disclosure: Nothing to declare

12 - Graft-versus-host Disease – Clinical

P259

EFFECTIVENESS OF BARICITINIB FOR CHRONIC GVHD. ONE CENTRE EXPERIENCE

Luisa Sisinni[1], David Bueno[1], Dolores Corral[1], Marta Feito[2], Antonio Pérez-Martínez[1]

[1]Pediatric HSCT Unit, La Paz Hospital, Madrid, Spain, [2]Dermatology, La Paz Hospital, Madrid, Spain

Background: Chronic graft versus host disease (GVHD) is a multi-organ disorder representing one of the main long-term complications and the leading cause of morbidity and mortality after allogeneic stem cell transplantation (HSCT). The clinical manifestations are heterogeneous and there is no standard treatment in steroids resistant cases. In the last years the advances in the knowledge of the biological mechanisms of GVHD has enabled the investigation of new immunomodulatory therapies. Baricitinib is a JAK 1/2 inhibitor that has shown potent modulatory effects on GVHD in preclinical models. Here we report three patients successfully treated with baricitinib at our centre.

Methods: All the patients were treated for chronic GvHD resistant to other lines of treatment. One patient had severe multi-organ involvement: mouth (score 1), esophageal tract (score 2), genitals (score 3), eyes (score 2), skin with sclerosis and an uncontrollable itching (score 3) and decreased P-ROM of the extremity joints (4 in the shoulder, 4 in the elbow, 4 in the wrist/finger and 3 in the ankle). The itching and dysphagia severely compromised her quality of life. She received several lines therapies however the sclerotic features and symptoms did not improve. The patient rejected steroid therapy due to multiple foci of avascular necrosis and ECP was stopped due to frequent central line infections. At 20 months after the diagnosis of chronic GVHD the administration of baricitinib (2 mg/day x 1 week and then 4 mg/day) was started. Patient 2 developed moderate chronic GVHD at 12 months post HSCT (cutaneous lichen-planus like score 2 and hepatic score 2), only partially controlled with cyclosporine and steroids. Baricitinib 4mg/day was started at 18 months after the start of symptoms. Patients 3 developed sclerotic cutaneous GVHD (moderate) at 15 months after HSCT and baricitinib 2 mg/day was started.

Results: The patients experienced very good response to baricitinib and no significant side effects. The drug was well tolerated. Cytopenias were observed only in one patient. Patient 1 experienced a quickly resolution of itching and progressively improvement of scleroderma. After 12 months since the start of baricitinib scleroderma is limited and superficial with no symptoms associated. Dysphagia and mouth lesions were solved and the other organs experienced stability of GVHD. The clinical improvement translated into a progressive recovery in her psychological state and quality of life, allowing to lead a normal life for her age. In the patient 2 response to baricitinib was quick and complete at 1.5 months after the initiation of treatment and persists after 8 months. Patient 3 experienced improvement of scleroderma after 4 months of treatment. Main side effects were episodes of no complicated respiratory infections in all patients. One patient experienced fatigue at the start of treatment. No dose changes were needed although in the patient 3 we had to stop the treatment during 2 weeks due to neutropenia.

Conclusions: In our experience the JAK 1/2 inhibitor baricitinib is an effective, safe and well-tolerated treatment for chronic GvHD. Responses were achieved rapidly without significant side effects.

Disclosure: No conflict of interest to declare

12 - Graft-versus-host Disease – Clinical

P260

NEUROOPHTHALMOLOGIC COMPLICATIONS IN GVHD. A CASE REPORT

Ana Gómez Martínez[1], Marta Moreno Carbonell[2], Eduardo González Gómez[3], Pilar Delgado Beltrán[1], Isabel Izquierdo García[1]

[1]Hospital Miguel Servet, Zaragoza, Spain, [2]Hospital Gregorio Marañón, Madrid, Spain, [3]Hospital del Mar, Barcelona, Spain

Background: Ophthalmologic complications are relatively frequent in patients receiving allogeneic hematopoietic stem cell transplantation (allo-HSCT) in graft-versus-host disease (GVHD). The most characteristic are keratoconjunctivitis and dry eye. However, there are described cases of ischemic microvascular retinopathy secondary to immunosuppressive treatment and central nervous system involvement due to GVHD (small vessel vasculitis, demyelinating processes or autoimmune encephalitis), all of them very infrequent processes although of greater severity.

Methods: Clinical case of a 62-years-old patient with no personal history, diagnosed with AML NPM1 with favorable cytogenetic risk (FLT3-ITD negative, normal karyotype and NGS: IDH1, NPM1, DNMT3A, NRAS, SH2B3 mutations) in October 2021. He achieved complete response with negative RMD after chemotherapy treatment according to PETHEMA protocol for AML NPM1 (Induction + Consolidation 1 according to 3 + 7 scheme and Consolidation 2 with Citarabine at high doses). Pretrasplant reevaluation confirmed negative RMD with absence of molecular response due to persistence of disease in peripheral blood, so an allo-HSCT of matched unrelated donor (10/10) with myeloablative conditioning (BU4FLU) and GVHD prophylaxis with ATG + CsA + MTX (in short regimen) was performed in May 2022. In successive reevaluations (last, month 6) he presented negative RMD, negative NPM1 and complete chimera. Post-transplant complications included: Acute GVHD (grade 2 skin and grade 1 gastrointestinal) with partial response on day +32 (prednisone at 0.5mg/kg/day suspended due to CMV reactivation on day +39). On day +56: otorhinolaryngologic infection by Candida albicans. On day +159 he presented sudden vision loss in right eye requiring admission.

Results: Neuroophthalmic study results were: Funduscopy (right eye: generalized papilla edema in status phase, not sectorial, without hemorrhages or exudates), campimetry (right eye: concentric reduction of the visual field with preservation of the central 20° without signs of altitudinal defects), evoked potentials (right eye: reduction of the amplitude, without abolition, of the P100 component and latency delay), optical coherence tomography (right eye: edema of all sectors) and magnetic resonance imaging (hyperintense lesions in T2 in white matter suggesting vascular pattern due to chronic small vessel ischemia). He started corticosteroid treatment and continued immunosuppression tapering with clinical improvement. All this suggested atypical right optic neuropathy due to infiltration in the context of GVHD, given his history and the results of the study performed as first diagnosis.

Conclusions: The incidence of ocular posterior segment complications is significantly lower than ocular surface lesions. When an optic neuropathy occurs, it is often difficult to determine its etiology; infections, drugs toxicity and inflammatory disorders due to GVHD should be considered. Cases of optic neuropathy have been described in the context of calcineurin inhibitors. However, nowadays, there is no report about neuropathy associated with GVHD (with documented confirmatory biopsy). After multidisciplinary consultation, optic neuropathy in this case was considered an atypical entity in the context of GVHD as the most likely cause due to

the results of the rest of complementary tests, the history of GVHD and low dose of inmunosupressor. Given the severity of the condition, early diagnosis and treatment (based on inmunosuppressors and steroids) reduce the morbidity of this serious entity.

Disclosure: The authors declare that there are no conflicts of interest.

12 - Graft-versus-host Disease – Clinical

P261

ECP AND COMBINATORY THERAPY FIRST-LINE FOR CHRONIC GVHD AFTER HEMATOPOIETIC STEM CELL TRANSPLANT

Giorgia Mancini[1], Francesco Saraceni[2], Ilaria Scortechini[1], Alessandro Fiorentini[2], Francesca Romana Colaneri[2], Selene Guerzoni[2], Antonio Federico Lotito[2], Bruna Puglisi[2], Irene Federici[2], Ilaria Scortichini[2], Rosella Bencivenga[3], Mauro Montanari[3], Attilio Olivieri[2]

[1]Hematology and Stem Cell Transplant, Azienda OspedaliероUniversitaria delle Marche, Ancona, Italy, [2]Hematology and Stem Cell, Azienda OspedaliероUniversitaria delle Marche, Ancona, Italy, [3]Transfusion Medicine, Azienda OspedaliероUniversitaria delle Marche, Ancona, Italy

Background: Chronic graft-versus-host disease (cGVHD) is still the leading cause of late mortality and morbidity after allogenic hematopoietic stem cell transplantation (HSCT). Steroids still represent the standard first- line treatment for moderate-severe cGVHD, but >60% of patients requires further lines of treatment.

Methods: We retrospectively analyzed the outcome of 16 consecutive patients with moderate-severe cGVHD receiving first line combination therapy ECP-based at our institution. The protocol has been approved by our internal review board.

Results: Stem cell source was PBSC in 75% of the patients. Conditioning was myeloablative (MAC) in 62.5%, reduced-intensity (RIC) in 31.5% or non-myeloablative in 6% of the patients.

cGVHD involved skin in 68.8% of cases (45.5% had sclerotic features), lung and liver in 50% and 37.5% of the patients, respectively; 43.8% had overlap cGVHD.

Seven (43,8%) patients previously experienced grade 2-4 aGVHD and 4 previously received ECP for aGVHD.

All patients received methylprednisolone (MPDN) 0.5-1 mg/kg along 4 weeks and subsequently in combination with extracorporeal photopheresis (ECP), two treatments per week for 4 weeks, every 15 days for 8 weeks and monthly for 2 months. 13 patients associate ECP to steroids after a median time of 25 days.

During ECP 13 patients (81.3%) stopped/reduced MPDN with a median of 139 days (31-345); the median days for MPDN stop was 9 days in 9 patients; 3 patients are still on steroids. In 9 patients the median for steroids discontinuation was 70 days.

14/16 patients combined ECP with other treatment: 5 patients received ECP plus imatinib; 6 patients with PR or stable disease and/or steroid-dependence received Ruxolitinib 20 mg (n = 5) and Rituximab 375 mg/mq weekly for 4 doses (N = 1) respectively. The median duration of the combination therapy was 130 days. During the combination treatment the main SAE were represented by torsade de pointes in 1 patient receiving Imatinib; 2 patients discontinued Ruxolitinib for intolerance.

At 3 months we observed: no response in 2 patients ; partial response in 11 and 1 complete response. Six patients needed second-line therapy; 2 patients died for relapse, 1 patient died for pulmonary embolism with GVHD in complete response, 1 patient for Covid infection and 1 patient died for TA-TMA. 2 patients continued treatment with second agent. Median overall survival of the global population was 124 months.

Conclusions: This preliminary experience with first line ECP-based combination therapy including both Imatinib and Ruxolitinib, shows that ECP can be safely combined with these drugs with promising response rate.

Disclosure: Nothing to declare

12 - Graft-versus-host Disease – Clinical

P262

TAILORED-MADE PHOTOPHERESIS TREATMENT IN A PEDIATRIC PATIENT WITH CHRONIC GRAFT-VERSUS-HOST DISEASE

Teresa Mota[1], Sara Lopes[2], Sérgio Machado Lopes[2], Rosa Branca Ferreira[2], Cristiana Couto[2], Ana Salselas[2], Susana Roncon[2]

[1]Centro Hospitalar Universitário de São João, Porto, Portugal, [2]Instituto Português de Oncologia do Porto Francisco Gentil, Porto, Portugal

Background: Graft-versus-host disease (GVHD) remains a devastating complication after allogenic hematopoietic stem cell transplant (allo-HSCT) in which steroids are the cornerstone of treatment, prognosis worsens dramatically for non-responders and mortality rate is high. Extracorporeal photopheresis (ECP) is a safe and efficacious approach for management of steroid resistant GVHD.

Methods: The treatment was ECP, offline method, using Spectra Optia® and Macogenic G2.

Demographic and clinical data were collected, and our protocol described.

Results: A 10-year-old girl who was diagnosed with B-Cell Acute Lymphoblastic Leukemia in 2016 and received, in October/2019, an allo-HSCT from an HLA-10/10 matched unrelated donor with complete remission of the disease. One month later, despite GVHD prophylactic treatment, the patient developed cutaneous, gastrointestinal and hepatic GVHD. Extensive skin involvement and refractoriness to treatment (steroid and Ruxolitinib) led the patient to be proposed for ECP treatment.

The proposed weekly treatment was ECP offline method, on an outpatient basis, using central venous catheter. This is a two-step procedure which, contrary to the inline method, allows customization of collection and photoactivation parameters. Despite being on the weight threshold, priming of the extracorporeal system is performed with saline. Acid citrate dextrose solution A is used as anticoagulant and, to prevent adverse effects, calcium gluconate is administered. The procedure is a discontinuous mononuclear cell (MNC) collection with final product's volume ≥50mL (M = 67; SD = 10.8) and maximum patient's total blood volume processed of 1.0-1.5; number and volume of chambers are adjusted during each procedure according to target values. To prevent fluid overload, small amounts of plasma are collected into a separated bag and discarded. After MNC collection, product concentration is adjusted to optimize methoxalene exposure and photoactivation with ultraviolet A. So, the cell suspension is diluted with saline solution to a hematocrit ≤4% and a final volume of 100mL; 1mL of methoxalene 0.2ug/mL is added; photoactivated cells are reinfused into the patient through a 200µm filter.

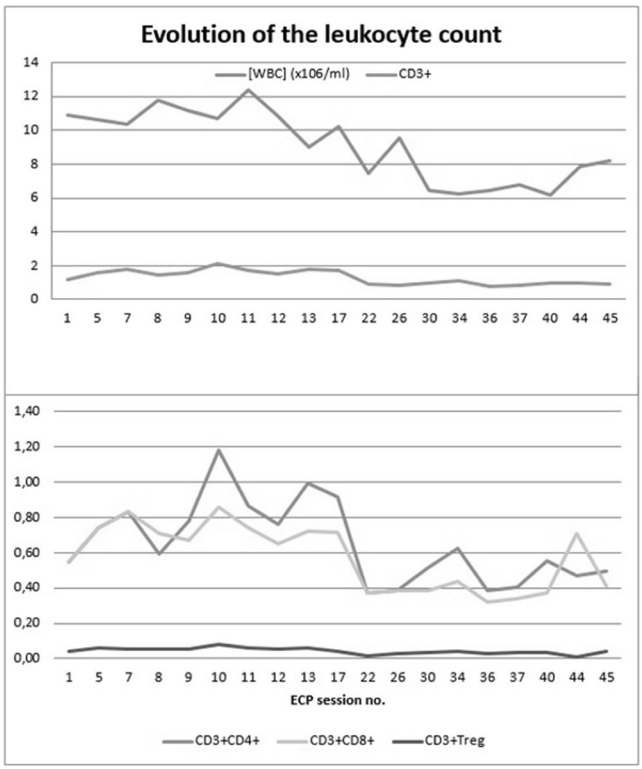
Our patient is monitored for GVHD classification, response to treatment and effect in blood cells counts. Results are summarized in Table and Figure. From the 12th treatment onwards there is a clinical improvement of GVHD organ involvement (performance status, skin, ocular, joints and fascia). With fifty five ECP sessions completed, we have struggled with several difficulties: risk of hypervolemia, citrate side effects and platelet aggregates; infection associated with immunosuppression and/or catheter requiring removal and replacement which is complicated by a

Clinical features evaluation since allo-HSCT		2019	2020	2021				2022				
Day/Month		31/10	26/08	17/05	21/07	04/11	16/12	14/01	27/01	21/07	28/10	16/12
Karnofsky Performance Status (%/score)		Allo-HSCT	NA	80/1	70/2	70/2	60/2	50/3	50/3	50/3	70/2	80/2
GVHD Classification (Jagasia et al BBMT 2015 pediatric adaptation A. Lawitschka 11/2015)	Overal GVHD Severity		Mod	Mod	Mod	Sev	Sev	Sev	Sev	Sev	Sev	Sev
	Oral mucosa		0	0	0	0	0	0	0	0	0	0
	Eyes		0	0	0	0	0	1	1	0	0	0
	Lung (symptom/ FEV1)		0/NA	0/NA	0/NA	0/1	0/1	0/1	0/1	0/1	0/1	0/1
	Gastrointestinal Tract		1	0	0	0	0	0	0	0	0	0
	Liver		1	0	0	0	0	0	0	0	0	0
	Genitals		0	0	0	0	0	0	0	0	0	0
	Joints and Fasciae		0	2	2	2	2	2	3	2	2	2
	Skin		1	2	2	2	3	3	3	3	3	3
GVHD Prophylaxis and Treatment	Methotrexate + Tacrolimus	Institutional protocol		-	-	-	-	-	-	-	-	-
	Ruxolitinib (mg)	-	-	-	2,5 + 2.5	5 + 2,5	5 + 2,5	5 + 5	5 + 5	5 + 5	5 + 5	5 + 5
	Prednisolone (mg/ kg/day)	-	1	0.34	1	0.94	0.88	1	1	0.94	0.74	0.76
	ECP offline 1x/week	-	-	-	-	1º	7º	10º	12º	37º	49º	55º

difficult venous anatomy; and need for frequent hospital admissions requiring supportive care measures.

Conclusions: Bone marrow transplant is associated with several complications, including GVHD. ECP has an excellent safety profile with limited toxicity, no increased concerns for viral reactivations and no documented interaction with other drugs. We reinforce that no consensus or guidelines are available for ECP treatment of GVHD in pediatric patients.

Despite all the distress during treatment and slow improvements, the multidisciplinary team that accompanies the patient (pediatrics, transplantation and cellular therapy department) maintains the confidence in ECP's benefits with this tailored-made treatment, as well as the patient and her mother who testify improvements in quality-of-life.



Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

P263

ABDOMINAL PAIN AND PERSISTENT DIARRHEA AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: DIFFERENTIAL DIAGNOSIS

Isabel Izquierdo Garcia[1], Ana Gomez Martinez[1], Marta Villalba Montaner[2], Marta Moreno Carbonell[3], Eduardo Gonzalez Gomez[4], Elena Del Valle Sanchez[1], Pilar Delgado Beltran[1]

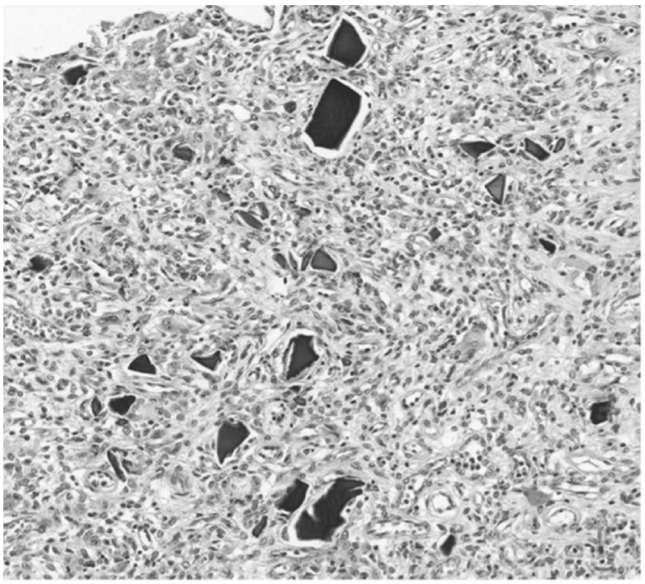
[1]Hospital Miguel Servet, Zaragoza, Spain, [2]Hospital La Fe, Valencia, Spain, [3]Hospital Gregorio Marañon, Madrid, Spain, [4]Hospital del Mar, Barcelona, Spain

Background: Gastrointestinal complications are the most frequent cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HCT) given the high vulnerability of the intestinal mucosa to damage caused by the cytotoxic effect of chemotherapy, the rich vasculature, the constant contact with the intestinal microflora and the high content of immunocompetent cells. The most common causes are infections, graft-versus-host disease (GVHD) and drug toxicity. However, given the non-specificity of the digestive symptoms it is essential to make a good differential diagnosis taking into account other less frequent entities.

Methods: A 39-year-old male with a history of AML (FAB subtype M1 with hyperleucocytosis and normal karyotype) treated with Idarubicin + Citarabine with persistence of 81% blasts in the BM. Subsequently, treatment with Fludarabine + Idarubicin + Cytarabine was administered without response (57% blast cells in the BM). Third-line treatment with gentuzumab + mitoxantrone + cytarabine was administered, with 3.6% of blast cells in the BM, and as a consecuence a sequential allo-HCT from sibling donor was performed. At day 30 a bone marrow biopsy showed absence of disease (negative MRD) but peripheral blood granulocyte donor chimerism was 86%. Progressive and rapid immune suppression tapering was performed. He received his first DLI on day 60. Ten days later, he was hospitalized due to cutaneous rash, sore throat, nausea, and severe fatigue, as well as diarrheal stools with intense abdominal pain (grade 3 skin GVHD, grade 1 hepatic, and grade 4 digestive. Grade 4 global GVHD). Corticosteroid 1.5 mg/Kg/day + beclomethasone was started with partial response, so extracorporeal photopheresis (ECP) was associated. Biopsies were compatible with acute GVHD. He had a

complete response in the skin and partial in the digestive tract. Since then, he presented watery diarrheal stools (7-8 per day) and difficult-to-control abdominal pain despite multiple changes in immunosuppressive treatment (cyclosporine, tacrolimus, ruxolitinib).

Results: On Month 14 was admitted due to worsening digestive symptoms. Infection was excluded. We started treatment with Resincholestyramine with improvement in the number of stools. Enteroresonance imaging was performed, showing 75% stenosis in the pelvic ileum. On Month 18 was admitted for mesoileal resection. The anatomopathological findings of the resected specimen showed ulceration of the entire intestinal mucosa, with an intense inflammatory process that included numerous foreign body particles, compatible with pharmacological toxicity (cholestyramine crystals) as well as an atypical cellular infiltrate, myeloperoxidase positive, with immunophenotype compatible with relapse of AML. MRD was undetectable in the BM.



Conclusions: Gastrointestinal complications after Allo-HCT are very common. An exhaustive differential diagnosis must be made between all the entities that can cause digestive symptoms, given the high mortality that this entails. In addition, the presence of a multidisciplinary team is essential to allow early diagnosis to improve the prognosis of these patients. Gastrointestinal extramedullary relapse is a rare entity and confers an unfavorable prognosis, so early diagnosis and treatment could increase the patient's survival.

Disclosure: Nothing to declare.

11 - Graft-versus-host Disease – Preclinical and Animal Models

P264

IMMUNE CELL COMPOSITION OF THE GASTROINTESTINAL MUCOSA IN PATIENTS WITH AND WITHOUT STEROID-REFRACTORY ACUTE GRAFT-VERSUS-HOST DISEASE

Lukas Gaksch[1], Johanna Strobl[2,3], Sandra Haingartner[1], Ariane Aigelsreiter[1], Christine Beham-Schmid[1], Peter Neumeister[1], Alexander Deutsch[1], Georg Stary[2,3,4], Hildegard Greinix[1]

[1]Medical University of Graz, Graz, Austria, [2]Medical University of Vienna, Vienna, Austria, [3]CeMM Research Center for Molecular Medicine, Vienna, Austria, [4]Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Vienna, Austria

Background: One of the most life-threatening complications of allogeneic hematopoietic stem cell transplantation (HCT) is acute graft-versus-host disease (GVHD). Established first-line therapy of acute GVHD is methylprednisolone, but only about 50 percent respond and steroid-refractory (SR) GVHD is associated with a poor long-term prognosis. There is an urgent need for biomarkers that predict response to glucocorticoid therapy. Innate lymphoid cells (ILCs) and tissue-resident memory T cells (TRMs) were found to contribute to the pathogenesis of GVHD in a diverging fashion.

In this study, we characterized the infiltration patterns of T cells, ILCs and TRMs in intestinal samples of patients with acute gastrointestinal (GI) GVHD, and related them to response to glucocorticoid therapy.

Methods: This retrospective study includes 253 patients treated with HCT at the Clinical Division of Haematology, Medical University of Graz since 2015. 109 patients (43.08%) developed acute GVHD grades II to IV MAGIC and 58 of them (53.21%) displayed involvement of the lower GI tract. Formalin-fixed paraffin-embedded (FFPE) samples of intestinal biopsies obtained for histological confirmation of GVHD were available from the time of first onset of acute GI GVHD taken prior to start of steroid treatment from 50 patients, 26 steroid-responding (CR cohort) and 24 steroid-refractory patients (SR cohort). FFPE intestinal biopsies from normal-appearing tissue from patients with bowel adenomas ($n = 13$) were included as a reference cohort.

For immunofluorescence staining, cells were labeled with the T cell markers CD3, CD4 and CD8, and the TRM marker CD103. ILC3 were defined as CD3-negative and transcription factor RORgt positive cells. Stained slides were visualized on a TissueFAXS (R) imaging system and analyzed using automated quantification with TissueQuest (R) software (TissueGnostics GmbH).

Results: Compared to the control cohort, samples of all 50 patients with acute GI GVHD showed no difference in the percentages of infiltrating CD4 and CD8 positive T cells. However, the median relative numbers of ILC3s were significantly higher in patients with acute GI GVHD (4.095 vs 1.850 cells/mm2; $p = 0.027$). In contrast, TRMs were significantly decreased in patients with acute GI GVHD (29.72 vs 35.64 cells/mm2; $p = 0.0067$).

The comparison of lymphocyte infiltration patterns of the three cohorts showed that the percentages of T cells and CD4-positive T cells were not significantly different between them. In SR GVHD, we detected a trend towards increased percentage of CD8-positive T-cells compared to the CR cohort and the reference. Regarding ILC3s, the CR cohort samples revealed a trend towards higher percentages compared to the SR cohort (37.44 vs 33.29 cells/mm2) and significantly higher proportions compared to the reference cohort (37.44 vs 18.73 cells/mm2; $p = 0.008$). Looking at the TRMs, we could show that CD103-positive memory T cells were significantly reduced in the CR cohort compared to the SR cohort (2.33 vs 35.94 cells/mm2; $p = 0.0261$) and the reference cohort (2.33 vs 44.08 cells/mm2; $p = 0.0014$).

Conclusions: Our study shows that cellular infiltrates in intestinal biopsies differ regarding TRM and ILC3 composition at GI GVHD onset in patients who subsequently respond to glucocorticoid therapy and, if findings are confirmed in larger independent patient cohorts, may serve as clinical prognostic markers.

Disclosure: Nothing to declare.

11 - Graft-versus-host Disease – Preclinical and Animal Models

P265

ACUTE GVHD IS DISTINGUISHED BY AN ERYTHROID SIGNATURE

334

Merav Bar[1], Darawan Rinchai[2], Mohammed El Anbari[2], Mohammed Toufiq[2], Dhanya Kizhakayil[2], Harshitha S. Manjunath[2], Rebecca Mathew[2], Irene Cavattoni[3], Sabine Forer[3], Hani Bibawi[2], Aesha I. Ali[2], Ahmad Alater[2], Clarisa Brown[1], Nancy Miles[1], Nellie Ratsamee[1], Phuong Vo[1], Davide Bedognetti[2], Sara Tomei[2], Ayman Saleh[2], Chiara Cugno[2], Damien Chaussabel[2], Sara Deola[2]

[1]Fred Hutchinson Cancer Center, Seattle, United States, [2]Sidra Medicine, Doha, Qatar, [3]Bolzano General Hospital, Bolzano, Italy

Background: High-temporal longitudinal monitoring may help to identify GVHD and GVT signatures and to intercept these events before their occurrence.

Methods: We implemented a targeted multiplex microfluidics q-PCR based transcriptional fingerprint assay (TFA, *Chaussabel Nat Rev, 2014*) on series of 50 ml micro-samples self-collected through fingerstick by 22 patients undergoing allo-HCT. The fluctuations of 264 genes were measured from engraftment to 149 days (19-149, median 72) after allo-HCT and correlated with the event of acute GVHD (aGVHD). AGVHD was graded according to Glucksberg modified criteria, and further sub-classified as "active" when clearly measurable in a GVHD clinical score (not "silenced" by therapeutic intervention).

Results: Total 19 samples pre- and 234 post allo-HCT were suitable for analyses, (median 11 sample/patient; 4-18).

Overall, 13 out of 22 patients developed G1-3 aGVHD (10 classical aGVHD only, 1 classical aGVHD+chronic overlap GVHD, 1 classical GVHD+late recurrent aGVHD and 1 late de novo aGVHD).

First, all post-alloHCT samples of patients developing GVHD ($n = 149$) were compared with samples collected from patients without GVHD ("Never_GVHD"; $n = 85$) in a *t*-test.

Eight differentially expressed genes (DEGs) were identified: RPS21, having oxidative phosphorylation functions, was the only gene downregulated in patients with GVHD ($P < 0.001$), while the IFN-related genes, IFI27 ($P = 0.004$) and LY6E ($P = 0.011$), the neutrophil-activation gene DEFA4 ($P = 0.003$) and surprisingly 4 genes related to erythroid cells, RBM38 ($P = 0.003$), CHPT1 ($P = 0.001$), SIAH2 and CDC34 ($P < 0.001$) were overexpressed in GVHD.

To assess gene signatures related to biological activity of GVHD, we repeated the analysis focusing on all "Active-GVHD" samples ($n = 42$). The previous GVHD signature was confirmed, except for LY6E gene, and further included CLIC1, related to monocytes, RAC2 and TXNIP related to neutrophils (all $P < 0.01$). Interestingly an unsupervised heatmap of this signature revealed a segregation in 2 main clusters (Signature 1 and 2) not correlated with the severity of GVHD, but rather with the persistence of active GVHD after onset, despite therapy. Specifically, aGVHD still active after mean 10.5 days showed an over expression of all above mentioned genes, while aGVHD persisting in active state after mean 45 days showed no more neutrophil-activation and IFN signatures, and an erythroid over-expression of only 2 of the 4 erythroid genes (CDC34 and CHPT1) along with CLIC1 monocytes-related gene.

Erythroid signatures are described in literature as linked with immune suppression, and mostly refer to rare populations of immune suppressive erythroblast precursors, so called Circulating Erythroid Cells (CEC) (VISTA +, CD71 +, CD45 +, Glycophorin+ Elahi, Nature 2013). Extensive flow cytometry analyses on an independent aGVHD patient cohort failed to retrieve the CEC, but identified after CD45+ cells gating a significant Glycophorin+ signature inside CD14+ monocytes, suggesting a phenomenon of erythrophagocytosis.

Conclusions: In conclusion our unbiased TFA assay revealed for the first time an erythroid signature associated with the event of aGVHD, emerging along with neutrophil activation and monocyte signature, more prominently in fresh-onset GVHD. This signature may be related to a specific population of red blood cells, at least partially phagocyted by CD14+ monocytes, possibly for an aberrant nature, or for an unknow immune-related mechanism.

Clinical Trial Registry: NA
Disclosure: Nothing to declare

1 - Haematopoietic Stem Cells

P266

AZACYTIDINE MAINTENANCE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION IMPROVES OUTCOME IN HIGH RISK MDS AND AML PATIENTS: A PROPENSITY SCORE ANALYSIS FROM THE SFGM-TC

Viviane Gournay[1], Vincent Alcazer[2], Déborah Desmier[3], Rémy Duléry[4], Stéphanie Nguyen Quoc[5], Sylvie François[6], Yves Chalandon[7], Marie-Thérèse Rubio[8], Gandhi Laurent Damaj[9], Anne Huynh[10], Edouard Forcade[11], Jean-Baptiste Mear[12], Pascal Turlure[13], Emmanuelle Tavernier[14], Alban Villate[15], Ana Berceanu[16], Bruno Lioure[17], Sébastien Maury[18], Marie Robin[1], Ambroise Marçais[19]

[1]Hôpital Saint Louis, Paris, France, [2]Hospices Civils de Lyon, Lyon, France, [3]CHU de Poitiers, Poitiers, France, [4]Hôpital Saint Antoine, Paris, France, [5]Hôpital Universitaire Pitié Salpêtrière, Paris, France, [6]CHU d'Angers, Angers, France, [7]Hôpitaux Universitaires de Genève, Geneve, France, [8]CHRU de Nancy, Nancy, France, [9]CHU de Caen, Caen, France, [10]CHU de Toulouse, Toulouse, France, [11]CHU de Bordeaux, Bordeaux, France, [12]CHU de Rennes, Rennes, France, [13]CHU de Limoges, Limoges, France, [14]Institut de Cancérologie Lucien Neuwirth, Saint Etienne, France, [15]CHU de Tours, Tours, France, [16]CHU de Besançon, Besançon, France, [17]Institut de Cancérologie Strasbourg Europe, Strasbourg, France, [18]Hôpital Henri Mondor, Creteil, France, [19]Hôpital Necker, Paris, France

Background: Despite therapeutic progress in high risk myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), relapse after-allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the major cause of treatment failure with up to half of patients sustaining relapse. The use of 5-azacytidine(5-aza) as maintenance therapy after allo-HSCT in order to prevent relapse remains a matter of debate with conflicting results according to clinical studies.

This study aims to show the feasibility and evaluate the benefit of 5-aza maintenance therapy after allo-HSCT for MDS and AML patients.

Methods: We conducted a retrospective multicentric study of patients receiving 5-aza as maintenance therapy after allo-HSCT for MDS or AML between 2015 and 2020 among 18 centers of the Société francophone de greffe de moelle et thérapie cellulaire (SFGM-TC). Inclusion criteria was the use of 5-aza as prophylaxis or preemptive (based on MRD or chimerism) maintenance therapy post allo-HSCT.

The "5-aza cohort" was then matched with a cohort of patients allografted for MDS and AML in the same period and who did not receive 5-aza as maintenance therapy. To minimize selection bias and confounding factors, we performed a propensity score (PS) matching analysis. The impact of 5-aza maintenance was analyzed through two models: (1) time-dependent Cox; (2) multistate for dynamic prediction.

Results: One hundred and ninety-four patients were included in the 5-aza cohort (AML, $n = 160$, MDS, $n = 34$). The first 129 patients were precisely monitored (AML, $n = 107$, MDS, $n = 22$). 5-aza was given as prophylactic and as preemptive treatment in 87 (67%) and 42 (33%) patients respectively. 5-aza was started at a median time of 89 days (IQR, 66-125) after allo-HSCT, with a median number of 12 cycles (IQR, 5-12), mainly at a dose of 32 mg/m^2, five days every 28 days. 5-aza was combined with donor lymphocyte infusions (DLI) in 56 patients (43%). Adverse events occurred in 34 patients (26%). 5-aza treatment was discontinued in 49 patients (38%) mainly for relapse ($n = 20$) and GvHD ($n = 14$).

Based on the nearest PS matching, we paired these 194 patients with 194 control patients selected from 2383 patients of the control cohort (Table 1). Median age was 57 [48-64] in the 5-aza group and 56 [46-63] in the control group. DLI rate was 38% in both groups.

The time-dependent Cox model, considering 5-aza treatment as a categorical time-dependent variable showed a favorable impact of 5-aza maintenance therapy. The 2-years relapse free survival was 75% in the 5aza group compared to 56% in the control group (HR 0.66, $p = 0.039$). Similarly, the 2-years overall survival was 78% in the 5-aza group and 66% in the control group (HR 0.67 $p = 0.045$). The cumulative incidence of relapse was 21% in in the 5aza group and 40% in control group (HR = 0.66, $p = 0.038$). The multistate model showed similar results, with a lower probability of relapse for patients treated with 5-aza.

Variable	Type	Control	AZA	Param. p-value
Age	Median [IQR]	56.39 [45.84-62.92]	57.41 [47.75-63.87]	0,5838
Disease risk index (DRI)	low	5 (2.58)	10 (5.15)	0,7134
	intermediate	104 (53.61)	101 (52.06)	
	high	72 (37.11)	71 (36.6)	
	very high	13 (6.7)	12 (6.19)	
DLI	No	120 (61.86)	121 (62.37)	1
	Yes	74 (38.14)	73 (37.63)	
Sex	Female	90 (46.39)	83 (42.78)	0,6646
	Male	104 (53.61)	111 (57.22)	
Disease	AML	150 (77.32)	160 (82.47)	0,4068
	MDS	44 (22.68)	34 (17.53)	
Conditioning	Myelobalative	129 (66.49)	120 (61.86)	0,5774
	Reduced intensity	65 (33.51)	74 (38.14)	
Donor	Matched related	63 (32.47)	58 (29.9)	0,1529
	Matched unrelated	81 (41.75)	83 (42.78)	
	Mismatched unrelated	2 (1.03)	11 (5.67)	
	Mismatched related	48 (24.74)	42 (21.65)	
aGVHD grade	Grade 3-4	15 (7.73)	13 (6.7)	0,1227

Conclusions: This real-life study suggests that post allo-HSCT maintenance therapy with 5-aza for high risk MDS and AML patients is feasible and may improves outcome by limiting relapse incidence without inducing major toxicity.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P267

PONATINIB AS A PROPHYLACTIC OR PRE-EMPTIVE STRATEGY TO PREVENT CYTOLOGICAL RELAPSE AFTER ALLO-SCT IN PATIENTS WITH PH-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA TRANSPLANTED IN COMPLETE CYTOLOGICAL REMISSION

Anna Candoni[1], Patrizia Chiusolo[2], Davide Lazzarotto[3], Cristina Papayannidis[4], Cristina Skert[5], Fabio Giglio[6], Francesco Onida[7], Michela Dargenio[8], Sabina Chiaretti[9], Silvia Trappolini[10], Chiara Sartor[4], Renato Bassan[5], Attilio Olivieri[10], Francesca Bonifazi[4], Mario Luppi[1], Renato Fanin[3]

[1]Section of Haematology, Dept. of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy, [2]Hematology and Stem Cell Transplantation Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, [3]Division of Hematology and Stem Cell Transplantation, ASUFC, University of Udine, Udine, Italy, [4]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. University of Bologna, Bologna, Italy, [5]Hematology Unit, Azienda Ulss3 Serenissima, Ospedale dell'Angelo, Venezia-Mestre, Italy, [6]Hematology and Bone Marrow Transplantation, San Raffaele Scientific Institute, Milan, Italy, [7]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico-University of Milan, Milan, Italy, [8]Ospedale Vito Fazzi, Unità Operativa di Ematologia e Trapianto, Lecce, Italy, Sapienza University of Rome, Rome, Italy, University of Ancona, Azienda Ospedaliera Universitaria Ospedali Riuniti di Ancona, Ancona, Italy

Background: The proper administration of TKIs after Allo-SCT in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) remains controversial and the TKI approach (prophylactic, pre-emptive or salvage) is still heterogeneous through transplant centers. In this context, very little is known about the efficacy and safety of third-generation TKIs. Here we present the preliminary results of the ongoing multicentre study to analyse efficacy and safety profile of therapy with ponatinib (PONA) after Allo-SCT to prevent Ph+ ALL cytological relapse.

Methods: We report the analysis of the first 48 included patients (pts) with Ph+ ALL (median age 49 years; range 20-70) who received PONA after their Allo-SCT (donors: 24 MUD, 11 siblings HLA Id and 9 Haplo and 4CB). All 48 pts received Allo-SCT while in complete cytological remission (cCR) and 26 pts (54%) had positive minimal residual disease (MRD+) before Allo-SCT. PONA was administered after Allo-SCT prophylactically (starting with MRD neg) in 26 pts or pre-emptively (starting with MRD positivity post-SCT and without hematological relapse) in 22 pts.

Results: The 26 pts treated prophylactically with PONA started treatment earlier, at a median of 4,3 months (range 1,5-6) after Allo-SCT, than the 22 pts treated pre-emptively, who started PONA at a median of 7,4 months (range 2-63) after Allo-SCT ($p = 0,01$). The median starting dose of PONA was 30 mg/day (range 15-45). Reduction of the initial dose was required in 15/48 (31%) of cases (mainly in those receiving an initial dose of 45 mg/day), but a permanent discontinuation of PONA, due to toxicity, was required in only 5/48 pts (10,4%). No deaths due to PONA-related adverse events were reported. The mean and median follow-up time after Allo-SCT was 40 ± 26 and 34 months (range 7,7-118), respectively. At last follow-up, the median duration of PONA therapy was 22 months (range 2-100). Detailed data on the safety profile of PONA were collected. In addition to PONA, 10 pts received donor lymphocyte infusions. The 5-year OS and RFS after Allo-SCT of all 48 pts were 92% and 71%, respectively. The 5-year RFS after Allo-SCT of pts who received PONA as prophylaxis was 95% and it was 57% for those who received PONA pre-emptively (log-rank $p = 0,02$).

Conclusions: Preliminary data obtained from this analysis, in a homogeneous population of Ph+ ALL undergoing Allo-SCT while in CcR, although with the caution of the retrospective data, support the efficacy and safety of PONA as a maintenance strategy after Allo-SCT, resulting in a high probability of OS and DFS and in a low rate of discontinuation due to PONA-related toxicity. However, in the majority of cases where a daily dose of 45 mg was started a dose reduction to 30-15 mg/day was required, which seems to be the appropriate dose to balance efficacy and tolerability.

Clinical Trial Registry: *ClinicalTrials.gov NCT03821727*

Disclosure: The authors declare no conflict of interest.

1 - Haematopoietic Stem Cells

P268

COMPARISONS OF SAFETY AND EFFICACY OF ALLO-HSCT AFTER CAR T-CELL OR CHEMOTHERAPY-BASED COMPLETE REMISSION IN PEDIATRIC T-ALL

Rui-Juan Sun[1], Jian-Ping Zhang[1], Min Xiong[1], Yue Lu[1], Yan-Li Zhao[1], Xing-Yu Cao[1], De-Yan Liu[1], Zhi-Jie Wei[1], Jia-Rui Zhou[1], Dao-Pei Lu[1], Pei-Hua Lu[2]

Hebei Yanda Lu Daopei Hospital, Langfang, China, Hebei Yanda Lu Daopei Hospital, Langfang, China

Background: Patients often undergo consolidation allogeneic hematopoietic stem cell transplantation (allo-HSCT) to maintain long-term remission following chimeric antigen receptor (CAR) T-cell therapy. Comparisons of safety and efficacy of allo-HSCT following complete remission (CR) achieved by CAR-T therapy versus by chemotherapy for T-cell acute lymphoblastic leukemia (T-ALL) has not been reported.

Methods: We performed a parallel comparison of transplant outcomes in 53 consecutive pediatric T-ALL who received allo-HSCT after achieving CR with CAR-T therapy (n = 13) or with chemotherapy (n = 40). Patients often undergo consolidation allogeneic hematopoietic stem cell transplantation (allo-HSCT) to maintain long-term remission following chimeric antigen receptor (CAR) T-cell therapy. Comparisons of safety and efficacy of allo-HSCT following complete remission (CR) achieved by CAR-T therapy versus by chemotherapy for T-cell acute lymphoblastic leukemia (T-ALL) has not been reported.

Results: With the median follow up 12 (1-25) months, 52 patients were successfully engrafted and had full donor chimerism. Efficacy measures 1 years following transplant were all similar in the CAR-T vs. the chemotherapy groups: cumulative incidences of relapse (CIR; 7.6% vs.0%) and overall survival (OS; 69.2% vs. 81.8%; p = 0.273). The incidence of Grade II-IV acute graft-versus-host disease was similar in both groups (aGVHD 35.8% vs.36.3% ; p = 0.806). And the incidence of Grade III-IV aGVHD was similar in both groups too (22.2% vs.22.4%, p = 0.945). The incidence of Cytomegalovirusemia and Epstein-Barr virusemia was different between groups(CMV 18.2% vs.41%;EBV 0% vs.10%).

Conclusions: In conclusion, our data indicate that, in Pediatric T-ALL patients, similar clinical safety and Efficacy outcomes could be achieved with either CD7 CAR T-cell therapy followed by allo-HSCT or chemotherapy followed by allo-HSCT.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P269

RISK FACTORS INFLUENCING TRANSPLANT OUTCOMES OF ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN FIRST COMPLETE REMISSION: A RETROSPECTIVE ANALYSIS FROM THE ALWP OF THE EBMT

Martina Calabrò[1], Myriam Labopin[1,2,3], Giorgia Battipaglia[4], Mutlu Arat[5], Ibrahim Yakoub-Agha[6], Urpu Salmenniemi[7], Jan Vydra[8], Didier Blaise[9], Régis Peffault de Latour[10], Caroline Besley[11], Jean Henri Bourhis[12], Renato Fanin[13], Nicolaus Kroger[14], Alessandro Rambaldi[15], Ben Carpenter[16], Péter Reményi[17], Tobias Gedde-Dahl[18], Sebastian Giebel[19], Arnon Nagler[20], Fabio Ciceri[21], Mohamad Mohty[1,2,3]

Hôpital Saint Antoine, Service d'Hématologie Thérapie Cellulaire, Paris, France, [2]EBMT Statistical Unit, Paris, France, [3]Sorbonne Universités, UPMC Univ Paris 06, INSERM, Centre de Recherche Saint-Antoine (CRSA), Paris, France, [4]Federico II University of Naples, Hematology and Bone Marrow Transplant Unit, Naples, Italy, [5]Demiroglu Bilim University Istanbul Florence Nightingale Hospital, Hematopoietic SCT Unit, Istanbul, Turkey, [6]CHU de Lille LIRIC, INSERM U995, Université de Lille, Lille, France, [7]HUCH Comprehensive Cancer Center, Stem Cell Transplantation Unit, Helsinki, Finland, [8]Institute of Hematology and Blood Transfusion, Prague, Czech Republic, [9]Programme de Transplantation&Therapie Cellulaire, Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, Marseille, France, [10]Hopital St. Louis, Dept. of Hematology – BMT, Paris, France, [11]Bristol Royal Hospital for Children, Dept. of Paediatric Oncology/BMT, Bristol, United Kingdom, [12]Gustave Roussy Cancer Campus, BMT Service, Villejuif, France, [13]Azienda Ospedaliero Universitaria di Udine, Division of Hematology, Udine, Italy, [14]University Hospital Eppendorf, Bone Marrow Transplantation Centre, Hamburg, Germany, [15]ASST Papa Giovanni XXIII, Hematology and Bone Marrow Transplant Unit, Bergamo, Italy, [16]University College London Hospital, London, United Kingdom, [17]Dél-pesti Centrumkórház – Országos Hematológiai és Infektológiai Intézet, Dept. Haematology and Stem Cell Transplant, Budapest, Hungary, [18]Oslo University Hospital, Rikshospitalet, Clinic for Cancer Medicine, Hematology Dept. Section for Stem Cell Transplantation, Oslo, Norway, Maria Sklodowska-Curie Institute - Oncology Center, Gliwice Branch, Gliwice, Poland, [20]Division of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Ramat Gan, Israel, [21]Hematology and Bone Marrow Transplant Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first complete remission (CR1) remains a standard of care for adult patients with acute lymphoblastic leukemia (ALL) at high risk of relapse, i.e. high-risk features at diagnosis (ex. Philadelphia(Ph)-positive ALL), or detectable minimal residual disease (MRD +). We investigated risk factors influencing transplant outcomes in ALL patients allografted between 2015 and 2021.

Methods: We included adults transplanted for ALL in CR1 with available data of phenotype, Ph-status, and MRD pre-transplant. All donor types and stem cell sources were elegible. Cord blood and ex-vivo T-cell depletion (TCD) represented exclusion criteria.

Results: We identified 2349 patients including 870 transplanted from HLA-matched sibling (MSD), 1150 from unrelated (79% 10/10 and 21% 9/10 UD), and 329 from haploidentical donors (Haplo). Median age was 42.6 (range 18-76.1) years. Median follow-up was 23.5 (95% CI 21.8-24.2) months. The cohort was composed of 28.4% of patients with Ph-negative B-ALL, 56.4% with Ph-positive B-ALL and 15.2% with T-ALL. Stem cell source was peripheral blood in 85.3% of cases. Conditioning regimen was reduced-intensity in 21% and myeloablative (MAC) in 79% of cases. Total body irradiation (TBI) was used in 65.8% of patients, mostly as a MAC (93.9%). Pre-transplant MRD was positive in 35.4% while in-vivo TCD was used in 51.5% of cases.

180-days cumulative incidence of grade II-IV and grade III-IV acute graft-versus-host disease (aGVHD) were 29.2% (95% CI 27.3-31.1) and 10.1% (95% CI 8.9-11.4), respectively. Two-years overall and extensive chronic GVHD (cGVHD) were 34% (95% CI 31.7-36.3) and 15% (95% CI 13.2-16.8), respectively. Two-years relapse incidence (RI), non-relapse mortality (NRM), leukemia-free survival (LFS), overall survival (OS) and GVHD-free/relapse free survival (GRFS) were 22.2% (95% CI 20.3-24.2), 15.4% (95% CI 13.8-17.1), 62.3% (95% CI 60-64.6) 73.9% (95% CI 71.7-76) and 48% (95% CI 45.6-50.3), respectively.

By multivariate analysis, factors predicting poor OS and LFS were: older age [HR 1.22 (1.13-1.32) p < 0.01 and HR 1.12 (1.05-1.19) p < 0.01], Ph-negative B-ALL compared to Ph-positive B-ALL [HR 1.70 (1.39-2.08) p < 0.01 and HR 1.40 (1.18-1.67) p < 0.01], MRD + pre-HSCT compared to MRD- [HR 1.31 (1.08-1.58) p < 0.01 and 1.41 (1.21-1.65) p < 0.01]; while factors predicting poor GRFS were: Ph-negative B-ALL compared to Ph-positive ALL [HR 1.24 (1.07-1.44) p < 0.01], MRD+ pre-HSCT compared to MRD- [HR 1.31 (1.14-1.49) p < 0.01], no in-vivo TCD [HR 1.28 (1.10-1.52) p < 0.01]. UD 10/10 and 9/10 are predictors of higher rate of aGvHD and NRM [UD 10/10 HR 1.43 (1.15-1.77) p < 0.01 and HR 1.55 (1.14-2.09) p < 0.01;

UD 9/10 HR 1.71 (1.29-2.28) p < 0.01 and HR 1.84 (1.24-2.75) p < 0.01]. HLA mismatches are associated with lower RI [UD 9/10 HR 0.68 (0.47-0.99) p = 0.04 and Haplo HR 0.61 (0.44-0.87) < 0.01], as well as TBI [HR 0.78 (0.61-0.99) p = 0.04], despite a higher rate of aGvHD and cGvHD [HR 1.54 (1.23-1.92) p < 0.01 and HR 1.47 (1.16-1.87) p < 0.01].

Conclusions: Pre-transplant MRD+ predicts poor prognosis after transplantation. Results in Ph-positive ALL are better compared to Ph-negative ALL. Use of TBI and HLA mismatches are both associated with lower RI despite a higher risk of GvHD.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P270

DIAGNOSIS BY LIVER STIFFNESS MEASUREMENT OF VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION: RESULTS FROM THE ITALIAN MULTICENTRIC PROSPECTIVE STUDY (ELASTOVOD)

Federico Ravaioli[1,2,3], Antonio Colecchia[3], Francesco Barbato[2], Jacopo Peccatori[4], Anna Grassi[5], Barbara Sarina[6], Maurizio Pompili[7], Simona Sica[7], Locatelli Franco[8], Simone Cesaro[9], Chiara Nozzoli[10], Anna Paola Iori[11], Lucia Prezioso[12], Stella Santarone[13], Franca Fagioli[14], Attilio Olivieri[15], Ester Vanni[14], Alessandro Busca[14], Giorgina Specchia[16], Edoardo Benedetti[17], Francesco Zallio[18], Fabrizio Pane[19], Francesca Carobolante[20], Mariacristina Menconi[21], Fabio Benedetti[22], Francesca Patriarca[23], Michele Malagola[24], Riccardo Varaldo[25], Francesco Onida[26], Vincenzo Pavone[27], Elton Dajti[1], Luigina Vanessa Alemanni[1], Giovanni Marasco[1], Fabio Ciceri[4], Arcangelo Prete[2], Andrea Pession[2], Davide Festi[1], Francesca Bonifazi[2]

[1]University of Bologna, Bologna, Italy, [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [3]University of Modena and Reggio Emilia, Modena, Italy, [4]IRCCS San Raffaele Scientific Institute, Milano, Italy, [5]ASST Papa Giovanni XXIII, Bergamo, Italy, [6]Humanitas Cancer Center, Rozzano, Italy, [7]Catholic University of Sacred Heart, Roma, Italy, [8]IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy, [9]Azienda Ospedaliera Universitaria Integrata, Verona, Italy, [10]Careggi University Hospital, Firenze, Italy, [11]"Sapienza" University of Rome, Roma, Italy, [12]Azienda Ospedaliero-Universitaria di Parma, Parma, Italy, [13]Transfusion Medicine and Biotechnologies, Ospedale Civile, Pescara, Italy, [14]Città della Salute e della Scienza di Torino, Torino, Italy, [15]Ospedali Riuniti di Ancona, Ancona, Italy, [16]University of Bari, Bari, Italy, [17]University of Pisa, Pisa, Italy, [18]SS Antonio & Biagio and C. Arrigo Hospital, Alessandria, Italy, [19]Azienda Ospedaliera Universitaria Federico II di Napoli, Napoli, Italy, [20]Ospedale dell'Angelo, Venezia, Italy, [21]Azienda Ospedaliera Universitaria Pisana, Pisa, Italy, [22]University of Verona, Verona, Italy, [23]Università di Udine, Udine, Italy, [24]University of Brescia, Brescia, Italy, [25]IRCCS Policlinico San Martino IST, Genova, Italy, [26], Fondazione IRCCS Ospedale Maggiore Policlinico/University of Milan, Milano, Italy, [27]U.O.C Ematologia e Trapianto, Tricase, Italy

Background: Veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), remains a serious complication for patients undergoing hematopoietic stem cell transplantation (HSCT). Improving diagnosis with non-invasive methods needs to be urgently investigated. Consequently, we aimed to evaluate the diagnostic role of the measurement of liver stiffness (LSM), assessed with different ultrasound elastography techniques, for diagnosing VOD/SOS.

Methods: This interventional prospective multicenter clinical trial, from April 2018 to December 2021, consecutively and prospectively examined 1089 patients from 25 Italian centres undergoing HSCT. Sixty-nine (6.3%) patients were excluded for inadequate data quality; among the remaining 1020 patients, 80 did not perform at least one LSM assessment after HSCT and were consequently excluded. Patients were followed according to the protocol by a dense clinical, laboratory, and imaging program during hospitalization for HSCT and until the diagnosis of VOD/SOS, death, or +100-day follow-up. LSM was performed before the HSCT(T0), on days +9/10(T1), +15/17(T2), and +22/24(T3) after the. The diagnosis of VOD/SOS was performed clinically by each participating centre. The primary endpoint of the study was the diagnostic role for VOD/SOS by LSM assessed by different elastographic methods (ClinicalTrials.gov-number-NCT03426358).

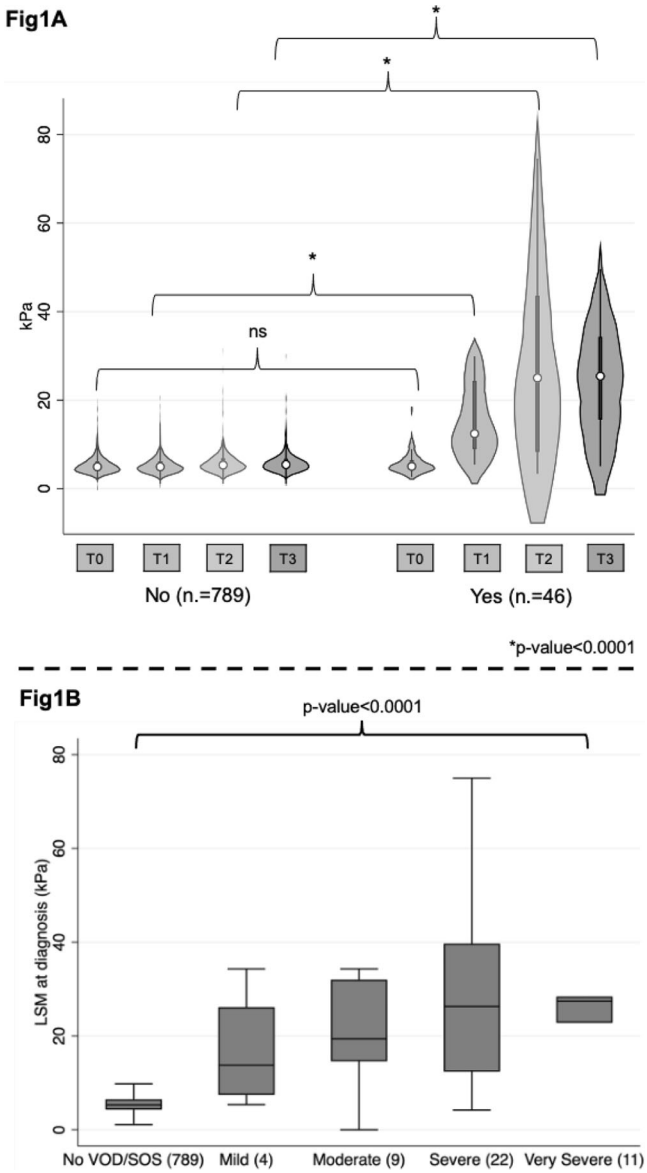
Results: Among the 941 patients, 774 were adults, and 167 were children. Characteristics of the populations enrolled were reported in Table. Sixty per cent of patients were male with a mean age of 43.7 (SD 20.25) at the time of HSCT; the main HSCT indication was AML(40.3%), ALL(16.9%), NHL(7.1%), and myelofibrosis(6.6%). Most HSCTs were allogeneic (95%) from peripheral blood stem cell sources(79.2%) and myeloablative intensity conditioning(63.3%).

Variables	Overall cohort (n.52)	Adults cohort (n.28)	Paediatrics cohort (n.24)	p-value
VOD/SOS incidence	5.53% [95% CI: 4.13–7.25]	3.62% [95% CI: 2.40–5.23]	14.37% [95% CI: 9.21–21.38]	<0.0001
EBMT risk factors; median(IQR)	5 (3–6)	6 (5–7)	3 (0–6)	0.021
Days post-HSCT; median(IQR)	18 (11–25)	19 (11–29)	17 (11–22)	0.358
Late-onset VOD/SOS; n. (%)	19 (36.5)	13 (46.4)	6 (25)	0.105
Severity grading SOS/VOD				
Mild	4 (7.6)	2 (7.1)	2 (8.3)	0.478
Moderate	11 (21.2)	4 (14.3)	7 (29.2)	
Severe	25 (48.1)	16 (57.1)	9 (37.5)	
Very Severe	12 (23.1)	6 (21.5)	6 (25)	
SOS/VOD needing treatment*; n. (%)	37 (71.2)	22 (78.6)	15 (62.5)	<0.0001
SOS/VOD therapy				
Defibrotide	44 (84.6)	24 (85.7)	20 (80.3)	0.812
Diuretics	35 (67.3)	17 (60.7)	18 (75)	0.274
UDCA	17 (32.7)	8 (28.6)	9 (37.5)	0.494
Others°	6 (11.5)	2 (7.1)	4 (16.7)	0.284
SOS/VOD evolution				
Resolution	38 (73.1)	18 (64.3)	20 (83.3)	0.187
MOF	12 (23.1)	6 (21.4)	6 (25)	0.761
SOS/VOD-related death	14 (26.9)	11 (39.3)	3 (12.5)	0.05

*severe & very severe VOD/SOS; °others SOS/VOD therapy: n = 2 steroids; n = 3 paracentesis; n = 2 dopamine

The +100-days overall survival was 96.5% [95%CI 90.2-100] in the whole population and 75.0% [95%CI 53.3–100] in the VOD/SOS group (78.6% [95%CI 39.2-100] in mild and moderate and 50.0% [95%CI 18.4-100] in very severe). LSM was measured in kilopascals (kPa) in 90.9% and meter-second (m/sec) in 9.1% of cases and

evaluated by transient elastography (FibroScan, Echosens, Paris), 2D shear wave elastography (2D-SWE), and point shear wave elastography (p-SWE) in 76%, 12.9%, and 11.1%, respectively. Median LSM values prior-HSCT (T0) were 4.9 kPa [IQR 3.9 – 6.13] and 1.18 m/sec [IQR 1.01 – 1.4] with no significant difference (p-value 0.350) according to VOD/SOS occurrence both by kPa (4.9vs5.0) and by m/sec (1.19vs1.02). LSM time point by time point (**Fig1A**), LSM values increased significantly in patients who developed VOD/SOS and differed between VOD/SOS severity grades (**Fig1B**). LSM values on the day of clinical diagnosis were significantly ($p < 0.0001$) associated both with VOD/SOS (OR 1.424 [95%CI 1.308-1.549]) and showed good diagnostic performance with a c-statistic of 0.975 [95%CI 0.948-1.000]. Comparable results were observed when LSM was evaluated in adults and paediatrics cohorts and by m/sec. Combination of the rule-in (25kPa) and rule-out (6kPa) cut-offs with deltaLSM(2x) in a stepwise algorithm achieved high values of PPV(84.2-98) and NPV(95-99) in all cohorts.



Conclusions: LSM, regardless of the elastographic modality, has proven to be an accurate diagnostic tool in diagnosing VOD/SOS. This non-invasive method, delivered in the hands of an expert haematologist and supported by a multidisciplinary team, will guide the diagnosis of VOD/SOS.

Clinical Trial Registry: NCT03426358
https://clinicaltrials.gov/ct2/show/NCT03426358

Disclosure: AC, FB participated in Advisory Board and received speaker fees from Jazz Pharmaceuticals.

1 - Haematopoietic Stem Cells

P271

OUTCOMES OF UPFRONT UNRELATED HEMATOPOIETIC STEM CELL TRANSPLANTATION AND IMMUNOSUPPRESSIVE THERAPY FOR ADULT WITH SEVERE APLASTIC ANEMIA: A MULTICENTER RETROSPECTIVE AND PROPENSITY SCORE-MATCHED STUDY

Liangliang Wu[1], Xin Zhao[2], Limin Liu[3], Yuping Zhang[1], Depei Wu[3], Fengkui Zhang[2], Shunqing Wang[1]

Guangzhou First People's Hospital, South China University of Technology, Guangzhou, China, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Tianjin, China, [3]The First Affiliated Hospital of Soochow University, Suzhou, China

Background: Immunosuppressive therapy (IST) is traditionally recommended first line therapy for adult patients not eligible for HLA-matched sibling donor (MSD)-HSCT. Unrelated donor HSCT (URD-HSCT) for adults with SAA is currently recommended after failure to respond to IST. Encouragingly, with the progression of transplantation technology, the survival outcomes of URD-HSCT have improved dramatically. No studies have focused on the compare the outcomes between upfront URD-HSCT and IST group in adults who lack an MSD. As such, we conducted a multicenter retrospective study and compared the outcomes of URD-HSCT or p-ALG based IST as an upfront treatment, to determine whether upfront treatment with URD-HSCT or pALG-based IST is a better option for adults with SAA when lack an MSD.

Methods: All patients in this study met the following eligibility criteria:

(1) had acquired AA according to the published criteria;
(2) the interval from diagnosis to treatment shorter than 6 months;
(3) age > 14 years;
(4) lack an MSD;
(5) voluntarily underwent URD-HSCT and p-ALG based IST.

For URD-HSCT group, patients had received ATG or pALG-based IST before transplantation were excluded. All patients with transplantation were enrolled from Guangzhou First People's Hospital and The First Affiliated Hospital of Soochow University. For pALG-based IST group, patients were enrolled by using propensity score matching (PSM) in a 1:1 nearest-neighbor matching (covariates: age, gender and severity of diseases) based on data of the patients who the interval from diagnosis to IST shorter than 6 months from the Institute of Hematology and Blood Diseases Hospital, CAMS & PUMC.

Results: Compared with pALG-based IST group, patients in the URD-HSCT achieved high percentage of overall response at 3 (94.0% vs. 39.6%, $p < 0.001$) and 6-month (95.8% vs. 62.4%, $p < 0.001$). There was a median follow-up of 1170 days (range, 105-3430) in patients with URD-HSCT, with both an 9-year estimated OS and FFS rate of 86.5 ± 4.0%. The GFFS was also calculated in the HSCT group, with an estimated probability of 78.8 ± 4.7%. With a median follow-up of 1790 days (range, 171-3350) in patients with pALG-based IST, 9-year estimated OS and FFS were 82.5 ± 4.5% and 47.1 ± 5.6%, respectively. Although, the median follow-up time longer in IST group than

HSCT group, no significantly different was found in 9-year estimated OS between the upfront URD-HSCT and pALG-based IST group (86.5 ± 4.0% vs. 82.5 ± 4.5%, $p = 0.887$). However, 9-year estimated FFS in HSCT was markedly superior to IST (86.5 ± 4.0% vs. 47.1 ± 5.6%, $p < 0.001$). Although with insignificant statistical difference was found in OS among age subgroup analysis (15-20, 21-39, and ≥40 years) ($p > 0.05$), upfront URD-HSCT was higher in FFS than pALG-based IST in respective groups ($p < 0.05$). Multivariable analysis showed that the choice of upfront URD-HSCT was favorable factor for FFS (HR 0.191, 95% confidence interval (CI) (0.097-0.379), $p < 0.001$), and the VSAA was a risk factor of OS (HR 2.297, 95% CI (1.041-5.067), $p = 0.039$) and FFS (HR 2.056, 95% CI (1.222-3.460), $p = 0.007$).

Table 1. Comparison of Patient Characteristics in the pALG-base IST and MUD-HSCT Groups

Characteristic	pALG-based IST (n = 101)	MUD-HSCT (n = 101)	P-value
Age at treatment, y, median (range)	26.0 (15, 55)	27.0 (15, 54)	0.877
Gender, n(%)			
Male	53 (52.5%)	59 (58.4%)	0.479
Female	48 (47.5%)	42 (41.6%)	
Diagnosis, n(%)			0.770
SAA/NSAA	65 (64.4%)	63 (62.4%)	
VSAA	36 (35.6%)	38 (37.6%)	
Conditon regimen, n(%)			
BUCy	-	47 (46.5)	-
FCA	-	42 (41.6)	-
PTCy	-	12 (11.9)	-
MNC, 108/kg, median (range)	-	9.02 (3.5-19.2)	-
$CD34^+$ cell count, 106/kg, median (range)	-	5.07 (0.26-19.8)	-
Neutrophil engraftment time, d, median (range)	-	11.0 (8-24)	-
Platelet engraftment time, d, median (range)	-	12.0 (7-98)	-
OR at 3-month, n(%)	40 (39.6)	95 (94.0)	<0.001
OR at 6-month, n(%)	63 (62.4)	91 (95.8)#	<0.001
#, 95 patients follow-up longer than 6 month for evluation			

Conclusions: These outcomes suggest that first-line URD HSCT might provide a better chance of success than first-line pALG-based IST for adults SAA.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P272

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN PATIENTS WITH THERAPY-RELATED MYELOID NEOPLASM FOLLOWING TREATMENT FOR LYMPHOMA: A STUDY OF THE CHRONIC MALIGNANCIES WORKING PARTY OF THE EBMT

Mitja Nabergoj[1], Diderik-Jan Eikema[2], Nienke Zinger[3], Uwe Platzbecker[4], Katja Sockel[5], Jürgen Finke[6], Nicolaus Kröger[6], Edouard Forcade[7], Arnon Nagler[8], Arnold Ganser[9], Johanna Tischer[10], A.E.C. Broers[11], Jürgen Kuball[12], Keith Wilson[13], Mathilde Hunault-Berger[14], Matthew Collin[15], Domenico Russo[16], Estefania Perez[17], Grzegorz Helbig[18], Alberto Mussetti[19], Kavita Raj[20], Christof Scheid[21], Donal P. McLornan[20], Marie Robin[22], Ibrahim Yakoub-Agha[23]

[1]Hematology Service, Institut Central des Hôpitaux (ICH), Hôpital du Valais, Sion, Switzerland, [2]EBMT Statistical Unit, Leiden, Netherlands, [3]EBMT Leiden Study Unit, Leiden, Netherlands, [4]Medical Clinic and Policinic 1, Leipzig, Germany, [5]University Hospital, TU Dresden, Dresden, Germany 6, University of Freiburg, Freiburg, Germany, [6]University Hospital Eppendorf, Hamburg, Germany, [7]CHU Bordeaux, Bordeaux, France, [8]Chaim Sheba Medical Center, Tel-Hashomer, Israel, [9]Hannover Medical School, Hannover, Germany, [10]Klinikum Grosshadern, Munich, Germany, [11]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [12]University Medical Centre, Utrecht, Netherlands, [13]University Hospital of Wales, Cardiff, United Kingdom, [14]CHRU, Angers, France, [15]Adult HSCT unit, Newcastle, United Kingdom, [16]Unit of Blood Diseases and Bone Marrow Transplantation, University of Brescia, ASST Spedali Civili, Brescia, Italy, [17]Hospital Clínico, Salamanca, Spain, [18]Silesian Medical Academy, Katowice, Poland, [19]Institut Català d'Oncologia-Hospital Duran i Reynals, Barcelona, Spain, [20]University College London Hospitals NHS Trust, London, United Kingdom, [21]University of Cologne, Cologne, Germany, [22]Hopital St. Louis, APHP, Paris, France, [23]CHU de Lille, Univ Lille, INSERM U1286, Infinite, Lille, France

Background: Therapy-related myeloid neoplasms (t-MNs) arise after cytotoxic treatment for a prior unrelated disease and present a dismal prognosis, thus allogeneic hematopoietic cell transplantation (allo-HCT) represents the only curative treatment. In this study, we analyzed the outcomes after allo-HCT of t- MN arising secondary to lymphoma treatment.

Methods: Retrospective EBMT registry analysis of adult patients who underwent a first allo-HCT for t-MDS or t-AML between 2006 and 2017. Both t-MN arising after completion of treatment for Hodgkin and Non-Hodgkin Lymphoma were included.

Results: We identified 378 patients, with a median age of 58 years at allo-HCT, with a median follow-up of 72 months. Males represented 62% of cases. t-MDS was the indication for allo-HCT in 222 (59%) and t-AML in 156 patients (41%). Most of the patients were previously treated for Follicular Lymphoma (22%), followed by Hodgkin's Lymphoma (22%) and Diffuse large B-cell Lymphoma (16%). Autologous HCT was a prior line of therapy in 38% of cases, with 15% of lymphomas not in complete remission (CR) at the time of allo-HCT. For t-MN, CR was recorded in 46% of cases, with a Karnofsky status >80 in 66%. Conditioning regimen was reduced intensity in 70% of patients. Stem cell source was peripheral blood in 90% of cases. Donor were MRD in 26%, MUD in 46%, MMRD in 4% et MMUD in 20% of cases. Five-year overall survival (OS) was 32%: in univariate analysis, OS was worse for patients transplanted for t-MDS (vs t-AML, p = .032), not in remission for t-MN (p = .013), and patients with a longer interval from lymphoma diagnosis to allo-HCT (p = .028). Five-year t-MN progression-free survival (PFS) was 28%: patients with active t-MN presented with lower PFS (p = .003) as did patients with t-MDS (vs t-AML, p = .022). t-MN Relapse incidence (RI) and Non-relapse mortality (NRM) at 5 years were 35% and 37%, respectively. Uncontrolled t-MN was associated with higher RI (p = .025); having an MRD was associated with a worse RI (p = .009), but to a significantly lower NRM (p < 0.001). A higher NRM was observed in patients older than 60 years (p = .034) and in those with heavily pretreated lymphoma (p = .028). Acute grade II-IV GVHD occurred in 33% of patients (14% grade III-IV), with a 12-months incidence of chronic GVHD of 32% (18% of extensive grade). In multivariable analysis, compared to t-MN in CR, uncontrolled t-MN was associated with significantly worse OS (HR = 1.54, p = 0.009), PFS (HR = 1.54, p = 0.008), and NRM (HR =

1.64, p = 0.04). Older age was associated with poorer OS (HR = 1.21 per decade, p = 0.007), PFS (HR = 1.15 per decade, p = 0.04), and NRM (HR = 1.23 per decade, p = 0.03). Having a MUD was associated with lower RI (HR = 0.54, 0.004), while MMUD with a higher risk of NRM (HR = 2.29, p = 0.002). At 5-year post allo-HCT, the relapse incidence of lymphoma was 3%, while the rate of secondary malignancies was 8%.

Conclusions: Our study demonstrates that patients with t-MN arising secondary to lymphoma treatment undergoing allo-HCT present with a satisfactory prognosis, however, significant rates of NRM and relapse remain of concern. A considerable rate of secondary malignancy was observed, although the lymphoma recurrence was rare.

	Total patients (number = 378)	t-MDS (number = 222)	t-AML (number = 156)
Median age, years (IQR)	58 (50-63)	59 (53-64)	54 (46-63)
t-MN status at allo-HCT, n (%)			
CR	172 (45)	59 (27)	113 (73)
Not CR	122 (33)	84 (38)	35 (24)
Untreated	81 (22)	77 (35)	4 (3)
Karnofsky status, n (%)			
>80	226 (66)	122 (61)	104 (72)
≤80	118 (34)	78 (39)	40 (28)
Donor, n (%)			
MRD	97 (26)	51 (23)	46 (30)
MUD	172 (46)	105 (47)	67 (43)
MMRD	17 (4)	9 (4)	8 (5)
MMUD	76 (20)	49 (22)	27 (17)
Stem cell source, n (%)			
Peripheral blood	342 (90)	198 (89)	144 (92)
Bone marrow	20 (5)	14 (6)	6 (4)
Conditioning intensity, n° (%)			
Standard	112 (30)	60 (27)	52 (33)
Reduced	265 (70)	161 (73)	104 (67)

Disclosure: None of the authors have anything to disclose.

1 - Haematopoietic Stem Cells

P273

SMART CONDITIONING WITH VENETOCLAX ENHANCED SEQUENTIAL FLAMSA + ALKYLATOR IN PATIENTS WITH HIGH-RISK MYELOID MALIGNANCIES

Felicitas Schulz[1], Paul Jaeger[1], Gesine Bug[2], Ben-Niklas Baermann[1], Patrick Tressin[1], Alexander Hoelscher[1], Annika Kasprzak[1], Kathrin Nachtkamp[1], Johannes Schetelig[3], Inken Hilgendorf[4], Ulrich Germing[1], Guido Kobbe[1]

[1]Universitätsklinikum Düsseldorf, Düsseldorf, Germany, [2]Universitätsklinikum Frankfurt, Frankfurt, Germany, [3]Universitätsklinikum Dresden, Dresden, Germany, [4]Universitätsklinikum Jena, Jena, Germany

Background: Allogeneic blood stem cell transplantation is the only potentially curative treatment for patients with high-risk myeloid malignancies like MDS, CMML or sAML. Depending on the underlying genetic risk profile, relapse rates after aHSCT remain high and up to 50% of patients die of relapse. Therefore, further improvement of conditioning regimens especially in elderly patients is an urgent medical need. Current sequential conditioning regimens combine intensive AML-like induction therapy with TBI or alkylators like Busulfan, Treosulfan and Melphalan. The first and currently widely accepted prototype of this treatment strategy is the Fludarabine/Amsacrine/Ara-C (FLAMSA) protocol, which has been modified multiple times by changing parts or adding additional cytotoxic drugs to further improve clinical results. Knowing that Venetoclax, an inhibitor of B-Cell Lymphoma-2 protein (BCL2), has synergistic effects to chemotherapy without increasing the level of non-hematologic toxicity, several German transplant centers added Venetoclax to the known FLAMSA+Alkylator protocol as an individualized treatment approach to improve long term cure in patients with high-risk myeloid malignancies.

Methods: In a retrospective survey among German transplant centers we identified 41 patients (median age 57 years, range 20 - 74, 23 female) with myeloid malignancies (26 AML, 11 MDS, 2 CMML, 1 CML) that had received FLAMSA + Alkylator based sequential conditioning including Venetoclax (20-400mg daily dose) between 2018 and 2022. All patients gave written informed consent for individualized treatment. All patients had active disease at time of transplant (12 untreated, 29 relapsed/refractory) and 31 (77.5%) had genetic high-risk features either by karyotype and/or by molecular mutation patterns.

Results: Patients received allografts from matched unrelated (22), matched related (9) or mismatched donors (6 unrelated 9/10, 4 haploidentical). ATG was used in 29 (70.7%), post-transplant cyclophosphamide in 8 patients (19.5%) in addition to GvHD prophylaxis with a calcineurin inhibitor and MMF. Median time to white blood cell recovery was 13 days (range 8 - 29) and median time to an unsupported PLT count greater than 50x10E9/l was 18 days (range 10 - 44). Tumor lysis syndrome occurred during conditioning in one patient (2.5%). No significant extrahematologic toxicity related to Venetoclax was observed. At day +30 a total of 37 patients (90%) were in complete remission. aGvHD II°-IV° occurred in 14 (34.1%) and cGvHD moderate - severe in 3 (7.3%) patients. TRM was 0% at 3 months and 16 patients experienced relapse after a median of 172 days (range 62 - 861). After a median follow up of 486 days after transplant (range 130 - 1300), 33 patients (80.5%) are alive (27 in remission, 14.8% after salvage therapy, and 5 in relapse receiving further treatment).

Conclusions: The combination of sequential FLAMSA+Alkylator with Venetoclax appears to be safe and highly effective without increasing the rate of non-hematologic toxicity. This may be a smart way to extend the limited therapy options of patients with high-risk myeloid malignancies. To further validate these insights and enhance the idea of smart conditioning, a controlled prospective clinical trial should be the next step.

Disclosure: Bärmann,B Travel Support: Kite-Gilead, Medac, Roche, Speaker Honoria: Incyte. Nachtkamp, K: Travel Support: Medac, Nachtkamp, K: Speaker Honoraria: Jazz, BSH Medical. Germing, U: Speaker Honoraria: BMS, Novartis, Institutional Research Support: BMS, Abbvie, Novartis, Advisory role: BMS. Kobbe, G: Advisory role or Speaker Honoraria: Abbvie, Amgen, Biotest, BMS-Celgene, Eurocept, Kite-Gilead, MSD, Novartis, Neovii, Pfizer, Takeda, Financing of Scientific Research: Abbvie, Amgen, BMS-Celgene, Eurocept, Medac. All other authors have nothing to declare.

1 - Haematopoietic Stem Cells

P274

DONOR-SPECIFIC ANTI-HLA ANTIBODIES (DSAS) IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM MISMATCHED DONORS, ON BEHALF OF GITMO AND AIBT

Ursula La Rocca[1,2], Roberto Ricci[1], Alfonso Piciocchi[3], Walter Barberi[1], Elena Oldani[4], Alida Dominietto[5], Raffaella Cerretti[6], Alessandra Picardi[6], Francesca Bonifazi[7], Riccardo Saccardi[8], Maura Faraci[9], Giovanni Grillo[10], Lucia Farina[11], Benedetto Bruno[12], Anna Grassi[4], Anna Proia[13], Elena Tagliaferri[14], Giuseppina De Simone[15], Michele Malagola[16], Michela Cerno[17], Simone Cesaro[18], Paolo Bernasconi[19], Lucia Prezioso[20], Paola Carluccio[21], Nicola Mordini[22], Matteo Pelosini[23], Attilio Olivieri[24], Patrizia Chiusolo[25], Stella Santarone[26], Michele Cimminiello[27], Roberto Crocchiolo[10], Franco Papola[28], Gianni Rombolà[29], Nicoletta Sacchi[30], Valeria Miotti[31,32], Massimo Martino[33], Fabio Ciceri[34], Anna Paola Iori[1]

[1]Hematology, Sapienza, Rome, Italy, [2]Italian National Institute of Health, Rome, Italy, [3]GIMEMA Data Center, Rome, Italy, [4]Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII, Bergamo, Italy, [5]IRCCS Ospedale Policlinico S.Martino, Genoa, Italy, [6]Stem Cell Transplant Unit, Policlinico Tor Vergata, Rome, Italy, [7]IRCSS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, Careggi University Hospital, Florence, Italy, [9]UOSD Bone Marrow Transplant Center-IRCCS Istituto G.Gaslini, Genoa, Italy, [10]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, [11]Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [12]S.S.C.V.D Trapianto di Cellule Staminali A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy, [13]Unity of Hematology and Stem Cell Transplant, Azienda Ospedaliera S. Camillo Forlanini, Rome, Italy, [14]Hematology and BMT Unit, Fondazione IRCCS Ca'Granda, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy, [15]Unità Operativa di Trapianto di Cellule Staminali Emopoietiche e Terapie Cellulari, Azienda Ospedaliera di Rilievo Nazionale Santobono-Pausillipon, Naples, Italy, [16]Unit of Blood Diseases and Stem Cell Transplantation, ASST-Spedali Civili di Brescia, University of Brescia, Brescia, Italy, [17]Division of Hematology and Stem Cell Transplantation, Azienda Sanitaria Universitaria Friuli Centrale, Piazzale S. Maria della Misericordia 10, Udine, Italy, [18]Pediatric Hematology Oncology, Azienda Ospedaliera Universitaria Integrata, Verona, Italy, [19]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy, [20]Hematology and Stem Cell Transplant Unit, Ospedale Maggiore, Parma, Italy, [21]Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy, [22]Hematology Division, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy, [23]Clinical and Experimental Medicine, Section of Hematology, University of Pisa, Pisa, Italy, University of Ancona, Azienda Ospedaliera Universitaria Ospedali Riuniti di Ancona, Ancona, Italy, Universita' Cattolica del Sacro Cuore, Rome, Italy, [26]Bone Marrow Transplant Center, Ospedale Civile, Pescara, Italy, [27]Hematology and Bone Marrow Transplantation Unit, S. Carlo Hospital, Potenza, Italy, [28]Regional Centre of Immunohaematology and Tissue Typing, S.Salvatore Hospital, L'Aquila, Italy, [29]Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy, [30]Italian Bone Marrow Donor Registry, E. O. Ospedali Galliera, Genoa, Italy, [31]Laboratory of Immunogenetics, Santa Maria della Misericordia University Hospital, Udine, Italy, [32]Associazione Italiana di Immunogenetica e Biologia dei Trapianti, AIBT, Italy, [33]Stem Cell Transplant and Cellular Therapies Unit, "Bianchi-Melacrino-Morelli" Hospital, Reggio Calabria, Italy, [34]University Vita-Salute San Raffaele, IRCCS, S. Raffaele Scientific Institute, Milan, Italy

Background: Antibodies (Ab) directed against donor-specific HLA allele(s)/antigen(s)(DSAs) represent a known risk factor for mismatched-hematopoietic stem cell transplantation (mmHSCT) engraftment. However, the overall management of DSAs still needs to be standardized. GITMO and AIBT run a survey on DSAs' management in Italian Transplant Programs (ITP).

Methods: Retrospective, multicentric study including all mmHSCT performed between January 2014 and June 2017 among 26 ITP. Primary endpoints were the description of the following clinical and laboratory approaches to DSAs: anti-HLAAb and DSAs detection, laboratory methods employed and management, donor selection criteria and desensitization strategies. Secondary endpoints were the role of DSAs on donor engraftment (E), graft failure(GF) and overall survival (OS).

Results: 955 patients were confirmed mmHSCT; 804 were evaluable (36% females, 64% males). The median age was 48(r: 0-72 years). Among females, 55% had previous pregnancies, 5% had abortions, and 88% of patients had previously received blood transfusions. Overall, 354 out of 804 patients (44%) were screened for anti-HLAAb by ITP: 91/354 were positive for anti-HLAAb (25.6%), 23 for DSAs (6.5 % of the evaluable patients; 25.3 % of anti-HLAAb positive patients). The Luminex platform was employed in 93% of tests. Anti-HLA immunization was significantly correlated with female sex and a history of at least 4 pregnancies before HSCT ($p = 0.003$ and $p = 0.024$, respectively). Eleven of the 23 (48%) patients with DSAs underwent desensitization, with various schedules and outcomes: 7 patients obtained DSAs clearance with full absolute neutrophil count(ANC) engraftment, while in 1 no platelets(PLTS) engraftment was reached; 2 patients showed DSA reduction, and 1 of them experienced graft failure; 2 patients showed DSA persistence:1 of them experienced graft failure; in 7 cases, no desensitization was employed, and 3 of them didn't reach PLTS engraftment. An alternative donor was selected for the remaining 5 patients, and all engrafted. ANC and PLTS engraftment were statistically associated with the absence of anti-HLAAb, ABO match, a higher number of infused nucleated cells and lack of a-GvHD. In addition, significant factors for PLTS engraftment were the use of leucodepleted transfusions ($p = 0.005$), HLA match ($p < 0.001$), younger age of the patient ($p = 0.021$). Graft failure was associated with the bone marrow stem cell source ($p = 0.032$) and a lower number of infused CD34+ cells($p = 0.033$). In univariate analysis, the following variables influenced OS: the detection of Ab against I-II HLA classes ($p < 0.001$), donor and patient age(in both cases $p < 0.001$), haematological remission at HSCT ($p < 0.001$), HLA match ($p = 0.007$), HSC source ($p < 0.001$), ANC E (< 0.001) and PLTS E($p = 0.001$), early ($p < 0.001$) and late GF(< 0.001), grade ≥ II a-GVHD ($p = 0.017$). In multivariate analysis, the detection of both classes anti-HLAAb ($p = 0.006$), patient age ($p = 0.020$), E ($p = 0.010$), and an early GF($p = 0.004$) maintained a role on OS.

Conclusions: In Italian Centers a uniform policy to screen and manage anti-HLAAb before mmHSCT is lacking. Anti-HLAAb and DSAs were documented in 25.6% and 6.5% of screened patients and were confirmed as a risk factor affecting OS. Pre-transplant detection of DSAs was managed with different approaches resulting in stable engraftment in 9/11 patients. Our study supports the clinical relevance of the anti-HLAAb/DSAs detection and management in mmHSCT.A standardized approach of desensitization is warranted.

Clinical Trial Registry: https://clinicaltrials.gov/ct2/show/record/NCT04888286

Disclosure: No conflicts of interest to disclose.

1 - Haematopoietic Stem Cells

P275

IMPROVED OUTCOME OVER TIME AFTER SECOND ALLOGENEIC STEM CELL TRANSPLANTATION IN RELAPSED AML. AN ANALYSIS OF 1540 PATIENTS ON BEHALF OF THE ALWP OF EBMT

Ann-Kristin Schmaelter[1], Maud Ngoya[2], Jacques-Emmanuel Galimard[2], Ali Bazarbachi[3], Jürgen Finke[4], Nicolaus Kröger[5], Friedrich Stölzel[6], Matthias Stelljes[7], Thomas Valerius[8], Johanna Tischer[9], Thomas Schroeder[10], Peter Dreger[11], Igor-Wolfgang Blau[12], Bipin Savani[13], Sebastian Giebel[14], Jordi Esteve[15], Arnon Nagler[16], Christoph Schmid[1], Fabio Ciceri[17], Mohamad Mohty[2,18]

Variable	Level	LFS		OS		RI		NRM	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Period of transplant	2000–2004	1		1		1		1	
	2005–2009	0.62 (0.39–0.99)	**0.05**	0.61 (0.38–0.98)	**0.04**	0.52 (0.3–0.91)	**0.02**	0.95 (0.34–2.7)	0.93
	2010–2014	0.5 (0.32–0.79)	**0.003**	0.48 (0.3–0.76)	**0.002**	0.41 (0.24–0.72)	**0.002**	0.73 (0.26–2.05)	0.55
	2015–2019	0.53 (0.34–0.83)	**0.01**	0.47 (0.3–0.74)	**<0.001**	0.44 (0.25–0.76)	**0.003**	0.77 (0.27–2.15)	0.61
Type of SCT2	MSD	1		1		1		1	
	Haplo	1.13 (0.89–1.44)	0.30	1.34 (1.04–1.73)	**0.02**	0.93 (0.68–1.28)	0.66	1.88 (1.2–2.97)	**0.01**
	URD	1.13 (0.92–1.38)	0.26	1.32 (1.05–1.66)	**0.02**	0.89 (0.69–1.14)	0.35	2.14 (1.42–3.23)	**<0.001**
Age at Transplant(by 5 years)		1.02 (1–1.05)	0.11	1.05 (1.02–1.08)	**0.002**	1 (0.96–1.03)	0.86	1.1 (1.04–1.16)	**<0.001**
Disease status at SCT2	CR	1		1		1		1	
	Rel	1.63 (1.39–1.91)	**<0.001**	1.59 (1.34–1.88)	**<0.001**	1.91 (1.56–2.34)	**<0.001**	1.35 (1.02–1.8)	**0.04**
In vivo T-cell depletion	No	1		1		1		1	
	Yes	0.92 (0.78–1.1)	0.37	0.89 (0.74–1.07)	0.20	1.05 (0.84–1.3)	0.68	0.7 (0.51–0.95)	**0.02**
Myeloablative regimen	No	1		1		1		1	
	Yes	0.79 (0.68–0.92)	**0.002**	0.82 (0.7–0.97)	**0.02**	0.7 (0.58–0.85)	**<0.001**	1.1 (0.84–1.44)	0.47
Karnofsky	< 90	1		1		1		1	
	≥ 90	0.84 (0.72–0.97)	**0.02**	0.74 (0.63–0.87)	**<0.001**	0.95 (0.78–1.15)	0.58	0.65 (0.49–0.85)	**0.002**
Delay SCT1 to 1st relapse	≥10.2mo	1		1		1		1	
	<10.2mo	1.72 (1.48–2)	**<0.001**	1.83 (1.56–2.15)	**<0.001**	1.86 (1.54–2.24)	**<0.001**	1.46 (1.11–1.93)	**0.01**

[1]University Hospital Augsburg, Augsburg, Germany, [2]EBMT Paris Study Office, Paris, France, [3]American University of Beirut Medical Center, Beirut, Lebanon, [4]University of Freiburg, Freiburg, Germany, [5]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [6]University Hospital Dresden, Dresden, Germany, [7]University of Münster, Münster, Germany, [8]University Medical Center Schleswig-Holstein, Kiel, Germany, [9]University Hospital of Munich, Munich, Germany, [10]University Hospital Essen, Essen, Germany, [11]University of Heidelberg, Heidelberg, Germany, [12]Charité Universitätsmedizin Berlin, Berlin, Germany, [13]Vanderbilt University Medical Center, Nashville, United States, [14]Maria Sklodowska-Curie Cancer Center and Institute of Oncology, Gliwice, Poland, [15]Hospital Clinic Barcelona, Barcelona, Spain, [16]Chaim Sheba Medical Center, Tel Aviv University, Tel Aviv, Israel, [17]IRCCS Ospedale San Raffaele, University Vita-Salute San Raffaele, Milano, Italy, [18]Saint Antoine Hospital, Paris, France

Background: Second allogeneic stem cell transplantation (alloSCT2) is increasingly used for acute myeloid leukemia relapsing after first alloSCT. Based on the ALWP registry, we analyzed patient characteristics, transplant settings and outcome over time to identify factors associated with improved results after alloSCT2.

Methods: 1540 patients receiving alloSCT2 after hematologic relapse between 2000 and 2019 were included, excluding alloSCT2 given for graft failure. Patients were grouped by transplant period in 5-year intervals.

Results: Median follow-up from alloSCT2 was 4.9 years. Over time, the number of alloSCT2 increased from 144 (2000-2004) to 619 (2015-2019), with remarkable changes in patient characteristic and transplant settings: In recent periods, patients were older (median age increasing from 43.4 to 48.6 years, $p = 0.012$), received more alloSCT2 in complete remission ($p < 0.0001$) and with a better Karnofsky performance score (KPS; $p < 0.001$). More donor change for alloSCT2 (increase: 27.5%-80.8%) and more unrelated (increase: 30.6%-61.7%) and haploidentical (increase: 0.7%-22.9%) donors were used over time ($p < 0.0001$ each). Finally, more myeloablative conditioning (MAC) ($p = 0.045$), in-vivo T-cell- depletion (TCD; $p < 0.001$), post-transplant cyclophosphamide ($p < 0.001$) and ciclosporin A/MMF for GVHD prophylaxis ($p < 0.001$) were used in more recent alloSCT2.

Overall survival (OS) and leukemia free survival (LFS) improved considerably over time: Two-year OS increased from 22.5% to 35%, LFS from 14.5% to 24.5%. Whereas no clear trend was observed for GVHD and non-relapse mortality (NRM), cumulative relapse incidence (RI) decreased from 64% to 50.7%.

In multivariate analysis (see table), a later period of alloSCT2 was closely associated with improved OS (HR:0.47, $p < 0.001$) and LFS (HR:0.53, $p = 0.01$). Furthermore, disease status at alloSCT2 influenced OS ($p < 0.001$), LFS ($p < 0.001$), RI ($p < 0.001$) and NRM ($p = 0.04$). Longer remission after alloSCT1 was associated with better OS ($p < 0.001$) and LFS ($p < 0.001$), lower RI ($p < 0.001$), higher NRM ($p = 0.01$) and more aGVHD ($p = 0.02$). AlloSCT2 from haploidentical or unrelated donors (URD), and older age were associated with significantly higher NRM and inferior OS ($p = 0.02$ for haplo-donors, $p = 0.02$ for URD, $p = 0.002$ for age). MAC for alloSCT2 was associated with decreased RI ($p < 0.001$) without increase in NRM ($p = 0.47$), leading to increased OS ($p = 0.02$) and LFS ($p = 0.002$). Further, LFS ($p = 0.02$) and OS ($p < 0.001$) were positively affected by a better KPS. In-vivo TCD was associated with lower aGVHD ($p < 0.001$), cGvHD ($p = 0.003$) and NRM ($p = 0.02$). Cytogenetics at diagnosis, donor-recipient sex match and the use of TBI for alloSCT2 did not influence outcome. Change to a new donor for alloSCT2 could not be included into the multivariable model due to missing information in 1/3 of patients. However, exploratory analysis on 1006 patients revealed no signal for a significant influence.

Conclusions: According to data from >1500 patients with a long follow-up, outcome after alloSCT2 has continuously improved over the last two decades despite increasing patient age. In the most recent period, 1/3 of patients could be rescued by alloSCT2. In particular, decreased RI, that did not come at cost of increased toxicity could be observed. This might be due to better disease control and improved KPS at alloSCT2, and an increasing use of MAC, in-vivo TCD and eventually post-transplant cyclophosphamide in alloSCT2.

Disclosure: The authors declare no conflicts of interest.

1 - Haematopoietic Stem Cells

P276

AKKERMANSIA AS EARLY GUT MICROBIOTA SIGNATURE PROTECT FROM ACUTE GRAFT-VERSUS-HOST DISEASE AND

PROMOTE SURVIVAL AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Zhuoyue Shi[1], Fang Li[2], Fei Gao[1], Jinmin Shi[1,3,4,5], Yi Luo[1,3,4,5], Jian Yu[1,3,4,5], Xiaoyu Lai[1,3,4,5], Lizhen Liu[1,3,4,5], Huarui Fu[1,3,4,5], Zhiyang Yuan[2], Zhongzheng Zheng[2], He Huang[1,3,4,5], Yamin Tan[6], Yanmin Zhao[1,3,4,5]

[1]Bone Marrow Transplantation Center, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, [2]Shanghai Dishuo Beken Biotechnology Co., Ltd., Shanghai, China, [3]Liangzhu Laboratory, Zhejiang University Medical Center, Hangzhou, China, [4]Institute of Hematology, Zhejiang University, Hangzhou, China, [5]Zhejiang Province Engineering Laboratory for Stem Cell and Immunity Therapy, Hangzhou, China, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou City, China

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the most effective treatment for hematological malignancies. However acute graft-versus-host disease (aGVHD) after HSCT still played an important role in transplantation-related mortality. Recent research have discovered a strong correlation between gut microbiota and aGVHD but the mechanism is incompletely understood. Our study aimed to explore the dynamic changes of gut microbiota from the start of transplantation and expected to find the reliable biomarker of aGVHD patients.

Methods: Between June 2018 and October 2019, we conducted a single-centerobservational study to examine the intestinal microbiota by 16S ribosomal RNA sequencing techniques in patients with hematological malignancies, who received allogeneic HSCT at First Affiliated Hospital of Zhejiang University School of Medicine. Fecal samples were collected in three periods: pre-HSCT (day-30 to day0), early post-HSCT (day1-day14) and late post-HSCT (day15 to day30). Patients with at least one stool sample over three time periods were included in the study.

Results: A total of 159 patients delivered 333 stool samples and finally 123 fecal specimens from 83 consecutive patients receiving allo-HSCT were analyzed after quality assessment. Forty one (49.4%) patients developed aGVHD, including 29 (34.9%) patients progressed to II-IV aGVHD (Table1). aGVHD patients owed a lower bacterial diversity in the pre-HSCT period compared with non-aGVHD patients (Shannon index: 3.2 vs 2.5, $P = 0.046$), while the difference became less pronounced over the next two periods after HSCT. An increased abundance of the phylum *Actinobacteriota* and a decreased abundance of phylum *Bacteroidota* were observed in those who developed aGVHD from the vertical development of time. The patients with aGVHD had a lower abundance of the genus *Akkermansia* ($P = 0.015$) and a lower abundance of the family *Ruminococcaceae* ($P = 0.002$) in the early post-HSCT. A lower abundance of the genus *Akkermansia* during early post-HSCT period also indicated lower overall survival (65.7 vs 83.3%, $P = 0.034$).

Table1: Characteristics and clinical outcomes of all patients

Characteristics and clinical outcome	No. (%)
Median patient age (years)	32 (15-67)
Median donor age (years)	36 (14-57)
Median follow up time (days)	874 (44-1288)
Patient sex	
Male	43 (51.8)
Female	40 (48.2)
Donor/Patient sex combination	
Female/ Male	31 (19.5)
Other	128 (80.5)
ABO blood mismatch	
Identical	50 (60.2)
Mismatch	33 (39.8)
Diagnosis	
AML	29 (34.9)
ALL	39 (47.0)
MDS	10 (12.0)
Other	5 (6.0)
Disease status at HSCT	
CR1	55 (66.3)
å CR1	28 (33.7)
Disease risk index	
Low/Int risk	56 (67.5)
High/Very high risk	27 (32.5)
Conditioning regimen	
MAC	81 (97.6)
RIC	2 (2.4)
ATG	
ATG-F	6 (7.2)
ATG-G	68 (81.9)
No ATG	9 (10.8)
HLA match	
MRD	12 (14.5)
Haploidentical	59 (71.1)
MUD	12 (14.5)
aGVHD	
Grade I-IV	41 (49.4)
Grade II–IV	29 (34.9)
cGVHD	
No	40 (48.2)
Mild	27 (32.5)
Moderate	8 (9.6)
Severe	8 (9.6)
Overall survival	56 (67.5)

Conclusions: Our study confirmed lower baseline bacterial diversity and lower abundance of the genus *Akkermansia* were associated with the development of aGVHD. Also the high abundance of the genus *Akkermansia* in the early post-HSCT periods could predict an improved overall survival, paving the way for rational interventions to restore microbiota integrity and develop strategies to support anaerobic intestinal commensals such as Akkermansia in patients who undergo HSCT.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P277

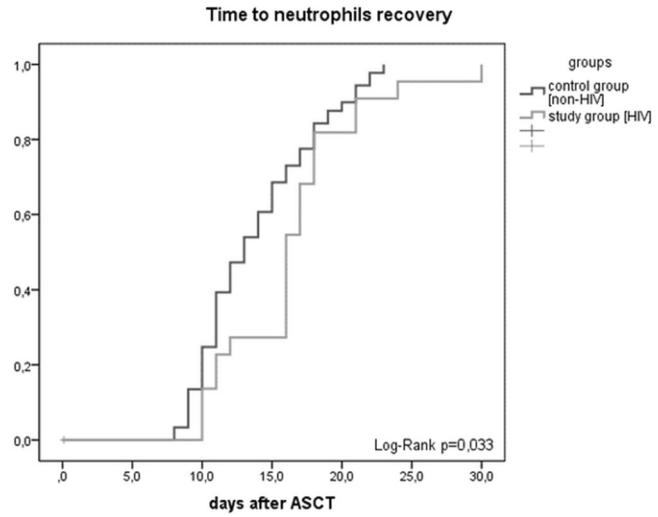
AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH HIV-RELATED LYMPHOMA: RESULTS OF PROSPECTIVE MULTICENTER MATCHED CASE-CONTROL STUDY

Marina Popova[1], Yulia Rogacheva[1], Ivan Tsygankov[1], Andrey Chekalov[1], Ilya Zyuzgin[2], Stanislav Volchenkov[2], Anna Zverkova[2], Olga Uspenskaya[3], Olga Ruzhinskaya[3], Victoria Ryabchikova[4], Kirill Lepik[1], Vadim Baykov[1], Natalia Mikhaylova[1], Alexander Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation, [2]N.N. Petrov National Medical Research Center of Oncology, Saint Petersburg, Russian Federation, [3]Leningrad Regional Clinical Hospital, Saint Petersburg, Russian Federation, [4]Saint Petersburg City Clinical Hospital No 31, Saint Petersburg, Russian Federation

Background: Despite the widespread use of antiretroviral therapy (ART) human immunodeficiency virus (HIV) infection is associated with an increased incidence of non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Concurrently autologous stem cell transplantation (ASCT) becomes a feasible approach to either rescue or consolidate HIV-related lymphoma patients. However, the number of prospective matched case-control studies to prove the safety and efficacy of ASCT in HIV-related lymphoma is limited. The aim of the study was to prospectively evaluate the safety and effectiveness of ASCT for patients with HIV-related lymphoma compared with patients without HIV.

Methods: Since 2016, 115 patients were enrolled in a prospective matched case-control study of ASCT for patients with HIV-related lymphoma. Four HSCT centers have performed twenty-three ASCT for patients with HIV-related lymphoma (study group, n = 23) between March 2016 and June 2022. Ninety-two non-HIV-infected patients were enrolled to the control group (n = 92, 1:4). In study group diagnosis were diffuse large B-cell - 7 (30,4%), plasmablastic - 4 (17,5%), Burkitt - 2 (8,7%), peripheral T-cell - 1 (4,3%), primary CNS - 1 (4,3%) and HL - 8 (34,8%); complete response at the moment of ASCT – 17 (74%); main conditioning regimen – BeEAM (Be-bendamustine) – 17 (74%); the median of CD34+ infused cells – 3,7 (2,7-26,0) 10*6/kg. The study and control groups were well matched in key demographic, clinical, and transplant characteristics, with the exception of the prevalence of plasmablastic lymphoma (27% to 0%) and etoposide dose reduction (61% to 21%) in study group. At the time of ASCT in study group HIV viral load was undetectable; the median number of CD4+ cells was 471,5 (210-715) cells/mcl; all patients were on ART. The median follow up time was 19,5 (0,1-80) months. The primary end points were overall survival (OS), progression-free survival (PFS) and time-to-progression (TTP) at 2 years after ASCT. Secondary end points were time to hematopoietic recovery and non-relapse mortality (NRM).



Results: The 2-year OS (n = 115) was 93%: 91,3% and 93,5% in study and control groups, respectively (p = 0,713). PFS at 2 years in study group was 78,3%, and was not different compared to the control group 75% (p = 0,850). TTP at 2 years was 13% in study group and 18,5% in control group (p = 0,624). The median time of leukocytes, neutrophils, and platelets recovery was D + 14 (10-25), D + 16 (10-30), D + 15 (7-31) respectively in study group and D + 12 (8-22), D + 13 (8-23), D + 13 (4-31) in control group. Neutrophil recovery was significantly delayed in study group (picture 1, log-rank p = 0,033; Mann–Whitney *U* test p = 0,018). NRM at 2 years was 8,7% in study group and 6,5% in control group (p = 0,673).

Conclusions: The data from the prospective multicenter matched case-control study provide further evidence that ASCT is a safe and effective approach for patients with HIV-related lymphoma. We found no difference in overall survival, PFS, TTP and NRM between patients with HIV-related lymphoma and control group. The only neutrophil recovery was significantly delayed after ASCT in patients with HIV-related lymphoma.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P278

TOWARD A CLINICAL PHENOTYPE INSPIRED DIAGNOSIS OF AUTOIMMUNE MANIFESTATIONS IN VEXAS SYNDROME: A GUIDE TO *UBA1*-TESTING FOR THE GENERALIST

Alessandro Bruno[1], Carmelo Gurnari[2,3], Raffaella Greco[1], Tobias Alexander[4], John Snowden[5]

[1]IRCCS Ospedale San Raffaele, Milan, Italy, Taussig Cancer Institute, Cleveland, United States, Italy, [4]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, [5]Sheffield Blood & Marrow Transplant and Cellular Therapy Programme, Sheffield Teaching Hospitals Foundation NHS Trust, Sheffield, United Kingdom

Background: VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) is a recently described adult-onset entity that links autoimmune/autoinflammatory syndromes and hematologic disorders. Somatic mutations of the *UBA1* gene in hematopoietic stem cells constitute its genetic basis. As an X-linked disorder, the majority of cases occur in men, usually during the 5th-6th decade of life. Patients may manifest a multiplicity of clinical features with limited responses to therapy. At the moment, the only curative treatment for VEXAS is allogeneic HSCT. No diagnostic guidelines currently exist as to whom to candidate for *UBA1* gene testing, thus representing a challenge in early recognize and treat such patients.

Methods: Reviewing currently available evidence, we have developed an evidence-based diagnostic scheme allocating VEXAS-associated characteristics into groups with different likelihood for the disease, with focus on the autoimmune features. Demographics, clinical and laboratory features and bone marrow findings were analyzed.

Results: Constitutional symptoms, such as noninfectious fever, are shared by many autoimmune/autoinflammatory conditions and are virtually present in all VEXAS patients. The skin is the most common involved organ with a frequency achieving 90% and various types of manifestations. Particularly, patients can develop a neutrophilic dermatosis resembling Sweet syndrome as well as other manifestations such as leukocytoclastic vasculitis and septal

panniculitis. Among these, only the Sweet's syndrome-like lesions are directly caused by mutated cells, while others seem secondary to inflammation and cytokine pathways activation.

The second most frequently involved organ is the lung (up to 70% of patients) with dyspnea and cough as the main symptoms. Radiologic findings include ground-glass infiltrates as the most frequent feature (90%), while other manifestations such as consolidations, reticulation, septal lines and pleural effusion are present in about half of the cases. Relapsing episodes of chondritis are another characteristic feature of VEXAS: ear and nose are the most frequent involved sites, followed by peripheral joint chondritis and tendinitis. Unprovoked venous thromboembolism is present in about half of the cases. Ocular manifestations are also possible (up to 40%) and encompass uveitis, scleritis, episcleritis and retinal vasculitis. Also the gastro-intestinal tract and the lymph nodes appear to be involved, albeit at lower rates. Furthermore, other conditions, such as acute-onset of chronic inflammatory demyelinating polyradiculoneuropathy and hemophagocytic lymphohistiocytosis, are reported. Common laboratory findings are elevation of inflammation markers and cytopenias (in particular macrocytic anemia), while vacuolization of myeloid precursors in the bone marrow, even in the absence of associated myelodysplastic syndrome, is a very sensitive diagnostic element, although not specific.

We suggest that testing for *UBA1* mutation is warranted for patients with features very strongly associated with VEXAS or with strongly associated features if no other cause is identifiable **(Table 1)**.

VEXAS association	Demographics	Clinical features	Laboratory findings	Bone marrow findings (if available)
Very strong	Male sex	Non-infectious fever	Macrocytic anemia	MDS
	Age > 60 years	Weight loss	Elevated ESR and CRP	Vacuolization in myeloid precursors ≥ 10%
		Sweet's syndrome-like skin lesions		
		Ground glass pulmonary infiltrates		
		Chondritis (ear and nose)		
		Tendinitis		
		Autoimmune symptoms with steroid dependency		
Strong	Age > 50 years but ≤ 60 years	Unprovoked venous thromboembolism	Lymphopenia	
		Chondritis (joints)	Elevated ferritin	
		Pulmonary involvement (consolidations, reticulation, pleural effusion)		
		Erythematous rash		
		Transfusion-dependency		
Possible	Age > 40 years but ≤ 50 years	Intestinal involvement	Thrombocytopenia	Plasma cell dyscrasias
	Female sex (Turner syndrome or clonal X-skewing)	Ocular involvement	Monoclonal gammopathy	CMML
		Unspecified arthritis	Neutropenia	Myelofibrosis
		HLH, CIDP		
		Kidney, heart involvement		

Conclusions: Raising clinical awareness and close collaboration between specialists are of paramount importance for prompt diagnosis and treatment. On the basis of the variegated autoimmune manifestations of VEXAS, we proposed simple criteria for diagnostic testing of *UBA1* that may help physicians in their daily practice. Identifying the disease in its early stages is crucial to candidate fit patients to HSCT before the onset of irreversible organ damage.

Disclosure: Tobias Alexander: speaking honoraria from Amgen, Roche, and Pfizer, travel grants from Neovii, and study support from Amgen, Janssen-Cilag, and Miltenyi Biotec.

John Snowden: advisory board membership from Medac.

Raffaella Greco: speaking honoraria from Biotest, Pfizer, Medac, and Magenta.

The rest of the authors declare that they have no relevant conflicts of interest.

1 - Haematopoietic Stem Cells

P279

DONOR LYMPHOCYTE INFUSION FOR THE TREATMENT OF RELAPSED HEMATOLOGICAL MYELOID MALIGNANCIES: RESULTS OF A RETROSPECTIVE MULTICENTER STUDY FROM THE EBMT REGISTRY

Louis Dumeignil[1], Amandine Charbonnier[1], Pierre Morel[1], Jean-Pierre Marolleau[1], Felipe Suarez[2], Marie Robin[3], Xavier Poiré[4], Anne De Meuter[5], Raynier Devillier[6], Ana Berceanu[7], Jérome Cornillon[8], Sebastien Maury[9], Patrice Chevallier[10], Yves Chalandon[11], Stéphanie Nguyen-Quoc[12], Natacha Maillard[13], Edouard Forcade[14], Claude-Eric Bulabois[15], Laurent Sutton[16], Jacques-Olivier Bay[17], Ibrahim Yakoub-Agha[18], Ali Bazarbachi[19], Michael Loschi[20], Anne Huynh[21], Sylvie Francois[22], Marie-Anne Couturier[23], Jean-Baptiste Mear[24], Johanna Konopacki[25], Cristina Castilla-Llorente[26], Hélène Labuissière-Wallet[27], Bruno Lioure[28], Marie-Thérèse Rubio[29], Malek Benakli[30], Yves Beguin[31], Mohamad Mohty[32], Patrice Ceballos[33], Nathalie Contentin[34], Pascal Turlure[35], Sylvain Chantepie[36]

[1]Amiens-Picardie, Amiens, France, [2]APHP - Necker-Enfants Malades, Paris, France, [3]APHP - Saint-Louis, Paris, France, [4]Section of Hematology, Cliniques Universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium, [5]Institut Jules Bordet, Brussels, Belgium, [6]Institut Paoli-Calmettes, Marseille, France, [7]Hôpital Jean Minjoz, Besançon, France, [8]CHU Saint-Etienne, Saint-Etienne, France, [9]Hôpital Henri Mondor, Creteil, France, [10]CHU Nantes, Nantes, France, [11]Geneva University Hospitals, Geneva, Switzerland, [12]APHP - Pitié Salpétrière, Paris, France, [13]CHU Poitiers, Poitiers, France, [14]CHU Bordeaux, Bordeaux, France, [15]CHU Grenoble, Grenoble, France, [16]CHU Tours, Tours, France, [17]CHU Clermont-Ferrand, Clermont-Ferrand, France, [18]Hôpital Claude Huriez, Lille, France, American University of Beirut Medical Center, Beirut, Lebanon, [20]Université Nice Sophia Antipolis, Nice, France, [21]IUCT Oncopole, Toulouse, France, [22]CHU Angers, Angers, France, [23]CHU Brest, Brest, France, [24]CHU Rennes, Rennes, France, [25]Service d'hématologie, Hôpital Percy, Clamart, France, [26]Institut Gustave-Roussy, Paris, France, [27]CHU Lyon, Lyon, France, [28]CHU Strasbourg, Strasbourg, France, [29]CHU Nancy, Nancy, France, Pierre and Marie Curie Center, Algiers, Algeria, [31]Division of Haematology, University and CHU of Liège, Liège, Belgium, [32]Saint-Antoine Hospital, Paris, France, [33]CHU Montpellier, Montpellier, France, [34]Centre Henri Becquerel, Rouen, France, [35]CHU Limoges, Limoges, France, [36]CHU Caen, Caen, France

Background: Post-transplant relapses of haematological myeloid malignancies have a poor prognosis. In this situation, one of the therapeutic strategies is to restore a graft-versus-tumor effect. The aim of this study is to assess the outcome of relapsed patients who received DLI in this indication.

Methods: We conducted a multicenter retrospective study from the EBMT register, including all patients who received at least one DLI for the management of post-transplant relapse of AML, MDS and Myelofibrosis. We evaluated the outcome of the overall cohort and prognostic factor influencing these outcome.

Results: We retrospectively analyzed 434 patients (354 with AML, 64 with MDS and 16 with MPN) with an M/F sex ratio of 1.3 and a median of age of 56. The median time to relapse was 181 days. Patients received a median of 1 DLI with a median dose of 10.10^6 CD3/kg. After the relapse, 12% of patients in the cohort

received intensive treatment, 53.5% received non-intensive treatment, mainly combinations including hypomethylating agents. Only 4.6% of patients in the cohort received DLI without any treatment (Missing treatment data was 30%). Median follow-up was 231 days. Overall survival at 1, 2, and 5 years was 45%, 32%, and 20%, respectively with a median survival of 293 days. Multivariate analyses showered that overall survival was better in patients with NPM1-mutated AML ($p = 0.03$), in patients who relapsed late ($p < 0.0001$) and in patients who were able to receive a 2nd allogeneic stem cell transplantation ($p = 0.004$). Overall survival was decreased in patients with AML with unfavorable cytogenetics ($p < 0.0001$), reduced intensity conditioning ($p = 0.03$), or sequential conditioning ($p = 0.008$).

Conclusions: Despite the poor prognosis of hematological malignancies in post-transplant relapse, the use of DLI still represents an effective therapeutic strategy but for a well-targeted population. Proliferative myeloid malignancies require cytoreductive therapy prior to DLI administration. When possible, a second allogeneic stem cell transplant can provide long-lasting disease control.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P280

TREOSULFAN BASED CONDITIONING FOR HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) IN PAEDIATRIC MALIGNANT DISORDERS: ON BEHALF OF THE UK PAEDIATRIC BMT GROUP

Archana Rauthan[1], Robert Wynn[2], Persis Amrolia[1], Geoff Shenton[3], Su Han Lum[3], Ben Carpenter[4], Oana Mirci- Danicar[5], Sanjay Tewari[6], Katharine Patrick[7], Anna-Maria Ewins[8], Salah Ali[9], Rachael Hough[4], Brenda Gibson[8], Beki James[9], Robert Chiesa[1], Giovanna Lucchini[1], Juliana Silva[1], Kanchan Rao[1]

[1]Great Ormond Street Hospital for Children, London, United Kingdom, [2]Royal Manchester Children's Hospital, Manchester, United Kingdom, [3]Great North Children's Hospital, Newcastle, United Kingdom, [4]University College London Hospital, London, United Kingdom, [5]Bristol Royal Hospital for Children, Bristol, United Kingdom, [6]Royal Marsden Hospital, London, United Kingdom, [7]Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom, [8]Royal Hospital for Children, Glasgow, United Kingdom, [9]Leeds Children's Hospital, Leeds, United Kingdom

Background: Treosulfan based conditioning in haematopoietic stem cell transplantation (HSCT) for malignant disorders is an option when myeloablative conditioning is unsuitable due to age or co-morbidities. This retrospective multicentre study reports transplant outcomes in 144 paediatric patients after treosulfan based conditioning for first HSCT in malignant disorders between 2015 and 2021 at 9 UK transplant centres.

Methods: The primary endpoints were overall survival (OS) and transplant-related mortality (TRM). Secondary endpoints were grade II-IV aGvHD, cGvHD and toxicities. Subgroup differences in OS was evaluated by log-rank test. Competing risks methods were used for the cumulative incidence of aGvHD, cGvHD and toxicities, with death as the competing event, subgroup differences were evaluated by Gray's test.

Results: 144 patients (median age of 6.7 years; range = 0.4 to 19 years) were included in the study with a median follow up of 3.4 years (range = 0.2 to 7.4 years). Indications for transplant were ALL (n = 42, 39%), AML (n = 45, 31%), biphenotypic leukaemia (n = 2, 1%), MDS (n = 35, 24%), JMML (n = 12, 8%), Lymphoma (n = 8, 7%). Donors were MFD (n = 35, 24%), MUD (n = 92, 64%), MMFD/MMUD (n = 15, 10%) and haploidentical donor (n = 2, 1%). Stem cell source was bone marrow (n = 87, 60%), PBSC (n = 25, 17%), Cord Blood (n = 30, 21%) and TCR ab/CD19 depleted PBSC (n = 2, 1%). The most common conditioning regimen was Fludarabine-treosulfan-thiotepa in 123 (85%) patients. The remaining 21 patients (15%) received other treosulfan conditioning (2 Treo alone; 9 Flu-Treo; 3 Treo-Thioetapa; 3 Treo-Cy; 6 Treo-Cy). Treosulfan dose was 42g/m^2 in 104 (74%) and 30-36gram/m^2 in 38 (26%). Serotherapy was ATG (n = 45, 31%), Alemtuzumab (n = 50, 35%) and none (n = 49, 34%).

Median days to neutrophil and platelet recovery was 18 (range of 10-41) and 22 days (range of 9-81) respectively. 3 year cumulative incidence (CI) of relapse was 41%. CI of Grade II-IV GVHD was 43% and of Grade III-IV acute GVHD was 13%. CI of chronic GVHD was 7%. CI of VOD and TMA was 4% (2-9%) and 4.2% (2-10%) respectively. 3 year OS was 72% for the entire cohort By indication, OS was 62% in ALL, 67% in AML, 91% in MDS, 85% in JMML and 88% in lymphoma ($p = 0.03$). TRM at 1 year post HSCT was 9%. CI of relapse was 58% in ALL, 62% in AML, 6% in MDS, 30% in JMML and 27% in lymphoma. Out of 25 deaths, 19 were due to relapse and 6 due to TRM.

Conclusions: Treosulfan based conditioning is safe in paediatric malignant disorders with low TRM and VOD rates.

Clinical Trial Registry: N.A

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P281

ONE DAY BUSULFAN FOR REDUCED TBF, IN PATIENTS WITH MYELOFIBROSIS OVER THE AGE OF 50: ENCOURAGING LOW TRANSPLANT RELATED MORTALITY AND CONTROL OF MYELOFIBROSIS

Federica Sorà[1], Sabrina Giammarco[1], Patrizia Chiusolo[2], Elisabetta Metafuni[1], Luca Laurenti[2], Simona Sica[2], Eugenio Galli[1], Idanna Innocenti[1], Alberto Fresa[1], Francesco Autore[1], Maria assunta Limongiello[1], Andrea Bacigalupo[2]

[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [2]Università Cattolica del Sacro Cuore, Rome, Italy

Background: Hematopoietic cell transplantation (HCT) is the only curative therapeutic modality for myelofibrosis also in the era of JAK 1/2 inhibitors, but the transplant related mortality (TRM) is a crucial obstacles for MF patients with myelofibrosis. The second problem is relapse of the original disease, and we have recently reported that the combination of thiotepa, busulfan and fludarabine (TBF) allows for a high rate of complete donor chimerism and less than 15% relapse rate **(Chiusolo et al., AmJ Hematol, 2021)**.

We have analyzed 84 MF patients over the age of 50 receiving thiotepa 10 mg/kg, fludarabine 150 mg/m^2 and busulfan 3.2 mg/kg x2 days (TBF2): the cumulative incidence of TRM at 3 years is 40%. In order to reduce TRM we have explored a reduced version of TBF, with only one day of busulfan (TBF1). GvHD prophylaxis was post transplant cyclophosphamide (PTCY) 50 mg/kgx2, cyclosporin (CSA) and mycophenolate (MMF), for all donor types.

Methods: We are now reporting 16 MF patients allografted with TBF1. The median age was 61 (range 51-71). Driver mutations were as follows : JAK2 (n = 11), CALR1 (n = 2) and MPL (n = 2). One patient was triple negative. Patients were classified as DIPPS Intermediate 2 (n = 40) or DIPSS high (n = 4). The donor was an

HLA identical sibling (n = 4), or an alternative donor (family mismatched or unrelated, n = 12) (75%).

Results: Neutrophil engraftment was seen in 15/16 patients at 24 days from HSCT (range 14-60); platelet engraftment was seen in 14 patients, at 11 days from HSCT (range 1-40). Donor chimerism at first marrow examination was complete in 14/16 patients (87%).

One patient died of infection on day +60, producing a TRM of 1/16 (6%). One patient relapsed and died with disease and cytopenia on day + 185. Two patients had reappearance of their driver mutation (JAK2) on day +83 and +110, with declining donor chimerism ; one was treated with DLI and the other discontinued CSA; both converted to full donor chimerism and JAK2 negativity. At last follow up 14/16 patients are alive, with full donor chimerism and a negative driver mutation, with a median follow up of 467 days (124-1514). The actuarial disease free survival at 2 years 85%.

Conclusions: We are running a prospective trial to confirm these early very encouraging results.

Disclosure: nothing to declare.

1 - Haematopoietic Stem Cells

P282

ROLE OF AUTOLOGOUS AND ALLOGENEIC STEM CELL TRANSPLANTATION IN PATIENTS WITH RELAPSED/ REFRACTORY T-CELL LYMPHOMAS

Jihyun Na[1], Juhyung Kim[1], Hee Jeong Cho[1], Ji Yeon Ham[2], Soon Hee Chang[1], Young Rok Do[3], Ji Woon Yea[4], Joon Ho Moon[1], Sang Kyun Sohn[1], Dong Won Baek[2]

[1]Kyungpook National University Hospital, Daegu, Korea, Republic of, [2]Kyungpook National University Chilgok Hospital, Daegu, Korea, Republic of, [3]Keimyung University Dongsan Hospital, Daegu, Korea, Republic of, [4]Yeungam University Medical Center, Daegu, Korea, Republic of

Background: Peripheral T cell lymphomas (PTCLs) are heterogeneous group which present diverse clinical and molecular characteristics. Patients who experienced relapse after the first-line chemotherapy have shown very poor prognosis. Stem cell transplantation (SCT) after salvage therapy has been known to improve survival outcomes. However, there are still no standard guidelines for choosing high-dose chemotherapy followed by autologous-SCT (auto-SCT) or allogeneic-SCT (allo-SCT) in patients with salvage setting.

Methods: We retrospectively reviewed the data from 209 patients with PTCLs who underwent auto-SCT or allo-SCT as a part of salvage therapy over the past 10 years. Patients between 15 and 70 years were included in this study. Progression-free survival (PFS) was determined from the date of SCT to the date of disease progression or death from any cause. Overall survival (OS) was determined from the date of SCT to the date of death or last follow-up.

Results: A total of 188 patients were analyzed, and the median age at the time of SCT was 47.7 (range, 15-71) years old. Histologic subtypes were PTCL-NOS (n = 74), extranodal NK/T lymphoma (n = 37), angioimmunoblastic T lymphomas (AITL, n = 37), anaplastic large cell lymphoma (ALCL, n = 34), and enteropathy-associated T cell lymphoma (EATL, n = 6). Disease status at the time of SCT was as follows: ≥CR2 in 65 patients (34.6%), ≥PR2 in 17 (9.0%), relapsed/refractory in 106 (56.4%). Overall, 3-year PFS and OS were 48.9%, and 58.6%, respectively. The relapse rate of the patients with allo-SCT was lower than those with auto-SCT, while, a higher one year mortality rate was reported in the allo-SCT group. In patients with CR or PR, auto-SCT reported better PFS (p = 0.027) and OS (p = 0.011) than those with allo-SCT. However, in patients with relapsed/refractory, allo-SCT showed better survival tendency in terms of PFS (p = 0.077) and OS (p = 0.058). Majority causes of poor outcomes in allo-SCT group were treatment related mortality. In patients with allo-SCT, total body irradiation and disease status of CR or PR at the time of SCT were identified as favorable factors in the multivariate analysis.

Conclusions: Auto-SCT as salvage therapy prolonged the survival outcomes in patients with T-cell lymphoma especially those with chemo-sensitive relapse. However, allo-SCT with TBI based conditioning regimen should be considered in patients with relapsed/refractory to salvage chemotherapy.

Clinical Trial Registry: Not applicable

Disclosure: There is nothing to disclose.

1 - Haematopoietic Stem Cells

P283

LOSS OF HETEROZYGOSITY (LOH) IN THE HLA REGION IN PEDIATRIC PATIENTS WITH RELAPSE OF HEMATOLOGICAL MALIGNANCIES AFTER HAPLOIDENTICAL HSCT

Liubov Tsvetkova[1], Aleksey Evdokimov[1], Ildar Barkhatov[1], Olesya Paina[1], Polina Kozhokar[1], Anastasia Frolova[1], Zhemal Rakhmanova[1], Anna Osipova[1], Denis Kozlov[1], Elena Babenko[1], Olga Epifanovskaya[1], Elena Semenova[1], Ivan Moiseev[1], Alexander Kulagin[1], Ludmila Zubarovskaya[1]

[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation, Saint Petersburg, Russian Federation

Background: Loss of heterozygosity (LoH) in HLA region is one of immune surveillance escape mechanisms observed in near 30% of acute leukemia relapses after allo-HSCT in adult patients. This assay may also be important in children in the context of treatment strategy of relapse.

Methods: We retrospectively analyzed 36 children with acute lymphoblastic leukemia (n = 23, 64%), acute myeloid leukemia (n = 13, 36%) relapsed after haploidentical-HSCT – *32 pts (89%) after 1st and 4 pts (11%) after 2nd allo-HSCT*. Median age was 6.8 years (range, 0.5-17.5). Twelve pts (33%) were in CR 1-2 before allo-HSCT, 24 pts (67%) – in relapse. *Myeloablative conditioning regimen was performed in 23 pts (64%). Thirty-four (94%) pts received ptCy-based graft vs host disease (GVHD) prophylaxis*. Short tandem repeated (STR) loci were detected using 6 STR loci assay for the HLA regions: D6S473, D6S291, D6S273, D6S265, D6S105, D6S277. Samples of peripheral blood cells of patients and donors before allo-HSCT and bone marrow of patients at relapse after allo-HSCT were collected. We assessed associations between incidence of LoH HLA and following factors in ALL and AML: patient gender, donor gender, ABO incompatibility, conditioning regimen, CD34+ and CD3+ in graft, number of HLA mismatched loci, acute and chronic GVHD, disease status before allo-HSCT, number of previous lines of therapy, persistence of MRD after allo-HSCT.

Results: All relapsed patients were divided into two groups: with LoH HLA loci and without. We detected 13/36 (36%) relapses with HLA loss: 5 B-ALL, 2 T-ALL, 6 AML. LoH of HLA was detected more frequently after second allo-HSCT (p = 0.012). HLA loss relapses occurred later than non-LoH HLA relapses (median 8 months vs 3 months, p = 0,018). Active disease before allo-HSCT (p = 0.067), higher number of prior treatment lines (median 6 vs 3, p = 0.004), MRD persistence after allo-HSCT (p = 0.053) were associated with LoH in AML. History of clinically significant GVHD

was related with LoH in ALL, p = 0.033. All patients in LoH group progressed after re-induction therapy: 100% vs 70% in non-LoH group, p = 0.12. Immunoadoptive therapy with donor lymphocyte infusion (DLI) was administrated in 7 (54%) and 13 (57%) pts in LoH and in non-LoH group respectively. Incidence of progression in pts treated with DLI was lower in non-LoH group compared with LoH group (54% vs 100%, p = 0.03), median RFS was longer (165 days vs 82 days). At the last follow up only 1/13 patient with LoH remains alive in remission after second haplo-HSCT.

Conclusions: Thirty-six percent of relapses after allo-HSCT were associated with LoH of HLA loci in pediatric population with acute leukemia. *Higher number of treatment lines are risk factors for HLA loss in AML, history of GVHD - for ALL. It is necessary to tested children with relapse after allo-HSCT for LoH HLA. Relapses with LoH HLA are characterized by* resistance to chemo- and DLI, extremely poor prognosis and requires search new options of treatment. Second allo-HSCT from alternative donor may be considered for these patients.

Disclosure: The study was funded by a grant from Russian Science Foundation № 22-15-00491.

1 - Haematopoietic Stem Cells

P284

DISEASE STATUS AT TRANSPLANT IS NOT IMPACTING ON LONG TERM SURVIVAL IN PATIENTS WITH ACUTE MYELOID LEUKEMIA ALIVE AT 2 YEARS: ANALYSIS ON 511 PATIENTS

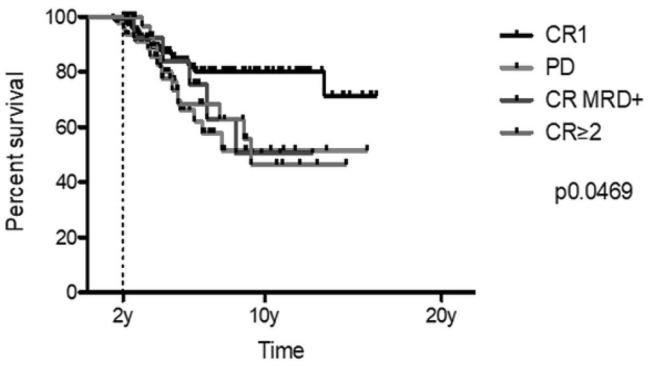
Alessandro Bruno[1], Matteo Giovanni Carrabba[1], Simona Piemontese[1], Raffaella Greco[1], Sarah Marktel[1], Sara Mastaglio[1], Elisabetta Xue[1], Daniela Clerici[1], Francesca Farina[1], Elisa Diral[1], Luca Vago[1], Andrea Assanelli[1], Consuelo Corti[1], Massimo Bernardi[1], Jacopo Peccatori[1], Fabio Ciceri[1,2], Maria Teresa Lupo-Stanghellini[1]

[1]IRCCS Ospedale San Raffaele, Milan, Italy, [2]Università Vita-Salute San Raffaele, Milan, Italy

Background: Acute myeloid leukemia (AML) is the most frequent indication for allogeneic hematopoietic stem cell transplant (allo-HSCT). The number of patients undergoing allo-HSCT for AML has steadily increased in the last decades, with improving outcomes. The risk of disease relapse and treatment related mortality (TRM) decrease over time after transplant. While risk factors for disease relapse and TRM in the first years after allo-HSCT are known, their correlation with long-term survivorship is unclear.

Methods: We retrospectively collected data of 511 consecutive patients (220 females and 291 males) with a diagnosis of AML who received allogeneic hematopoietic stem cell transplant in our center between 2004 and 2019. Forty-six (9%) were second or third transplants. One-hundred patients had a matched related donor, 268 a mismatched related donor (MMRD), 123 an unrelated donor (UD) and 20 underwent allo-HSCT from a cord blood unit. Seventy-two (14%) patients had secondary AML. Patients were included regardless of conditioning intensity and graft-versus-host disease (GvHD) prophylaxis.

Results: Two-hundred and fifty-nine patients (51%) were alive 2 years after allo-HSCT, with a median follow-up of 5.1 years. Twelve patients had an allo-HSCT from CBU, 57 from a matched related donor, 77 from an UD and 113 from a MMRD. 50 patients (19%) alive at 2 years were in active disease at the time of transplant, while 209 (81%) were in complete remission (CR1 or >1, regardless of minimal residual disease (MRD) status). Among the patients alive at 2 years, 182 (70%) were alive at the last follow-up, 23 (9%) were lost at follow-up and 54 (21%) are deceased, 33 due to disease relapse, 20 due to TRM (10 for second cancers) and 1 of unknown cause. Two-hundred and fifty-two patients (49%) died within 2 years from transplant (median death day +140 from transplant). Of these, 148 had an active disease at transplant. 108 patients died because of relapse, 133 because of TRM and 1 of unknown cause. The most relevant causes of TRM were GvHD (40 deaths) and infections (40 deaths). As expected, the 5 year overall survival (OS) is associated with the disease status at the time of the transplant: 62% in CR1 patients, 54% in CR1 MRD+ patients, 39% in CR > 1 patients, 18% in active disease patients. For patients alive at 2 years post allo-HSCT, the probability of being alive at 5 years was 80%: interestingly, we found that the 5-year OS probability was similar regardless of disease status (84% in CR1, 73% in CR1 MRD + , 75% in CR > 1 and 73% in active disease) (Figure 1).



Conclusions: Our study showed that relapse is a relevant cause of death even for long-term survivors, while second malignancies are a frequent cause of NRM in this category of patients. On the contrary, early mortality is mostly caused by relapsing disease, infections and GvHD, as expected. The impact of disease status at transplant seems to be mitigated for patients alive and in CR at 2 years after transplant, fostering the importance of deepen the anti-leukemic effect in the first 24 months after transplant.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P285

THE SARS-COV-2 PANDEMIC DID NOT DISRUPT THE SUPPLY OF HAEMATOPOIETIC STEM CELLS BUT IMPOSED AN UNNECESSARILY HIGH BURDEN ON DONORS: A WMDA REVIEW

Rachel Pawson[1], Chloe Anthias[2], Meghann Cody[3], Mirjam Fechter[4,5], Diane Fournier[6], Elizabeth O'Flaherty[7], Danielli Muniz de Oliveira[8], Eefke van Eerden[5], Thilo Mengling[9,5]

[1]British Bone Marrow Registry, Bristol, United Kingdom, [2]Anthony Nolan Research Institute, London, United Kingdom, [3]National Marrow Donor Program, Minneapolis, United States, [4]Matchis Foundation, Leiden, Netherlands, [5]World Marrow Donor Association (WMDA), Leiden, Netherlands, [6]Hema-Quebec Stem Cell Donor Registry, Montreal, Canada, [7]Royal Melbourne Hospital, Parkville, Australia, [8]Registro Nacional de Doadores Voluntarios de Medula Ossea (REDOME), Rio de Janeiro, Brazil, [9]DKMS German Bone Marrow Donor Center, Tübingen, Germany

Background: The SARS-CoV-2 pandemic has deeply impacted hematopoietic stem cell (HSC) transplantation and the field

responded by adapting its practice. It is vital to monitor the impact of these changes on donations and transplants.

Methods: The World Marrow Donor Association (WMDA) asked that member registries and cord blood banks report SARS-CoV-2-related adverse events to the WMDA Serious Product Events and Adverse Reactions (SPEAR) Committee using an online tool. The Committee reviewed each SPEAR report following EU definitions of a serious adverse event or reaction and determined the imputability of their link to donation or transplantation and the nature of impact on donor or recipient. Reports of SPEARs occurring January 1st-December 31st, 2020, were included in this analysis.

Results: During this period, 32 organisations submitted 474 incident reports. The WMDA Committee considered 74 of these incidents to be related to SARS-CoV-2. Forty-one (55.4%) of these were classified as donor-related, 3 (4.1%) were classified as recipient-related, 31 (41.8%) were classified as technical issues (i.e., unexpectedly low cell dose or viability, or cryopreservation or storage issues), and 4 (5.4%) were classified as transport issues. Among the 41 donor-related incidents, 13 were reports of donors testing positive for SARS-CoV-2 during stem cell mobilisation, including 6 aborted collections and 6 unused donations. Back-up donors were available for 12 patients and 1 donation was used. Six donors tested positive for SARS-CoV-2 in the 30 days after donation, none of which were thought to be hospital-acquired. Twenty-one were reports of unnecessary donor burden when a donated product remained unused and when this situation may have been prevented. Among the 3 recipient-related incidents, all were related to DMSO toxicity, but none were fatal. Among the 31 technical issues, 20 were reports of cells that were not used because of low viability, including 8 where the viable cell dose after cryopreservation was above the minimum typically accepted for transplant. The accuracy of cell viability testing was questionable in 4 of the 20 cases. Among the 4 transport-related issues, 1 was due to lockdown restrictions completely blocking the transport of a donation and 3 were products that remained unused because of prolonged transit times and clotting or thawing. 5 cases fell into 2 categories.

Conclusions: The commonest adverse events reported were of unused cell products. Many of these cases were caused by the uncoupling of the donation and transplant timing, consequent on the cryopreservation of products, and patients were found to be unsuitable for transplant with persistent disease or inadequate fitness once cells were collected. It is vital that transplant centres and registries ensure mechanisms are in place to confirm patient suitability at the time of cell collection. Most reassuringly there was only one event where a patient failed to receive cells due to transport issues and no reports of SARS-CoV-2 transmission to recipients.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P286

TBI-BASED *VERSUS* CHEMOTHERAPY-BASED AMSA/ARA-C CONDITIONING REGIMENS IN PRIMARY REFRACTORY AML – SIGNIFICANTLY WORSE OUTCOMES IN YOUNGER PATIENTS CONDITIONED WITH TBI

Rama Al Hamed[1,2], Myriam Labopin[2], Wolfgang Bethge[3], Arnold Gangser[4], Arne Brecht[5], Johanna Tischer[6], Nicolaus Kröger[7], Donald Bunjes[8], Herman Einsele[9], Mareike Verbeek[10], Igor Wolfgang Blau[11], Martin Kaufmann[12], Eolia Brissot[2], Ali Bazarbachi[13], Christophe Schmid[14], Alexandros Spyridonidis[15], Arnon Nagler[16], Fabio Ciceri[17], Mohamad Mohty[2]

Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, United States, [2]EBMT Paris Study Office / CEREST-TC, Saint Antoine Hospital, INSERM UMR 938, Sorbonne University, Paris, France, [3]Universitaet Tuebingen, Medizinische Klinik, Tuebingen, Germany, [4]Hannover Medical School, Hemostasis, Oncology and Stem Cell Transplantation, Hannover, Germany, [5]Deutsche Klinik fuer Diagnostik KMT Zentrum, Wiesbaden, Germany, [6]Klinikum Grosshadern, Med. Klinik III, Munich, Germany, University Medical Center Hamburg, Hamburg, Germany, [8]Klinik fuer Innere Medzin III, Universitätsklinikum Ulm, Ulm, Germany, [9]Universitaetsklinikum Wuerzburg, Med. Klinik und Poliklinik II, Wuerzburg, Germany, [10]Klinikum Rechts der Isar, III Med Klinik der TU, Munich, Germany, [11]Medizinische Klinik m. S. Hämatologie, Onkologie und Tumorimmunologie, Charité Universitätsmedizin Berlin, Berlin, Germany, [12]Robert-Bosch-Krankenhaus, Abt. Hämatologie / Onkologie, Stuttgart, Germany, [13]Bone Marrow Transplantation Program, American University of Beirut Medical Center, Beirut, Lebanon, [14]Augsburg University, Augsburg, Germany, [15]Hematology Stem Cell Transplant Unit, School of Medicine, University of Patras, Patras, Greece, [16]Hematology and Bone Marrow Transplant Unit, Chaim Sheba Medical Center, Tel Hashomer, Israel, [17]Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Background: Allogeneic stem cell transplantation (allo-SCT)is fundamental in the management of acute myeloid leukemia (AML) and is recommended for patients with relapsed disease or in first complete remission (CR1) with intermediate- and high-risk cytogenetics. The optimal conditioning regimen in preparation for SCT is controversial, specifically, whether total body irradiation (TBI) is a critical component of conditioning or if chemotherapy (CT) regimens alone are appropriate. With improvement in CT delivery and the introduction of IV busulfan, the use of TBI has decreased.

Methods: This is a retrospective, multi-center, registry-based, European Society of Blood and Marrow Transplantation (EBMT) study which compared outcomes of allo-SCT with amsacrine (AMSA)/cytarabine (ARA-C) followed by TBI conditioning to chemotherapy alone. We identified 466 adult patients (58.8% male, median age: 55 years, range: 18-75) with primary refractory AML (73.6% de novo) transplanted between the years 2001 and 2021 (median: 2013) from matched sibling donors (MSD) or matched unrelated donors (MUD: 59.2%), who had received AMSA and ARA-C conditioning in combination with CT or TBI. Karnofsky score at the time of transplant was >90 in 57.8% of the patients. The majority (73.1%) received a combination cyclosporine (CSA) and mycophenolate mofetil (MMF) for graft-versus-host disease (GVHD) prophylaxis and 92.7% underwent in vivo T-cell depletion.

Results: Of the 466 eligible patients identified, 237 (50.8%) received CT-based conditioning with busulfan-fludarabine (BuFlu) or busulfan-cyclophosphamide-fludarabine (BuCyFlu) and 229 received TBI-based conditioning with a total of 4 Gy and cyclophosphamide-fludarabine (CyFlu). There was a significant difference in age between the two conditioning groups whereby patients receiving CT-based conditioning were older (59.9 years *vs* 49.7 years, $p < 0.0001$). Moreover, there was a significant difference in the proportions of MSD/MUD between the two groups with 67.9% being allografted from MUD in the CT group compared to 50.2% in the TBI group ($p = 0.0001$). Given the significant interaction between age and conditioning, we stratified our sample by median age (< 55 *vs* $> = 55$). In patients younger than 55 years, 2-year leukemia-free survival (LFS) was significantly higher in the CT group (51.9% *vs* 25.1%, $p = 0.02$), as was overall survival (OS) (57.5% *vs* 38.3%, $p = 0.021$). CT-based conditioning was also associated with higher rates of grades II-IV and III-IV acute GVHD (38.1% *vs* 24.7%, $p = 0.02$ and 19.8% *vs* 8.9%, $p = 0.022$). In multivariate analysis, the use of TBI- *vs* CT-based conditioning

significantly influenced relapse (hazard ratio [HR] 1.98, p = 0.018), non-relapse mortality (NRM: HR 2.7, p = 0.038), LFS (HR 2.03, p = 0.004), OS (HR 1.86 p = 0.016) and acute GVHD II-IV (HR 0.45, p = 0.014). In patients aged 55 years or older, there was no significant difference in post-allo-SCT outcome between patients who received TBI-based *vs* CT-based conditioning.

Conclusions: The above results highlight significantly worse outcomes in younger AML patients conditioned with AMSA/ARA-C followed by 4Gy TBI and CyFlu, likely related to TBI-associated side effects but also inability to achieve deeper responses with only 4Gy TBI.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P287

MOBILE HEALTH IN THE MANAGEMENT OF ALLOGENIC STEM CELL TRANSPLANT RECIPIENTS (MY-MEDULA STUDY): IMPLEMENTATION PHASES AND PILOT STUDY RESULTS

Sara Redondo[1,2,3], Anna De-Dios[4], Albert Esquirol[1], Olga Aso[5], Merce Triquell[5], M. Estela Moreno-Martinez[6], Mireia Riba[6], Julia Ruiz[7], Iria Gonzalez[5], Jorge Sierra[1], Rodrigo Martino[1], Mar Gomis-Pastor[4], Irene García-Cadenas[1,2,3]

Hospital de la Sant Creu i Sant Pau, Barcelona, Spain, [2]IIB-Sant Pau and José Carreras Leukemia Research Institutes, Barcelona, Spain, [3]Universitat Autónoma de Barcelona, Barcelona, Spain, Hospital de la Sant Creu i Sant Pau, Barcelona, Spain, [5]Hematology Nursing Deparment, Hospital de la Sant Creu i Sant Pau, Barcelona, Spain, Hospital de la Sant Creu i Sant Pau, Barcelona, Spain, Hospital de la Sant Creu i Sant Pau, Barcelona, Spain

Background: Advances in hematopoietic cell transplantation (HCT) have led to an increasing number of transplant survivors. However, post-transplant survival is challenged by several complications and allogeneic HCT survivors need continued lifelong surveillance for screening, early detection and timely treatment of different circumstances such as graft-verus-host disease (GVHD), infections and organ toxicity.

In this line, mobile health (mHealth) has proven to be an effective strategy improving chronic illness care without adding costs. MY-Medula is a new mHealth tool designed to improve the post-HCT recovery process, offering personalized care by an interdisciplinary team.

This study describes the different design phases of MY-Medula platform and the most remarkable results of a pilot study assesing feasibility and usability, as well as the degree of satisfaction and acceptance by patients/caregivers and healthcare professionals.

Methods: Prospective, non-randomized single-center study carried out in a tertiary university hospital by an interdisciplinary team with members from Hematology, Pharmacy, Nursing, Dietetics, and Psycho-oncology departments (Study code: IIBSP-EME-2019-44, approved by the hospital's ethics committee). It included 4 implementation phases: 1) Contextualization and design; 2) Technological development of a web page for healthcare professionals and a mobile phone application for patients; 3) Pre-testing phase; 4) Prospective non-randomized pilot study with 1 month inclusion period and 2 months of follow-up.

MY-Medula has several funcions, including a medication diary, self-monitoring of vital signs, physical exercise, food intake tracker, mood log and adverse effects register. In addition, it includes a bidirectional patient-health professional real time messaging service. Moreover, patients can access a library that contains general information about their condition as well as videos designed by their healthcare team. Early intervention is provided based on the individualized evaluation of patient's records.

Results: The implementation process, that started in the late 2016, consisted of the different phases mentioned above and included multiple patients and healthcare professionals' opinion. Lastly, between October 2021 and January 2022, 28 volunteer allo-HCT recipients were included in the pilot study. Fifty percent (n = 14) were outpatients in the first year post-alloHCT. The remaining 50% were affected by steroid-refractory graft-versus-host disease (Table 1).

All patients used MY-Medula application during the follow-up period, including vital signs registration and messaging, with a median number of visits to the application of 143 (range 6-477). A total of 205 messages were received, the most frequent being those related to the description of symptoms (47%) followed by doubts about medication (21%).

At the end of the pilot study, 27 participants (96.4%) completed a 6-question Likert-type questionnaire, showing a high degree of satisfaction (19/20 points) with the new care pathway.

Table 1. Patient characteristics

Variables	Total HSCT patients, N = 28 (% in parentheses)
Age, median [range]	52 [26-75]
Sex, male	18 (64%)
Underlying disease: Acute Leukemia/ Myelodysplastic syndrome/ Others	14 (50%)/ 3 (11%) / 11 (39%)
Disease status at HCT: Complete response	20 (71%)
Source, Peripheral blood	27 (96%)
Donor Type: Related HLA identical/ Unrelated identical/ Haploidentical/ Unrelated mismatch	12 (43%)/ 10 (36%)/ 5 (17%)/ 1 (4%)
Conditioning regimen: Myeloablative	14 (50%)
CD34+ cells infused (x 10^6/kg), median	6.3
GVHD prophylaxis: Sirolimus-Tacrolimus/ Post-transplant Cyclophosphamide	7 (25%)/ 17 (61%)

Conclusions: The introduction of mobile health as a complementary tool in post-allo-SCT follow-up was complex and required multiple phases, but seems feasible in our setting. The high usability and degree of satisfaction observed in the pilot study have generated sufficient evidence to support the initiation of an ongoing randomized clinical trial.

Disclosure: The study has the collaboration of the pharmaceutical company Amgen S.A. which assumed the cost of the technological development and those derived from the implementation of the tool. Amgen had no influence on the study design, data collection or data analysis.

1 - Haematopoietic Stem Cells

P288

R-IPSS STRATIFICATION AND SURVIVAL AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN MYELODYSPLASTIC SYNDROME

Fernando Duarte[1], Talyta Ellen Jesus Santos Sousa[2], Vaneuza Funke[3], Vergílio Antônio Rensi Colturato[4], Nelson Hamerschlak[5], Neysimelia Villela[6], Maria Cristina Martins de Almeida Macedo[7], Afonso Celso Vigorito[8], Rodolfo Daniel Almeida Soares[9], Alessandra Paz[10], Lilián Diaz[11], Mariana

Stevenazzi[11], Abrahão Elias Hallack Neto[12], Gustavo Bettarello[13], Breno Moreno Gusmão[14], Marco Aurélio Salvino[15], Rodolfo Froes Calixto[16], Maria Cláudia Rodrigues Moreira[17], Gustavo Machado Teixeira[18], Cinthya Corrêa Silva[5], Eduardo José de Alencar Paton[19], Vanderson Rocha[20], Alicia Enrico[21], Carmem Bonfim[22], Ricardo Rabello Chiattone[23], Anderson João Simioni[4], Celso Arrais[24], Erika Oliveira de Miranda Coelho[25]

[1]Hospital Universitário Walter Cantídio, Fortaleza, Brazil, [2]Laboratório Central de Análises Clínicas, Fortaleza, Brazil, [3]Hospital das Clinicas-Universidade Federal do Paraná, Curitiba, Brazil, [4]Hospital Amaral Carvalho, Jau, Brazil, [5]Hospital Israelita Albert Einstein, Sao Paulo, Brazil, [6]Hospital de Câncer Infantojuvenil de Barretos, Barretos, Brazil, [7]Instituto de Controle do Câncer, São Paulo, Brazil, [8]Universidade Estadual de Campinas - UNICAMP / Hemocentro, Campinas, Brazil, [9]Natal Hospital Center, Natal, Brazil, [10]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [11]Integral Medical Service, Montevideo, Uruguay, [12]Hospital Universitario Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil, [13]Unidade de Transplante de Medula Óssea Pletro Albuquerque, Brasília, Brazil, [14]Hospital São José, São Paulo, Brazil, [15]Hospital Universitário Prof. Edgard Santos, Salvador, Brazil, [16]Real Hospital Português de Beneficência em Pernambuco, Recife, Brazil, [17]Instituto Nacional do Câncer, Rio de Janeiro, Brazil, [18]Hospital das Clínicas- Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [19]ONCOBIO Serviço de Saúde S.A., Nova Lima, Brazil, [20]Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [21]Hospital Italiano La Plata, La Plata, Argentina, [22]Hospital Pequeno Príncipe, Curitiba, Brazil, [23]Hospital Samaritano de São Paulo, São Paulo, Brazil, [24]Hospital Sírio Libanês, São Paulo, Brazil, [25]Hospital Santa Joana, Recife, Brazil

Background: Myelodysplastic Syndrome (MDS) is a heterogeneous group of hematologic neoplasms. Diagnosis of MDS may be complex and requires evaluation of morphologic, cytogenetic and molecular features. These elements are fundamental also for defining prognosis stratification and appropriate therapy as Hematopoietic Stem Cell Transplantation (HSCT), which is a single curative therapy and its precise indication is essential to select the best donor, cell source and type of conditioning. Mutations in MDS have become increasingly relevant from diagnosis to follow-up post HSCT, being used for new prognostic stratification approaches; however, it is not available in many HSCT centres, which count only with morphologic and/or cytogenetic tools. In this context, we decided to study the correlation of R-IPSS stratification with overall survival, considering that we do not have molecular analysis as a tool in many places in Latin America. The aim of the study was to evaluate the role of R-IPSS stratification on outcomes of HSCT in MDS patients.

Methods: Data from 341 patients with MDS from the transplant registry of 32 centers in Latin America from 1989 to 2022 analyzed. Statistics were performed using SPSSv.23.1, considering a significant $p < 0.05$.

Results: Mean age was 46,43 years. Most patients were ≤ 50 years (48,97%), about 21,41% were between 50 and 61 and 29,62% were > 60 years. There was a predominance of males (58,36%). Regarding to the Prognosis Scoring System (IPSS-R), patients were classified as: Very low risk (n = 2; 0.59%), Low risk (n = 35; 10,26%), Intermediate (n = 82; 24,05%), high risk (n = 63; 18,48%) and very high risk (n = 19; 5,57% %). A total of 140 (41,06%) patients had no data about R-IPSS stratification due to absence of caryotype. Myeloablative conditioning (MAC) was performed in 250 patients (73,96%). The predominant donor type was related 69,79% followed by non-related (22,58%) and haploidentical (7,62%). In 65,10% (n = 222) of cases, a prior treatment was performed. From these patients, 61,71% used chemotherapy, 27,03% hypomethylating and 11,26% used both. The main cell source was bone marrow (BM) 53,08%. Peripheral blood (PB) was performed in 45,16% of cases and umbilical cord in 1,76%. The frequency of death was 40,47% (n = 138). The 5-years overall survival was 56,2%. High/very high-risk patients had a lower 2-years overall survival when compared to Intermediate and low/very low risk patients ($p = 0,014$). For patients without R-IPSS stratification the 2-years overall survival was 67.50%. When compared with R-IPSS groups there was a significant difference regarding to "Very High risk" patients but similar to other categories ($p = 0,00043$). A multivariate analyses demonstrated the association between High risk category and increase in the risk of death ($p = 0,025$; HR: 1,56; CI: 1,13 - 2,14).

Conclusions: Data demonstrated that R-IPSS stratification influenced the outcomes of HSCT in patients with MDS, particularly the risk of death. Patients underwent HSCT without stratification presented outcomes equivalent to of lower risks groups, raising a discussion about the real need indication of HSCT in these cases. Therefore, use of R-IPSS scores associated with other features as age and comorbidities can improve the management of MDS patients, mainly where molecular analysis is not a reality.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P289

NO EFFECT OF VITAMIN C ADMINISTRATION ON NEUTROPHIL RECOVERY IN AUTOLOGOUS STEM CELL TRANSPLANTATION FOR MYELOMA OR LYMPHOMA: A BLINDED, RANDOMIZED PLACEBO-CONTROLLED TRIAL

Gwendolyn van Gorkom[1], Lara Boerenkamp[1], Birgit Gijsbers[1], Heidi van Ojik[1], Will Wodzig[1], Lotte Wieten[1], Catharina Van Elssen[1], Gerard Bos[1]

[1]Maastricht University Medical Center, Maastricht, Netherlands

Background: Vitamin C is an important micronutrient for various immune cells. It increases phagocytic cell function and is necessary for T and natural killer cell development. During admission for an autologous hematopoietic stem cell transplantation (SCT), patients are often vitamin C-depleted. In this randomized Phase-III study, we investigated the role of vitamin C supplementation on the immune recovery of patients that received high-dose chemotherapy in combination with an autologous SCT to rescue the bone marrow toxic effect of the high-dose treatment.

Methods: This was a single-center, blinded, placebo-controlled trial in which patients were randomized to either vitamin C or placebo, and stratified for disease (myeloma or lymphoma). Administration started intravenously on the first day of the intensive chemotherapy until discharge. After discharge oral vitamin C or placebo was administered twice daily until day 42 of the study. The primary endpoint was the day of repopulation after the autologous SCT. Other endpoints were hospitalization time, incidence of neutropenic fever, bacteremia, 3-month relapse, overall survival, quality of life, serum and intracellular vitamin C levels, and lymphocyte subsets.

Results: In total, 44 patients were included in this study: 21 patients received vitamin C, and 23 patients placebo. Baseline characteristics were similar between the 2 groups. As was expected, the vitamin C concentration in the serum at baseline was similar in the two treatment arms but was significantly higher in the vitamin C group at all other time points (day 8, repopulation and end of study). However, this did not lead to an increase in

intracellular vitamin C. Moreover, the time to neutrophil recovery did not differ between the two groups at 11.2 days ($p = 0.96$). There were also no differences in hospitalization time (19.7 vs. 19.1 days, $p = 0.80$), the incidence of neutropenic fever (57% vs. 78%, $p = 0.20$), or 3-month overall survival (90.5% vs. 100%, $p = 0.13$). However, bacteremia seemed to occur less frequent in the vitamin C group (10% vs. 35%, $p = 0.07$). There was also a difference in lymphocyte subsets at the time of repopulation. Patients in the vitamin C group had significantly higher numbers of cytotoxic T cells. This difference was no longer present at the end of the study period. All other immune cell numbers were comparable between the two treatment groups. Serious adverse events related to the intervention did not occur.

Conclusions: Our study shows no benefit from vitamin C supplementation on neutrophil recovery and hospitalization, despite possible lower rates of bacteremia in the vitamin C group. We therefore do not advice vitamin C supplementation in patients with myeloma or lymphoma treated with autologous SCT. Interestingly, vitamin C supplementation increased T cell proliferation, a finding that suggests vitamin C might be useful in other cellular therapies.

Clinical Trial Registry: Clinicaltrails.gov NCT03964688

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P290

TRAINING IN TRANSPLANTATION AND CELLULAR THERAPY IN LATIN AMERICA: A CROSS-SECTIONAL STUDY OF THE LABMT

Andres Gomez-De Leon[1], Rafaella Ribas-Muratori[2], Marco A. Vargas-Hernández[3], Andres Noyola-Perez[1], Laura Saavedra-Salazar[4], Cristobal Frutos[5], Carmem Bonfim[6], Fernando Barroso-Duarte[7], Sebastian Galeano[8], Gregorio Jaimovich[9,10,11], Amado Karduss[12]

[1]Universidad Autonoma de Nuevo Leon, Monterrey, Mexico, [2]Hospital de Clínicas, Curitiba, Brazil, [3]Universidad Autónoma de Baja California, Mexicali, Mexico, [4]Unidad de Trasplante Dr. Abraham Sumoza, Valencia, Venezuela, [5]Hospital Central. Instituto de Previsión Social, Asunción, Paraguay, [6]Hospital Pequeno Príncipe, Curitiba, Brazil, [7]Hospital Universitario Walter Cantídio UFC, Fortaleza, Brazil, [8]Hospital Británico, Montevideo, Uruguay, [9]Favaloro, University Hospital, Buenos Aires, Argentina, [10]Anchorena Hospital, Buenos Aires, Argentina, [11]ITAC, Buenos Aires, Argentina, [12]Instituto de Cancerología Las Américas, Medellín, Colombia

Background: Access to hematopoietic stem cell transplantation (HSCT) is limited globally. Its availability depends on training and capacity building among other factors. Insights into existing transplant training programs (TP) are needed. The characteristics and curricula of TP among Latin American (LA) transplant centers have not been evaluated.

Methods: A cross-sectional study focused on HSCT training capacity was performed. An online survey based on the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines for training in HSCT was adapted, translated to Spanish and Portuguese, and sent to all LA transplant centers known to LABMT in December 2022. The number of active TP was previously unknown. The primary objective was to determine the number and characteristics of TP currently active in LA and the secondary objectives were to determine barriers for further development in the region and strategies to overcome them according to surveyed TP.

Results: So far, we have received responses from 31 TP in 10 countries in the region (Figure 1), of which 71% are considered formal training experiences. The survey was answered by TP directors in 58.1%, professors in 32.3% and students in 3.2% of cases.

Most TPs are in public, government-funded institutions that train a median of 2 trainees per year (range 1- ≥ 100) with a median duration of 6-12 months; 48.4% of TP offer trainees a salary or stipend and 22.6% charge a fee to trainees for enrollment. In most TP, a relatively small number of HSCT

Table 1. Characteristics Hematopoietic Cell Transplant training programs in Latin America

Variable		N	% (Med)	Variable		N	% (Med)
Institutions	Public	15	48.4	**TC**	Formal	22	71
	Private	7	22.6		Informal	9	9
	Mixed	9	29		Established curriculum	25	80.6
Payors	Government	15	48.4		Learning sessions	27	87.1
	Private insurance	13	41.9		Lab experience	18	58.1
	Mixed	3	9.7		Duration (months)	6-12	(1-24)
Population	Adult	14	45.2		Enrollment cost	7	22.6
	Pediatric	5	16.1		Cost USD (Med)	400	(200-5000)
	Both	12	38.7		Salary	15	48.4
Attendings	1-3	11	35.5		Salary USD (Med)	788.5	(500-2500)
	4-9	17	54.8	**Mobility**	Allowed	24	77.4
	≥10	3	9.7		International	14	45.2
Trainees	Per year	2	(1 to 100)		Funding for mobility	9	29.1
HSCT #*	Autologous	26-50	(1 to ≥100)	**Research**	Basic	4	12.9
	Matched sibling	1-10	(1 to ≥100)		Observational	27	87.1
	Unrelated	1-10	(0 to 26-50)		Trials	17	54.8
	Haploidentical	11-20	(0 to 51-75)		Industry	19	61.3
	Umbilical cord	0	(0 to 10-25)		International trainees	17	54.8

HSCT hematopoietic stem cell transplantation; *TC* training center; mo: months; *Med* median; *USD* United States dollars.
*Refers to the median range of procedures considering all training programs.

procedures are performed yearly, with autologous and mismatched-related donor transplants being the more frequent types (Table 1). Only 1 center performs chimeric antigen receptor T-cell therapy. Most TP include a learning curriculum, and half include laboratory and clinical trial experiences. International mobility programs are available in almost half of the TPs but funded in less than a third (Table 1).

Barriers for development in the region identified by surveyed physicians included lack of funding (48.4%), lack of supprof for TP staff (25.8%), informality or lack of recognition by local authorities and/or regulators and lack of trainee interest (both 9.7%), and lack of mobility and centralization (both 3.2%). Potential solutions included further growth and development of active TP (61.3%), increasing regional and international mobility and connectivity (58.1%), increasing funding (38.7%), official recognition by authorities (19.4%) and trainee financial support (12.9%). The survey will continue accruing responses until February 2023.

Figure 1. Map of Latin America showing the distribution of transplant centers that answered the LABMT HSCT training survey.

Conclusions: Most TP in LA are from government funded, public institutions with relatively low transplant activity and face financial and administrative challenges. Research education is not formally integrated in most TP. Local institutional development, networking and funding advocacy are potential solutions for improving transplant education in LA.

Clinical Trial Registry: No registry was requried.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P291

LONG-TERM OUTCOME ANALYSIS OF ALLOGENEIC STEM CELL TRANSPLANTATION (ALLOHCT) IN PATIENTS WITH LYMPHOMA: RETROSPECTIVE EXPERIENCE FROM SINGAPORE OVER A 15-YEAR PERIOD

Jean Catapia[1], Lip Kun Tan[1], Liang Piu Koh[1], Joanne Lee[1], Yelly.[1], Hui Li Lim[1], Arifah Maziah Bte Moin[1], Gwan Foong[1], Jedidah Lieow[1], Trina S.J. Tan[1], Chay Lee Low[2], Francesca Lim[2], Jeffrey Quek[2], Hein Than[2], Yeow Tee Goh[2], Yeh Ching Linn[2], Aloysius Ho[2], William Hwang[2], Lawrence Ng * Co-last Author (both authors contributed equally)[2], Li Mei Poon * Co-last Author(both authors contributed equally)[1]

[1]National University Hospital Singapore, Singapore, Singapore, [2]Singapore General Hospital, Singapore, Singapore

Background: Allogeneic transplantation (alloHCT) offers a potential curative option for lymphomas that have failed autologous transplant or for high risk lymphomas in the upfront setting. Large studies evaluating contemporary outcomes of alloHCT for lymphoma in the Asian setting remains limited. We performed a retrospective analysis over a 15-yr period, to assess the efficacy and safety of alloHCT for lymphomas in our country and to identify factors affecting post-transplantation outcomes.

Methods: Our study examined the outcomes of 107 patients who underwent alloHCT for both Hodgkin (HL) and non-Hodgkin lymphomas (NHL) over a 15-year period (2007 -2022) at two national cancer centres in Singapore.

Results: 107 patients with a median age of 41 (range 17 – 71 years) were analysed. Diagnoses included Large B cell lymphoma (B-NHL) (N = 27: DLBCL n = 21, PMBCL n = 6), T-NHL (N = 33), NK T cell (NK-T) lymphoma (N = 24), HL (N = 16) and other B-NHLs (N = 7). Eighty-five percent received a reduced intensity conditioning (RIC), and 37% had a prior autoHCT. 19% had transplant done in first remission. Donor types included sibling (N = 45), unrelated donors (N = 34) and alternative donors (N = 28: haplo n = 20, cord n = 7 and mismatched unrelated, n = 1). With a median follow up of 1 year, the 5-yr OS and PFS were 41% and 38% respectively. Non-relapse HCT-related mortality (NRM) was 11% and 21% at day 100 and 1 year respectively, while the cumulative incidence of acute GVHD was 37% with 5 patients having grade IV GVHD. RIC conditioning and disease in complete remission (CR) at the time of alloHCT were associated with improved OS on univariate analysis while RIC was associated with improved PFS. Prior ASCT and donor source did not affect outcomes.

In the subset analyses, outcomes of alloHCT for relapsed/refractory Hodgkin lymphoma appeared best with 5-yr OS and PFS of 62% and 42% respectively, while patients transplanted for T-NHL, Large B-NHL and NK-T had lower survival rates (5-yr OS 50%/29%/29% and PFS 35%/29%/25% respectively). In addition, there also appeared to be a trend towards improved PFS and OS in the transplants performed after 2015 (N = 52) compared to those transplanted in 2010-2015 (N = 38) and before 2010 (N = 17), with 5-yr PFS of 47% vs29% vs 22% respectively (p = 0.12) and 5-yr OS (55% vs 35% vs 35% respectively (p = 0.2).

Conclusions: AlloHCT provides a chance for long term disease control in patients with relapsed/refractory (RR) and high risk lymphomas, with best outcomes seen in patients with HL. There is a trend towards improved outcomes over the last decade. These real world results form a historical benchmark for future studies for high risk and RR lymphomas in Singapore.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P292

THROMBOPOIETIN RECEPTOR AGONISTS IMPROVED PLATELET ENGRAFTMENT AFTER AUTOLOGOUS

354

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

Xiaozhe Li[1], Juan Li[1]

[1]*First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: Multiple myeloma (MM) is a malignant tumor of plasma cells. Autologous stem cell transplant (ASCT) remains the therapy of choice for young patients with newly diagnosed multiple myeloma (NDMM). The high-dose conditioning regimen of ASCT always causes myelosuppression which might lead to thrombocytopenia. Platelet engraftment could be delayed beyond 21 days after ASCT, in as high as 5%–37%, of MM patients. For patients with sustained thrombocytopenia, bleeding increases the mortality and morbidity of ASCT, Hence, it is of clinical significance to explore methods to decrease the incidence of platelet engraftment delay and to accelerate the platelet engraftment.

Thrombopoietin receptor agonists (TPO-RA) (such as eltrombopag or avatrombopag) can bind to TPO-R site to improve the differentiation and proliferation of megakaryocytes and have a possible immune regulatory mechanism to enhance platelet engraftment after ASCT. But the efficacy and safety of the prophylactic use of eltrombopag or avatrombopag for improvement on the platelet recovery post ASCT has not been published before.

Our study aimed to evaluate the efficacy and safety of TPO-RA for platelet reconstitution after ASCT in patients with NDMM.

Methods: We performed a randomized controlled study of eltrombopag or avatrombopag to promote platelet engraftment after ASCT. Participants were randomly assigned at a rate of 1:1:1 with a web- based, electronic system. Eligible patients were randomized to receive either oral eltrombopag (75mg, daily, TPO-RA group), avatrombopag (40 mg, daily, TPO-RA group) or receive nothing (control group) for consecutively 14 days from day 4 after stem cell reinfusion. Eltrombopag or avatrombopag would be discontinued before schedule if platelet counts reached 100×10^9 /L or increased by more than 50×10^9 /L in a single day or severe side effects occurred. Conditioning regimen was high-dose melphalan.

Results: From May 2021 to October 2022, a total of 52 participants underwent randomization. 17,17 and 18 patients were randomized to the eltrombopag, avatrombopag and control groups, respectively. The median platelet engraftment time were the 10th day (range 9th to 22th) in TPO-RA group and 11th day (range 8th to 37th) in control group after the stem cell reinfusion, respectively ($p = 0.024$). There was no significant difference in the platelet engraftment time between the eltrombopag group and the avatrombopag group. The platelet engraftment incidence at the 18th day post-transplant was significantly higher for the TPO-RA group than that for the control group (94.1% vs. 72.2%, $p = 0.029$). The median platelet transfusion need was the same of the 3units in the TPO-RA group and the control group ($p = 0.559$). In the multivariate analysis including TPO-RA administration (Yes vs. No), stem cell source, CD34+ cell count, platelet counts before transplant, ISS staging, and age at diagnosis, TPO-RA administration and platelet counts ≥100*10^9/L before ASCT were the independent facilitating factor for the platelet. All the 34 patients tolerated TPO-RA well and no patient discontinued eltrombopag or avatrombopag because of side effects.

Conclusions: TPO-RA accelerated the platelet engraftment after ASCT in patients with NDMM with good tolerability and safety. TPO-RA might be recommended to be used early after ASCT for patients with NDMM.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P293

PROHYLACTIC DONOR LYMPHOCYTE INFUSION FOR PREVENTION OF RELAPSE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION IN PATIENTS WITH HIGH-RISK ACUTE LEUKEMIA

Maria Liga[1], Dimitrios Tsokanas[1], Eleftheria Sagiadinou[1], Alexandros Gkikas[1], Evangelia Triantafyllou[1], Krisela Valera[1], Anastasia Christopoulou[1], Vassiliki Zacharioudaki[1], Alexandros Spyridonidis[1]

[1]*University Hospital of Patras / BMT Unit, Patras, Greece*

Background: Relapse remains a major cause of failure after allogeneic hematopoietic cell trnaplantation (allo-HCT). Prophylactic donor lymphocyte infusion (pDLI) could be used to reduce relapse, however, its widespread application has been restricted mostly due to concerns regarding the development of Graft versus Host Disease (GvHD). We report on consecutive patients who received a novel method of pDLI based on repetitive administration of a fixed low CD3+ cell dose.

Methods: To ensure availability of DLIs, we routinely isolated and froze small aliquots of DLIs from sufficiently large (> 5x106 cells/kg) peripheral blood stem cell grafts. pDLI administration was planned to commence 2-4 weeks after cessation of the prophylactic cyclosporine or earlier in case of increasing mixed chimerism. Patients were eligible for pDLI if they had high risk cytogenetic acute myeloid disease, acute lymphoblastic leukemia, or other high risk disease, no evidence of relapse, no active infection or other transplantation-related complications requiring therapy, no history of acute GvHD grade III-IV or active GvHD at the time of planned DLI, and provided written informed consent. The dose of pDLI was 0.5-0.8 $\times 10^6$/kg $CD3^+$ cells which was repeated every two months for a total of 6 infusions.

Results: Fifty eight patients with a median age of 41 years (range 17-66) who underwent allo-SCT between August 2005 and November 2022 were included. 34 patients had acute myeloid leukemia, 13 acute lymphoblastic leukemia, 6 myelodysplastic syndrome and 5 other hematological malignancies. Twenty-five patients were transplanted from matched sibling donor (MSD), 32 from volunteer unrelated donor (VUD) and one from haploidentical donor. 40 patients were in first complete remission (CR1), 8 in CR2 or beyond, and 8 had relapsed/refractory disease at the time of transplant. Disease risk index (DRI) was high and intermediate in 20 (34.48%) and 35 (60.34%) patients, respectively. Conditioning was myeloablative (MAC) in 51 and reduced intensity (RIC) in 7 patients, while GvHD prophylaxis consisted of cyclosporine in combination with low-dose alemtuzumab, except 1 patient (haplo-HCT). Details of patient's characteristics are listed in Table 1.

The first pDLI was given at a median of 162 days (range, 78-426 days) after HCT. The median number of infusions was 4 (range, 1-10), and the median cumulative dose given was $2x10^6$ $CD3^+$ cells/kg (range, 0.7-$2.65x10^6$). No patient developed any kind of infusion toxicity. Twelve patients, 12/58 (20.68%) patients developed GvHD (3 MSD, 9 VUD) after a median cumulative $CD3^+$cell dose of $2x10^6$ cells/kg and at a median of 75 days (range, 33-343 days) after the first pDLI and 36 days (range, 11-126 days) after the last pDLI, respectively. Three patients died due to GvHD complications. Sixteen patients (27.5%) relapsed. After a median follow up of 1185 days (range 6 – 4013), 47/58 (81%) are alive.

Table 1. Patient's characteristics

Characteristic	Number (%)
Age	
Median (range)	41 (17-66)
Sex	
Male	30/58
Female	28/58
Diagnosis	
Acute Myeloid Leukemia	34/58
Acute Lymphoblastic Leukemia	13/58
Myelodysplastic Syndrome	6/58
Hodgkin Lymphoma	2/58
Other	3/58
Disease Status at Transplantation	
CR-1	40/58
≥CR-2	8/58
Relapse	3/58
Refractory	5/58
PR	2/58
Disease Risk Index	
Low	2/58
Intermediate	35/58
High	20/58
Very High	1/58
Post DLI GvHD	**12/58**
Mild	2/58
Moderate	4/58
Extensive	6/58
Relapse	16/58
Day, median (range)	397 (70-975)
Overall Survival	47/58
Day, median (range)	1185 (6-4013)

Conclusions: We report the feasibility of pDLI given in a non-escalated low dose after conditioning with alemtuzumab in patients with haematological malignancies.

Clinical Trial Registry: NA

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P294

GAMMA DELTA T CELLS RECONSTITUTION IN LONG-TERM SURVIVORS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Faisal Alagrafi[1,2], Arwen Stikvoort[1], Ahmed Gaballa[1], Lucas Arruda[1], Thomas Poiret[1], Michael Uhlin[1,3]

[1]Karolinska Institutet, Stockholm, Sweden, [2]King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia, [3]Karolinska University Hospital, Stockholm, Sweden

Background: The clinical outcome after allogeneic hematopoietic stem cell transplantation (allo-HSCT) relies principally on the efficient recovery of T lymphocytes. In this regard, gamma delta (γδ) T cells, a subset of T cells, have received increased attention during the past decade as several lines of evidence indicate their favorable role in patient outcome. Nevertheless, unlike conventional T cells, little is known about their reconstitution particularly in long-term survivors.

Methods: In this study, we sought to analyse γδ T cells at phenotypic, clonotypic, and functional level to in-depth characterize their reconstitution several years after HCT using flow cytometry and next-generation sequencing (NGS) of TCR γ-chain (TRG). Samples from 20 recipient/donor pairs that underwent allo-HSCT during (1983-2005) were analyzed.

Results: Results showed that the proportions of total, Vδ2, Vδ1, and $Vδ1^{neg}$ $Vδ1^{neg}$ γδ T cells were comparable between the recipients and their corresponding donors. However, recipients showed higher frequencies of NKG2D + Vδ2 +, CX3CR1 + Vδ2 + T cells, and $CD8^{neg}$ $CD4^{neg}$ Vδ1 + T cells compared to their donors. Immunosequencing of TCR γ chain revealed a remarkable decrease in the TCR repertoire diversity of the recipients. Additionally, there is no difference in TRGV9 usage in donors and recipients and few clonotypes were found to be shared within the donor- recipient pairs.

Conclusions: Our data suggest that long term after HSCT, γδ T cells reconstitute and seems to reach homeostasis. Also, there is a possible association between an increased frequency of CX3CR1 + Vδ2 + T cells in patients with moderate and severe cGVHD. The role of different transplant-related factors on γδ T cell subsets warrants further investigation.

Disclosure:

The authors declare the absence of any conflict of interest. This study was supported by the Stockholm County Council, Swedish Research Council, and Cancerfonden Sweden.

1 - Haematopoietic Stem Cells

P295

SAFETY AND EFFICACY OF ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANT IN INHERITED PLATELET DISORDERS: A SINGLE CENTER EXPERIENCE FROM PAKISTAN

Saima Humayun Toor[1], Nighat Shahbaz Khan[1], Qamar un Nisa Chaudhry[1], Tariq Ghafoor[1], Tariq Azam Khattak[1], Mehreen Ali Khan[1]

[1]Armed Forces Bone Marrow Transplant Center/National Institute of Blood and Marrow Transplant, Rawalpindi, Pakistan

Background: Inherited platelet disorders are heterogenous group of rare diseases with pleiotropic clinical presentation. Allogenic Hematopoietic stem cell transplantation (HSCT) is the only available curative option for most of these disorders with severe disease phenotype.

Methods: To analyze the efficacy and safety of Allogenic HSCT in patients with Inherited Platelet Disorders (IPDs), we conducted an observational, retrospective study at Armed Forces Bone Marrow Transplant Centre/ National Institute of Blood and Marrow Transplant (AFBMTC/NIBMT) Rawalpindi, Pakistan.

From April 2018 till December 2022, a total of 28 patients of IPDs were registered at AFBMTC/NIBMT. Out of these,11 patients underwent allogenic HSCT and were included in the final retrospective analysis. IPDs were divided in two subgroups i.e. Inherited platelets function defects and Inherited thrombocytopenias. Platelet function disorders were confirmed by Platelet aggregation studies and flowcytometry while Inherited thrombocytopenias were diagnosed on basis of clinical history and Bone marrow examination. Median time from diagnosis to HSCT was 730 days. Indication for HSCT was recurrent bleeding episodes, life threatening bleed, strong family history of life-threatening bleed and risk of disease progression in 54.6% (n = 6), 27.4% (n = 3), 9%

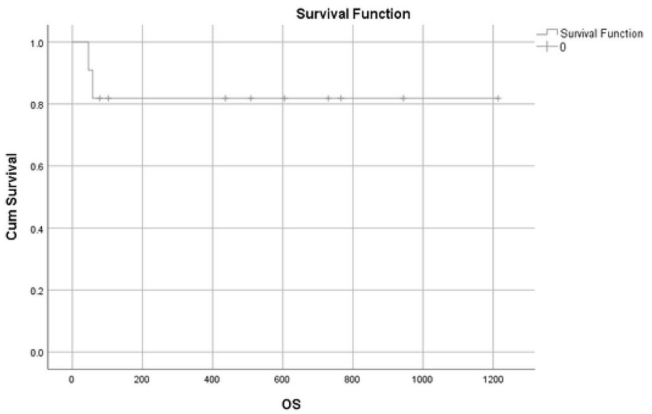
(n = 1) and 9% (n = 1) patient respectively. Patients and HSCT characteristics are shown in Table 1.

Table:1 Patients and HSCT Characteristics

	Inherited platelets function disorders	Inherited thrombocytopenias	All patients
No. Of patients	7 (63.6%)	4 (36.4%)	11 (100%)
Male	5 (71.4%)	2 (50%)	7 (63.6%)
Female	2 (28.6%)	2 (50%)	4 (36.4%)
Age:			
<10yrs	3 (43%)	4 (100%)	
10-20yrs	2 (28.5%)	-	
>20yrs	2 (28.5%)	-	
Diagnosis:			
1-Glanzmann thrombasthenia	5 (71.4%)	-	
2-Bernard-Soulier síndrome	2 (28.6%)	-	
3-Congenital amegakaryocytic thrombocytopenia	-	2 (50%)	
4-X-linked Thrombocytopenia	-	2 (50%)	
HSCT Indication			
Recurrent bleeding episodes	6 (85.7%)	-	6 (54.6%)
Life threatening bleed	1 (14.3%)	2 (50%)	3 (27.3%)
Others		2 (50%)	2 (18.1%)
HSCT Characteristics			
Sex mismatch (female to male)	3 (43%)	2 (50%)	5 (45.5%)
ABO mismatch	2 (28.5%)	2 (50%)	4 (36.4%)
Conditioning intensity			
MAC	7 (100%)	4 (100%)	11 (100%)
RIC	-	-	-
GVHD prophylaxis			
Cyclosporin +MTX + ATG	6 (85.7%)	2 (50%)	8 (72.7%)
Cyclosporin+MTX	1 (14.3%)	2 (50%)	3 (27.3%)
Stem cell source			
BMH	6 (85.7%)	4 (100%)	10 (91%)
BMH + PBSC	1 (14.3%)	-	1 (9%)

Results: Median age of the study cohort was 9 years (range, 1 to 23 years). 63.6% (n = 7) were male and 36.4% (n = 4) were female. Allogenic Bone marrow transplant was done for Inherited Platelet function disorders in 63.6%(n = 7) patients and for Inherited thrombocytopenias in 36.4%(n = 4) patients. All patients received HLA matched related donor HSCT. Stem cell source was Bone marrow harvest (BMH) and BMH plus peripheral blood stem cell (PBSC) in 91% (n = 10) and 9% (n = 1) patients respectively. Myeloablative conditioning i.e. $Bu^{16}Cy^{120\text{-}200}$ was used in all patients. Graft versus host disease (GVHD) prophylaxis was with Antithymocyte globulin (ATG) + Cyclosporin (CSA) + Short course Methotrexate (MTX) in 72.7%(n = 8) patients and with CSA and MTX in 27.3% (n = 3) patients.

All patients achieved successful engraftment with median time to neutrophil and platelet engraftment was day +14 and day +22 respectively. At day +90, low grade stable mixed chimerism was seen in 27. 3% (n = 3) patients, all were from Inherited platelet function disorders group although disease relapse in term of bleeding phenotype was seen in none of them. Platelet function studies or flowcytometry to assess for disease relapse was not done. Incidence of acute GVHD grade I/II and chronic GVHD was seen in 45.5% (n = 5) and 27.2% (n = 3) patients respectively. Extensive chronic GVHD was observed in 9% (n = 1) patient. At a median post-transplant follow-up of 16 months (range, 1.5 to 40) overall survival (OS), Disease free survival (DFS) and GVHD free Relapse free survival (GRFS) was 81.8%, 81.8% and 72.7% respectively.



Conclusions: This retrospective analysis demonstrates that allogenic HSCT is a valid treatment option in IPDs with severe disease phenotype and it carries good overall survival rate and acceptable treatment related toxicities.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P296

AN EFFICIENT AND SIMPLE MULTIPARAMETER FLOW CYTOMETRY PROTOCOL TO DETECT MINIMAL RESIDUAL DISEASE (MRD) FOR ACUTE MYELOID LEUKEMIA (AML)

Ke Li[1], Hui Wang[1]

[1]Hebei Yanda Lu Daopei Hospital, Langfang, China

Background: The European Leukemia Network (ELN) consensus on minimal residual disease (MRD) for AML is a important basis for multi-parameter flow cytometry (MFC) analysis. In this study, the detectable rate of the revised panels based on ELN are discussed.

Methods: Between August 10 and September 15, 2022, 301 patients with AML were detected for MRD in BM by MFC at our Hospital. Samples with more than 0.1% of primitive cells and more than 500,000 acquired cells were selected for this study. A total of 220 patients were enrolled, including 113 males and 107 females. The median age was 32 years (range: 1-73), with a median BM blast proportion of 7.92% (range: 0.1-96.8%). We used a two-tube

parallel detection panel. Panel 1 was for AML M1/M2: 1) CD33 FITC/CD96 PE/CD34 PerCP-cy5.5/CD117 APC/CD13 PE-CY7/HLA-DR APC-CY7/CD11b BV421/CD45 v500, 2) CD7 FITC/CD117 PE/CD34 PerCP-Cy5.5/CD19 PE-Cy7/CD56 APC/HLA-DR APC-Cy7/ CD38 BV421/CD45 V500. Panel 2 was for AML M4/M5 and other unknown or ambiguous subtypes: 1) CD7 FITC/CD117 PE/CD34 PerCP-cy5.5/CD33 APC/CD13 PE-CY7/HLA-DR APC-CY7/CD11b BV421/CD45 v500/CD56 BV605, 2) CD15 FITC/CD64 PE/CD34 PerCP-Cy5.5/CD117 PE-Cy7/CD14 APC/HLA-DR APC-Cy7/ CD38 BV421/CD45 V500. One-hundred patients (45.45%) were enrolled into panel 1, and 120 patients (54.55%) into panel 2. Diva, kaluza and flowjo softwares were used to analyze the data, and merge data were used for the multi-dimensional radar or tSNE photos. latter The following gating methods were used: FSC-A/H was used to set the single cell gate, FSC/SSC was used to set the living cell gate, and the other gates was set synchronously from the single live cells. CD45/SSC was used to set different lineage gates. If the proportion of primitive cells was low, CD34/SSC, CD117/SSC, or CD45dim/HLA-DR/SSChi/CD11b- were used to set the blast or immature cell gates.

Results: There were 105 (47.73%)MRD+ samples, including 52 in panel1 and 53 in panel2. 72 cases (68.57%) could be detected according to the 2021 ELN gate and analysis scheme. The detection efficiency of the ELN method was 71.2% (37/52 cases) in panel 1 and 66.4% (35/53 cases) in panel 2. The contribution of a single marker was listed as follows: Abnormal expression including enhancement or weakness of CD33 accounted for 40.00%, CD13 26.67%, HLA-DR 30.48%, CD38 14.29%, and CD34 21.90%. Aberrant acquired of CD7 was 20.95%, CD56 39.05%, CD11b 7.62%, CD96 40.38%, CD19 13.46%, CD15 16.98%, and CD64 3.77%. Contribution of combinations were, CD34/CD33 48.57%, HLA-DR/CD34 37.14%, CD33/CD13 53.33%, HLA-DR/CD33 58.10%, CD7 and/or CD56 49.52%. Three cases (2.86%) were CD34-, and CD117-/dim. Analyzed by multi-dimensional radar plots, the detectable rate was 84.62%-92.31% for six to eight-dimensional radar plots of panel1, and 88.68%-94.34% of panel2. The detection sensitivity of AML MRD by flowjo tSNE was 95%.

Conclusions: MFC detected AML MRD using Revised gate and analysis panels based on 2021 ELN consensus, we can get higher detectable rate.

Clinical Trial Registry: no

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P297

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR HIGH RISK EWING SARCOMA IN CHILDREN

Eun Sun Song[1], Bo Kyung Kim[1], Kyung Taek Hong[1], Jung Yoon Choi[1], Hyun Jin Park[1], Hyoung Jin Kang[1]

[1]Seoul National University College of Medicine, Seoul, Korea, Republic of

Background: Ewing sarcoma is malignant small round cell tumor arising from bone or soft tissue and the second most common bone tumor in pediatric and adolescent patients after osteosarcoma. The prognosis of high risk Ewing sarcoma is very poor and the relapse rate of that is high. We perform this study to demonstrate the efficacy of high-dose chemotherapy and autologous hematopoietic stem cell rescue in pediatric patients with high risk Ewing sarcoma.

Methods: We retrospectively analyzed 32 pediatric patients with high risk Ewing sarcoma who underwent autologous hematopoietic stem cell transplantation (HSCT). The high-risk Ewing sarcoma was defined as metastasis, axial site, and bulky size. Basically, we intended to perform tandem HSCT since 2014. However, if there were severe side effect, secondary malignancy or patients' refusal after first HSCT, single HSCT was done for these patients.

Results: We report the retrospective results of 32 patients (median age 9.5, range 0.1-16.3) who had high risk Ewing sarcoma and underwent autologous HSCT in Seoul National University Children's Hospital from 2007 to 2021. The patients were 12 female and 20 male. The median flow-up period was 46 (range 4-168) months after diagnosis. There were 23 patients with tumor originated from bone and 9 patients with tumor from soft tissue. The number of chemotherapy before HSCT was median 8 (range 6-13). Twenty four patients (75%) underwent tumor removal surgery before HSCT, of which 8 patients had no residual tumor after surgery. The risk factors that patients had were axial location of tumor in 19 patients (59.4%) and metastasis of tumor in 13 patients (40.6%). Disease status of patients before SCT were 16 complete remission (50.0%), 15 partial remission (46.9%), and 1 stable disease (3.1%). Half of the patients underwent single HSCT and the other underwent tandem HSCT. The engraftment rate was 100%. There were no treatment-related mortality. Nine patients (28.1%) had acute complications after SCT, which were 2 severe VOD, 4 moderate VOD, 1 hemorrhagic cystitis, 1 sensorineural hearing loss, 1 seizure event after conditioning chemotherapy. Five patients (15.6%) had late complications after SCT, including 2 secondary malignancy, 1 transplant-associated thrombotic microangiopathy, 1 pulmonary hypertension, and 1 treatment-related myelodysplastic syndrome. The 4-year event free survival was 56.9% and overall survival rate was 79.2%. The relapse rate was 43.1%.

Conclusions: This study suggests autologous HSCT is an effective treatment in pediatric patients with high risk Ewing sarcoma. Large scale and prospective studies are needed.

Disclosure: I have no personal or financial interests to declare.

1 - Haematopoietic Stem Cells

P298

IMPACT OF 3 DOSES OF ANTI-SARS-COV-2 MRNA VACCINE ON SEROLOGICAL AND CELLULAR RESPONSES AND CLINICAL INFECTION IN RECIPIENTS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Umberto Pizzano[1], Gabriele Facchin[1], Chiara Marcon[1], Martina Fabris[2], Marta Lisa Battista[1], Michela Cerno[1], Antonella Geromin[1], Martina Pucillo[1], Giuseppe Petruzzellis[1], Giampaolo Vianello[1], Giulia Battaglia[1], Roberto Peressutti[3], Lucrezia Grillone[4], Carlo Tascini[1], Francesco Curcio[2], Renato Fanin[1], Francesca Patriarca[1]

[1]Division of Hematology and Stem Cell Transplantation, University Hospital ASUFC, Udine, Italy, [2]Division of Laboratory Medicine, University Hospital ASUFC, Udine, Italy, [3]Regional Transplant Centre, Friuli Venezia-Giulia Region, Udine, Italy, University of Udine, Udine, Italy

Background: Immunosuppressive status linked to GvHD prophylaxis and treatment translates into a reduced response to vaccines In patients undergoing allogeneic stem-cell transplantation (allo-SCT). In our study we compared humoral responses

to anti-SARS-CoV-2 mRNA vaccine and clinical infection according to patients and transplant features; moreover, we evaluated cellular response in patients without seroconversion after two doses.

Methods: We tested antibodies (Ab) titer at 30 and at 90 days after second dose and at 150 days after third dose of mRNA vaccine. The Ab test for SARS-CoV-2 immunoglobulin G (IgG) anti-Spike protein was performed using an automated electrochemiluminescence immunoassay with a reactive (positive) cut-off above 0.79 U/mL anti-Spike IgG. In a patients' subgroup without seroconversion, we tested cell-mediated responses evaluating interferon-gamma release by T-lymphocytes exposed to virus spike protein. Seventy four patients were tested after second dose and 36 patients were evaluated after third dose because of patient refusal or logistic problems (26 cases), or recent SARS-CoV-2 infection (12 cases). No patient was vaccinated prior to allo-SCT and no patient received monoclonal antibodies as prophylaxis during the study period.

Results: Seroconversion rate increased from 66% at 30 days to 81% at 90 days after the second dose; it was 97% 150 days after the third dose. We found a significant association between seroconversion after the second dose and 2 variables: shorter interval between allo-SCT and vaccination ($p = 0.001$); ongoing immunosuppression ($p = 0.004$). There was no association between humoral response and patient age, hematological disease, GvHD prophylaxis, conditioning regimen and GvHD needing treatment. Twelve of 19 patients (63%) without antibodies after the second dose didn't show cellular responses: all these twelve were transplanted within one year. No patient developed infection between second and third dose. Nineteen per cent of patients developed SARS-CoV-2 infection after the third dose, during Omicron variants spread, despite an early seroconversion just after the second dose in the majority of them (83%); the clinical infection showed a favourable outcome in all cases. Patients within 12 months after allo-SCT showed a significantly higher infection risk ($p = 0.004$).

Conclusions: Our study suggests that an interval shorter than 12 months between allo-SCT and first vaccine dose and/or ongoing immunosuppression were associated with humoral and cellular response deficiency after 2 doses. Third dose induced an increased and sustained humoral response in the majority of patients, and we can hypothesize that it offered a good protection against severe forms of the disease, even if a lower virulence of Omicron, and less tropism for the lower respiratory tract in comparison with prior waves had to be taken into account. However, patients within 1 year after allo-SCT remained at higher infection risk and may be candidated for prophylaxis with anti-SARS-CoV-2 monoclonal antibodies.

Disclosure: No disclosures to declare.

1 - Haematopoietic Stem Cells

P299

INCIDENCE AND RISK FACTORS OF GRAFT FAILURE AFTER CORD BLOOD HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH MUCOPOLYSACCHARIDOSIS : A SFGM-TC RETROSPECTIVE MULTICENTER STUDY

Laura Danhardt[1], Arnaud Wiedemann[2], Gerard Michel[3], Fanny Rialland[4], Yves Bertrand[5], Charlotte Jubert[6], Johan Maertens[7], Anne Sirvant[8], Nimrod Bunchbinder[9], Christine Devalck[10], Benedicte Brichard[11], Catherine Paillard[12], Dominique Plantaz[13], Virginie Gandemer[14], Benedicte Bruno[15], Miguel Abboud[16], Simona Pagliuca[17], Nicole Raus[18], Raynier Devillier[19], Jean-Hugues Dalle[20], Benedicte Neven[21], Cécile Pochon[1]

Nancy, France, [2]Pediatric Intensive Care Unit, Nancy, France, La Timone Hospital, Marseille, France, Nantes, France, [5]Institut of Hematology and Pediatric Oncology, HCL, Lyon, France, Children Hospital, Pellegrin Group, Bordeaux, France, Leuven, Belgium, Montpellier, France, [9]Pediatric Immunology and Onco-Hematology, Charles-Nicolle Hospital, Rouen, France, Children Hospital Reine Fabiola, Bruxelles, Belgium, University St-Luc, Bruxelles, Belgium, Hautepierre Hospital, Strasbourg, France, [13]Pediatric Immunology and Onco-Hematology, Grenoble, France, Rennes, France, [15]Unit of Pediatric Onco-Hematology, Jeannes de Flandres Hospital, Lille, France, Beyrouth, Lebanon, Nancy, France, [18]Data Manager of SFGM-TC, Lyon, France, [19]Vice President of SFGM-TC, Marseille, France, Robert Debre Hospital, Paris, France, Necker Hospital, Paris, France

Background: Hematopoietic stem cell transplantation (HSCT) holds a central role in the cure and prevention of neurologic damages in some forms of mucopolysaccharidosis (MPS), due to the capacity of restoring defective enzymatic production. Cord blood (CB) has been shown as an excellent source of stem cells for transplantation in these disorders due to its rapid availability. The use in recent years of reduced-toxicity conditioning (RTC) Busulfan-Fludarabine (Bu-Flu) has reduced the morbidity and mortality of this treatment.

Methods: Here we conducted a retrospective multicenter study, assembling data from a French multicentric cohort on behalf of the Société Française de Greffe de Moelle et Thérapie Cellulaire (SFGM-TC), aiming to compare the incidence and risk factors of graft failure (GF) in patients receiving a HSCT for a MPS with particular attention of differences in CB vs other graft sources (BM/PBSC).

Results: Between 2000 to 2020, we were able to identify 93 patients transplanted for MPS from 13 pediatric centers. Half of them received CB. With a median follow-up of 6 years, one-year overall survival was 90%, with no difference between BM/PBSC and CB groups ($p = 0.65$).

The majority received a myeloablative regimen combining Busulfan and Cyclophosphamide (BuCy) (51%), or Busulfan and Fludarabine (BuFlu) (40%).

We observed a different temporal-defined tendency in terms of the choice of conditioning regimen reflecting known changes in transplant practices, with BuCy preferred before 2010 (87% of the patients) and BuFlu especially administered after 2010 (70%).

No differences between BM/PBSC and CB were seen in incidence of acute and chronic graft-versus-host disease as well as endothelial complications such as veno-occlusive disease.

Overall 19 (21%) patients experienced GF, primary in 84% and secondary in 16%, with similar incidences between CB and BM/PBSC (25% vs 17%, $p = 0.35$). In CB group GF was exclusively primary and thus characterized by a shorter time of occurrence from HSCT as compared to the other group (37 *vs* 70 days, $p = 0.005$).

Through the application of univariable models on the whole cohort, advanced age at diagnosis ($p = 0.006$), high number of HLA mismatches ($p = 0.003$) and lower graft richness ($p = 0.021$) impacted the likelihood of engraftment, while neither graft type, nor the conditioning regimen, emerged as risk factors for GF, even if a trend was shown in favour of BuCy ($p = 0.079$).

Conclusions: HSCT with CB in MPS was not significantly associated with a higher incidence of graft failure, by comparison with BM, even if the incidence was as high as 25%, with a consequent delay of enzyme reconstitution. The use of the most

compatible and richest graft possible, especially in cases of advanced age at diagnosis, would reduce the risk of GF. Monitoring the pharmacokinetics of Busulfan should also be important to improve engraftement. Even if the regimen was not significantly associated with GF, the addition of Thiotepa to the BuFlu conditioning should also be discussed to reduce the high incidence of GF, especially in case of mismatched HLA CB. However, we lack data regarding the use of Treosulfan, and the addition of Thiotepa to Treosulfan (or Busulfan) - Fludarabine regimen in this disease.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P300

RESULTS OF ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN FANCONI ANEMIA: SINGLE-CENTER EXPERIENCE OF 10 YEARS

Alba Peretó[1], Josune Zubicaray[2], Blanca Molina[2], Elena Sebastián[2], June Iriondo[2], Julián Sevilla[2], Mauel Ramirez[2], Ana Castillo[2], Miguel Angel Díaz[2], Marta González[2]

[1]Hospital Clínico Universitario de Valencia, Valencia, Spain, [2]Hospital Infantil Universitario Niño Jesús, Madrid, Spain

Background: Fanconi anemia (FA) is an inherited chromosomal instability syndrome that presents clinically with progressive bone marrow failure (BMF) associated with a variety of congenital anomalies and a high predisposition to malignancies. Allogenic hematopoietic stem cell transplantation (HSCT) is currently the only curative treatment for BMF. Due to the high sensitivity of FA-affected cells to alkylating agents, conventional conditioning regimens and radiation are associated with a high incidence of toxicity. With the evolution of conditioning regimens, graft-versus-host disease (GVHD) prophylaxis, and better donor availability, the outcomes of HSCT in FA have improved in recent years. In this study we report the results of HSCT for FA-associated BMF at a single center.

Methods: We retrospectively analyzed the records of patients with FA who underwent HSCT with reduced-intensity conditioning regimen along with a manipulated graft infusion at the Hospital Infantil Universitario Niño Jesús between 2010 and 2020. We analyzed patients' sex, age at transplantation, number of pretransplant transfusions, incidence of androgen use, extent of congenital malformations, and time from diagnosis to transplantation. Donor type, sex, and age; degree of HLA match between donor and recipient; stem cell source[JI1] ; GVHD prophylaxis; post-transplant complications; chimerism analysis; and mortality were also recorded from the patients' files. We report immune reconstitution for the first time in these patients.

Results: A total of 20 patients underwent HSCT during the study period. Median age at transplantation was 8 years (range 4-13). Regarding the donor source, 9 (45%) were transplanted from matched related donors (MRDs) and 11 (55%) from an alternative donor (AD). The median infused CD34+ cell dose was 7.89 x 10^6/kg (range 0.1 to 16.5). All patients but 1 achieved primary neutrophil engraftment (95%). With a median follow-up of 4 years, overall survival was 100% in the MRD group and 80% in the AD recipients. The cumulative incidence of grades I to IV acute GVHD was 15% and 15% for chronic GVHD. None have developed a second neoplasm.

Of note, these data show that the recovery kinetics follows the patterns also described for patients with other hematological neoplasms transplanted with manipulated peripheral blood. We also highlight the prevalence of cytomegalovirus reactivation, present in 40% of patients. In our series, this has been related to a higher number of CD8+ lymphocytes one year after the transplant (p 0.012).

Conclusions:

- Allogeneic HSCT with reduced-intensity conditioning is a good therapeutic option for hematological manifestations in patients with FA and marrow failure, even when an HLA-identical family donor is not available.
- Immune reconstitution follows the patterns also described for patients with other hematological neoplasms transplanted with manipulated peripheral blood.
- The high prevalence of cytomegalovirus reactivation is related to a higher number of CD8+ lymphocytes one year after the transplant.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P301

HIGH-RISK CYTOKINE PROFILES PREDICT LOWER SURVIVALS IN AML AFTER ALLOTRANSPLANTATION

Pierre Peterlin[1], Joelle Gaschet[2], Maxime Jullien[1], Thierry Guillaume[1], Alice Garnier[1], Amandine Le Bourgeois[1], Michel Cherel[3], Marie-Christine Béné[1], Patrice Chevallier[1]

[1]Nantes University Hospital, Nantes, France, [2]CRCI2NA INSERM U 1307 CNRS 6075 - IRSUN, Nantes, France, [3]INSERM U 1232 - CNRS ERL 6001 - CRCINA Team 13, Nantes, France

Background: In a context of Allo-HSCT for AML, the impact of peripheral cytokine (Ck) levels has been poorly studied so far.

Methods: This prospective study aimed to analyze peripheral levels of 8 Cks in 35 AML patients (pts) before conditioning (BC) at Day (D) 0, 30, 60 and 100 post-Allo-HSCT by comparison to median levels from 20 healthy controls (C) (16 males, median age 48.5 yo). The levels of FLt3-ligand (FL), TNF-alpha, stem-cell factor (SCF), c-kit, IL-1 beta, IL-6, IL-10 and granulocyte-monocyte colony-stimulating factor (GM-CSF) were assessed (ELISA). 1313 and 157 samples were analyzed in pts and C, respectively. The impact of BC, D0, D30 levels and secretion (secretors = pts with detectable Ck levels) on OS, DFS and GRFS was assessed.

Results: At D0, IL-6 ($p = 0.0006$), FL ($p < 0.001$) and SCF ($p = 0.003$) levels were higher in pts than C and for SCF levels on D30 ($p = 0.0009$), D60 ($p = 0.001$) and D100 ($p = 0.01$). Median GM-CSF and c-kit levels were lower in pts at any time ($p < 0.001$). Two-by-two paired Ck comparisons showed no correlation.ELN2017 classification and disease-risk index (DRI) were associated with OS and LFS by univariate analysis (UA), only the former remaining associated with both OS (HR 8.51; 95%CI 1.18-61.54, $p = 0.034$) and LFS (HR 8.10; 95%CI 1.20-54.82, $p = 0.032$) in multivariate analysis (MA). Only SCF, IL-6 and c-kit levels impacted survivals. Higher BC SCF levels were associated with lower OS ($p = 0.02$), LFS ($p = 0.01$) and GRFS ($P < 0.001$) by UA and with lower GRFS (HR 3.19; 95%CI 1.48-6.88, $p = 0.003$) in MA, with a trend for lower LFS (HR 1.96; 95%CI 0.94-4.08, $p = 0.07$). There was an association between the absence of SCF secretion and better OS, LFS and GRFS ($p = 0.02$, $p = 0.02$, $p = 0.03$); c-kit secretion was associated with better OS ($p = 0.03$) in UA an in MA for OS (HR 0.30; 95%CI 0.10-0.92,

p = 0.03). Higher IL-6 levels at D0 were associated with lower OS (p = 0.01) by UA and lower LFS both by UA (p = 0.01) and MA (HR: 2.83; 95%CI: 1.04-7.70, p = 0.04), with a trend for lower OS (HR: 2.55; 95%CI: 0.90-7.29, p = 0.07) in MA. ROC curve analysis identified 7pg/mL as the best cut-off for D0 IL-6 levels which resulted, for pts under this level, in better 4-year OS (80% (62-1) vs 35.7% (18-69), p = 0.02) and LFS (73.3% (54-99) vs 28.6% (13-63) p = 0.01). At D30, higher c-kit and lower SCF levels were associated with better OS (p = 0.003 and p = 0.01) and LFS (p = 0.009 and p = 0.04) by UA while c-kit levels remained associated with LFS (HR: 0.37; 95%CI: 0.17-0.80, p = 0.01) by MA. The absence of SCF secretion was associated with better OS (p = 0.03) and a trend for better LFS (p = 0.07). c-kit secretion was associated with better OS (p = 0.008), LFS (p = 0.01) and a trend for better GRFS (p = 0.07). Only c-kit secretion remained associated with better OS (HR: 0.15; 95%CI: 0.04-0.57, p = 0.005), LFS (HR: 0.19; 95%CI: 0.06-0.62, p = 0.006) and GRFS (HR: 0.40.95%CI: 0.16-1.00, p = 0.05) by MA.

Conclusions: Early higher IL-6 and SCF and lower c-kit levels are associated with lower survivals in AML pts after Allo-HSCT allowing to propose therapeutic intervention by modulating Ck levels.

Clinical Trial Registry: NCT02693899 https://clinicaltrials.gov

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P302

THE ROLE OF AUTOLOGOUS VERSUS ALLOGENEIC STEM CELL TRANSPLANT FOR RELAPSED OR REFRACTORY PERIPHERAL T CELL LYMPHOMA IN SINGAPORE

Natasha Fay Anthony[1], Lawrence Ng[1], Jeffrey Quek[1], Yunxin Chen[1], Chandramouli Nagarajan[1], Francesca Lorraine Lim[1], Colin Diong[1], Yeh Ching Linn[1], Tertius Tuy[1], Melinda Tan[1], William Hwang[1], Yeow Tee Goh[1], Hein Than[1], Aloysius Ho[1]

[1]Singapore General Hospital, Singapore, Singapore

Background: Relapsed or refractory peripheral T-cell lymphomas (PTCL) comprise a rare group of lymphomas with unfavourable outcomes. Transplant has been shown to confer better survival in this setting but it remains unclear whether autologous (ASCT) or allogeneic (alloSCT) is preferable. The purpose of this study was to compare and describe the role of ASCT and alloSCT as salvage therapy for relapsed or refractory PTCL in Singapore.

Methods: This was a single-centre retrospective study of patients with relapse refractory PTCL who underwent their first transplant (either autologous or allogeneic) after 2 or more lines of systemic therapy between 2002 and 2020 from the Haemato-poietic Stem Cell Transplant Registry of Singapore General Hospital. The primary endpoint was PFS with secondary endpoints of OS, relapse risk, non-relapse mortality and transplant-related complications.

Results: The cohort consisted of 32 patients with relapsed or refractory PTCL (PTCL-NOS, AITL, ALCL) of which 20 underwent ASCT and 12 underwent alloSCT. There was no significant difference in recipients baseline characteristics between both groups **[Table 1]**. Patients with more prior lines of chemotherapy (3 or more) were more likely to undergo alloSCT (50% vs 28%). Status of primary induction failure did not appear to affect the decision on transplant type.

The median follow-up of survivors was 41 months in ASCT group and 47 months in alloSCT group. The 24-month PFS was similar between ASCT and alloSCT groups at 40% [95% CI 18-61] and 48% [95% CI 19-72], with median PFS at 7 months and 9 months, respectively. There was a trend of improved 24-month OS in ASCT at 67% [95% CI: 37-85%] versus 42% [95% CI: 14-67%], with median OS 14 months versus 9 months, respectively but this is not statistically significant, p = 0.15. The cumulative incidence of relapse was lower in alloSCT recipients at 8.33% (n = 1) versus ASCT recipients 55% (n = 11), p = 0.008. Non-relapse mortality (NRM) was higher in alloSCT group (n = 6) versus ASCT group (n = 0) from pneumonia (n = 2), neutropenic sepsis (n = 2), GVHD (n = 1) and unclear cause (n = 1). There was no significant difference in survival in patients with primary induction failure who underwent ASCT versus alloSCT.

3 out of 10 ASCT recipients relapsed and went on to receive allogeneic transplant. The patients who received alloSCT following ASCT had a median OS of 117 months compared to those patients who relapsed following ASCT and did not proceed to a second transplant of which 6 out of 7 (85%) died and median OS was 8 months.

Table 1. Patient's characteristics, disease and transplant outcomes

	Autologous (n = 20)	Allogeneic (n = 12)	*P*
Age at HSCT			
Median (range)	46 (21-67)	42 (17-69)	
<60	16	11	
Gender			
Male:Female	14:6	7:5	
Median follow up survivors, months (range)	41 (2-189)	47 (16-60)	
Histology			
PTCL-NOS	10	7	
AITL	6	2	
ALK + ALCL	2	3	
ALK- ALCL	1	0	
Treatment Failure Status			
Primary Induction Failure	10 (59%)	7 (41%)	
Relapse After First Remission	10 (67%)	5 (33%)	
Prior lines of treatment			
2	13 (72%)	5 (28%)	
3 to 4	7 (50%)	7 (50%)	
Disease status at transplant			
CR	13 (62%)	8 (38%)	
PR	7 (62.5%)	4 (36%)	
Conditioning regime			
BEAM / Thiotepa-based	19 / 1		
Myeloablative / Reduced Intensity		4 / 8	
Relapse	11 (55%)	1 (8%)	0.01
Median Time to Relapse (months)	3	5	
Non-Relapse Mortality	0	6	0.005
Death	6	7	
Survival			
24-month OS	67%	42%	
Median OS	14	9	
24-month PFS	40%	48%	
Median PFS	7	9	

Conclusions: Autologous transplant remains a suitable modality for consolidation treatment in relapsed or refractory PTCL in patients with response to salvage chemotherapy, regardless of primary induction failure status. A proportion of patients who relapse following autologous transplant in this setting were able to achieve extended remission from subsequent allogeneic transplant. Although the relapse rates for alloSCT are significantly lower than ASCT, the benefit of the graft versus lymphoma effect is balanced against higher NRM often due to infective complications following transplant.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P303

MYELODYSPLASTIC SYNDROME PATIENT'S JOURNEY TO HEMATOPOIETIC STEM CELL TRANSPLANTATION: SURVEY OF THE LATIN AMERICAN REGISTRY

Fernando Duarte[1], Rodolfo Daniel Almeida Soares[2], Abrahão Elias Hallack Neto[3], Anderson João Simione[4], Vergílio Antônio Rensi Colturato[4], Erika Oliveira Miranda Coelho[5], Vaneuza Araujo Moreira Funke[6], Nelson Hamerschlak[7], Rodolfo Froes Calixto[8], Maria Claudia Rodrigues Moreira[9], Alicia Enrico[10], Marco Aurelio Salvino[11], Eduardo José Alencar Paton[12], Mariana Stevenazzi[13], Neysimelia Costa Villela[14], Carmem Bonfim[15], Gisele Loth[16], Breno Moreno Gusmão[17], Maria Cristina Martins Almeida Macedo[18], Isabella Araujo Duarte[19], Talyta Ellen Jesus Santos[20]

[1]Hospital Universitário Walter Cantídio, Fortaleza, Brazil, [2]Natal Hospital Center, Natal, Brazil, [3]Hospital Universitário- Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil, [4]Hospital Amaral Carvalho, Jau, Brazil, [5]Hospital Santa Joana, Recife, Brazil, [6]Universidade Federal do Paraná, Curitiba, Brazil, [7]Hospital Israelita Albert Einstein, Sao Paulo, Brazil, [8]Real Hospital Português de Beneficência em Pernambuco, Recife, Brazil, [9]Instituto Nacional do Câncer, Rio de Janeiro, Brazil, [10]Hospital Italiano La Plata, La Plata, Argentina, [11]Universidade Federal da Bahia, Salvador, Brazil, [12]ONCOBIO Serviço de Saúde S.A., Nova Lima, Brazil, [13]Servicio Médico Integral-SMI, Montevideo, Uruguay, [14]Hospital de Câncer Infantojuvenil de Barretos, Barretos, Brazil, [15]Hospital Pequeno Príncipe, Curitiba, Brazil, [16]Hospital das Clinicas- Universidade Federal do Paraná, Curitiba, Brazil, [17]Hospital São José, São Paulo, Brazil, [18]Instituto Brasileiro de Controle do Câncer, São Paulo, Brazil, [19]Centro Universitário Christus, Fortaleza, Brazil, [20]Laboratório Central de Análises Clínicas, Fortaleza, Brazil

Background: Myelodysplastic syndromes (MDS) comprises a heterogeneous group of myeloid disorders with diverse genotypes and phenotypes. Hematopoietic Stem Cell Transplantation is the only curative therapy available for MDS patients. Nevertheless important factors related to patient, donor and health service may contraindicate the procedure. The access to HSCT for eldery patients has increased due strategies adopted as incorporation of geriatric scores, reduced intensity conditioning and improvement of post HSCT strategies. In Latin America (LA), lack of epidemiologic and demographic data, limited access to diagnostic and therapeutic tools may difficult the availability of reliable information as the number of patients who are referred to transplant centers with MDS diagnosis and those who manage to do so. The study aimed to understand the journey of patients referred to HSCT centers of LA and identify critical points in the process of driving patients to HSCT.

Methods: A survey was directed to members of the Latin America Registry for Myelodysplastic Syndrome (available at: http://www.tmo.med.br). A questionnaire was applied through Google-Forms tool, from 2 to 13 May 2022 with the questions: how many patients were seen at the pre-transplant service in the last 24 months; how many had a karyotype result; the center used some geriatric score for BMT decision making; age group of patients; IPSS-R stratification, how many patients were attended but contra-indicated to HSCT; how many patients were indicated but could not be transplanted and the causes; what were the comorbidities; how many centers had cases of transfusion dependence and alloimmunization. Data analysis was performed using the Excel program.

Results: A total of 18 centers answered the questionnaire, including adult and pediatric centers. Most centers (38.9%) attended less than 5 patients and only 11.1% had seen more than 20 patients. A total of 27.8% of centers used geriatric scores in the HSCT decision. Data from 162 patients were entered. From the patients attended pre-HSCT, 23 (14.2%) had the transplant contraindicated, with comorbidities and disease refractoriness being the main causes. Regarding risk stratification by the R-IPSS, there was a predominance of high-risk (61.30%) and 25.5% were referred for transplantation without risk stratification. Transfusion dependence was reported by 89.2% of the participating centers, and 22.3% alloimmunized patients. Considering specifically Brazil, where most of centers were from, those who answered (16) were responsible for performing approximately 85% of MDS transplants in the country in 2021.

Conclusions: The results highlight noteworth aspects as the heterogeneous number of patients attended, the difficult in stratify all patients underwent to HSCT, mainly due absence of Karyotype, the number of younger patients (from 31 to 50) years, the reasons for the HSCT be not performed even with indication, especially the number of patients without a compatible donor. Although the limitations of the study, it constitutes a useful tool for comprehend the HSCT frame in LA as it reflects issues like access to not only to HSCT but also to medical service for a diagnosis of MDS, especially in eldery patients and the need for a deeper consideration aiming the quality improvement of the HSCT.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P304

SAFETY AND FEASIBILITY OF RH-GCSF COMBINED WITH LOW-DOSE DECITABINE AS POST ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT MAINTENANCE THERAPY FOR HIGH-RISK MYELOID NEOPLASM

Rami Basmaci[1], Jade Kutzke[1], Gabriel Bartoo[1], Aref Al-Kali[1], Murthy Hemant[2], James Foran[2], Abhishek Mangaonkar[1], William Hogan[1], Mark Litzow[1], Mithun Shah[1], Hassan Alkhateeb[1]

[1]Mayo Clinic, Rochester, United States, [2]Mayo Clinic, Jacksonville, United States

Background: Relapse of myeloid neoplasms accounts for ~40% of treatment failures following allogeneic hematopoietic stem cell transplant (allo-HSCT). Gao et al JCO 2020[1] showed that rhG-CSF combined with low-dose Decitabine as a post-transplant maintenance therapy in adverse risk AML following myeloablative conditioning chemotherapy, can reduce risk of relapse. Herein we describe our experience with the feasibility of this regimen in high-risk MN following allo-HSCT.

Methods: After IRB approval, patients who underwent allo-HSCT and received rhG-CSF+Decitabine regimen were identified. Disease characteristics and treatment outcomes were reviewed for patients

with AML, MDS and MPAL. Risk stratification of AML and MDS utilized ELN 2022 and IPSS-R/IPSS-M, respectively. Overall survival (OS), progression free survival (PFS) and GVHD-free relapse-free survival (GRFS) were estimated using Kaplan Meier method.

Results: A total of 24 patients (13, 54.2% females) were identified in the study with a median follow up of 14.9 months (range: 6.6-24.9 months). (**Table 1**).

Twenty (83.3%) patients had AML, 3 (12.5%) had MDS and 1 (4.2%) had MPAL. Median age at transplant was 65.5 years (IQR: 59.5-68 years). Among AML patients 14 (70%) had adverse risk disease, while all MDS patient had high/very high-risk disease. Seven (29.2%) patients had complex karyotype, 5 (20.8%) had chromosome 7 abnormalities and 5 (20.8%) had chromosome 17 abnormalities. The most seen mutations were *RAS* (5, 20.8%), *ASXL1* (5, 20.8%), *RUNX1* (4, 16.7%), *IDH1/2* (3, 12.5%), and *TP53* (3, 12.5%). Among AML patients most of the patients were in CR1 (15, 75%), while two (10%) had active disease at time of transplant.

Most of the patients received RIC/NMA regimen (18, 75%), which was followed by a matched unrelated donor (15, 62.5%), T-cell replete PBSC graft (22, 91.7%).

The median time from transplant to maintenance therapy was 3.7 months (range: 2.2-9 months) and patients received a median of 4 cycles (IQR: 3-6 cycles). All evaluable AML patients were in CR_{MRD-} prior to maintenance therapy.

Sixteen (66.7%) patients had adverse events (AE) after receiving the maintenance therapy, however only 3 (12.5%) had grade 3-4 AE (catheter infection/febrile neutropenia/thrombocytopenia requiring transfusion). Cytopenias were the most common adverse effects, with anemia being the most frequent (7, 29.2%).

Eleven (45.8%) patients experienced GVHD after maintenance therapy initiation, 4 (16.7%) developed acute GVHD grade III-IV while 7 (29.2%) suffered chronic GVHD requiring systemic steroids.

Median OS and PFS were not reached, while median GRFS was 17.4 months (95% CI 9.57-*NA* months).

Relapse was noted in two (8.3%) patients at 7.8 and 12.6 months from starting maintenance therapy. (**Table 1**) At last follow up both were alive, one achieved CR and underwent a second allo-HSCT while the other remains alive in relapse.

Two (8.3%) deaths were noted; secondary to septic shock in the context of GVHD therapy, both in the absence of relapse.

Table 1: characteristics of the cohort patients compared to relapsed patients.

	All cohort (n = 24)	**Relapsed patients (n = 2)**
Age at transplant; median(IQR)	65.5(59.5-68)	58.5(54.25-62.75)
Sex; n(%)		
female	13(54.2)	2(100)
Diagnosis; n(%)		
AML	20(83.3)	1(50)
MDS	3(12.5)	1(50)
MPAL	1(4.2)	
Karyotype; n(%)		
Complex only	2(8.3)	1(50)
Monosomal only	2(8.3)	0
Complex+monosomal	5(20.8)	1(50)
AML ELN 2022 risk classification; n(%)		
Favorable	1(5)	0
Intermediate	5(25)	0
Adverse	14(70)	1(50)
Secondary AML; n(%)	6(30)	0
MDS risk classification; n(%)		
IPSS-R score		
High	1(33.3)	0
Very high	2(66.7)	1(100)
IPSS-M score		
High	1(33.3)	0
Very high	2(66.7)	1(100)
Disease status at transplant; n(%)[1]		
CR/CRi MRD-	16(66.7)	1(50)
CR/CRi MRD+	3(12.5)	0
Marrow CR	2(8.3)	1(50)
Active disease	3(12.5)	0
AML Disease status at transplant; n(%)		
Active disease	2(10)	0
CR1	15(75)	1(100)
CR2 or more	3(15)	0
Donor type; n(%)[2]		
MUD	15(62.5)	0
MRD	7(29.2)	0
Haploidentical	1(4.2)	1(50)
Mismatched unrelated	1(4.2)	1(50)
Functional evaluation of patient; n(%)		
HCT-CI > 3	5(20.8)	0
KPS < 80	5(20.8)	0
Conditioning type; n(%)		
MAC	6(25)	1(50)
RIC/NMA	18(75)	1(50)
Disease status prior to maintenance initiation; n(%)		
CR MRD-	22(91.7)	1(50)
Marrow CR	2(8.3)	1(50)
Number of cycles of maintenance received ; median(IQR)	4(3-6)	4.5(3.75-5.25)
Patients experienced GVHD after maintenance; n(%)	**11(45.8)**	**0**
aGVHD(III-IV)	4(16.7)	0
cGVHD(requiring systemic steroids)	7(29.2)	0
Adverse effects after maintenance; n(%)	**16(66.7)**	**1(50)**
Anemia	7(29.2)	1(50)
Neutropenia	6(25)	0
Thrombocytopenia	6(25)	1(50)
infection	1(4.2)	0
Grade of adverse events after maintenance; n(%)		
Grade 1-2	13(54.2)	1(50)
Grade 3-4	3(12.5)	0
Time of follow-up after transplant; median(range)	14.9(6.6-24.9)	18.7(17.9-19.5)
Time to relapse from transplant; median(range)	-	16(14.7-17.4)

Conclusions: We demonstrate the encouraging safety and feasibility of rhG-CSF+Decitabine maintenance approach in elderly patients following RIC allo-HSCT for high-risk myeloid neoplasms. The low risk of relapse will need to be confirmed upon longer follow-up.

Disclosure: Nothing to declare.

Table 1: Adjusted and unadjusted odds ratios of the primary and secondary endpoints.

Variable	CKD group	Without CKD group	Unadjusted Odds ratio	P value	Adjusted Odds ratio	P value
All-cause Mortality (%)	9.6	6.4	1.56 95% CI (1.25-1.94)	<0.001	1.31 95% CI (1.01-1.70)	0.04
AKI (%)	49.6	14.7	5.69 95% CI (5.00-6.48)	<0.001	4.85 95% CI (4.19-5.61)	<0.001
Acute Pulmonary Edema (%)	2.8	1.9	3.00 95% CI (2.02-4.46)	<0.001	2.16 95% CI (1.42-3.26)	<0.001
Cardiac Arrhythmias (%)	16.2	7.0	2.57 95% CI (2.15-3.07)	<0.001	1.61 (95% CI 1.33-1.95)	<0.001
Cardiogenic Shock* (%)	1.1	0.2	5.53 95% (2.91-10.5)	<0.001	2.93 95% CI (1.44-5.93)	0.003
Septic Shock (%)	7.0	3.0	2.38 95% CI (1.84-3.08)	<0.001	2.64 95% CI (2.16-3.23)	<0.001
GVHD (%)	13.3	11.1	1.23 95% CI (1.02-1.49)	0.03	1.10 95% CI (0.90-1.34)	0.37
Hemodialysis (%)	1.6	0.4	3.68 95% CI (2.19-6.20)	<0.001	1.67 95% CI (0.97-2.87)	0.07
Mechanical Ventilation (%)	9.8	5.9	1.74 95% CI (1.40-2.17)	<0.001	1.20 (95% 0.93-1.54)	0.17

*: less than 11 total events were reported in the control group. Per HCUP guidelines, the sample size was inadequate to consider significant.

1 - Haematopoietic Stem Cells

P305

EARLY-TO-MODERATE STAGE CHRONIC KIDNEY DISEASE IMPACT ON HOSPITALIZATION OUTCOMES IN ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS: A NATIONWIDE ANALYSIS USING THE NATIONAL INPATIENT SAMPLE DATABASE

Moazzam Shahzad[1,2], Mohammad Ammad-Ud-Din[1,2]

[1]Morsani College of Medicine, University of South Florida, Tampa, United States, [2]H. Lee Moffitt Cancer Center and Research Institute, Tampa, United States

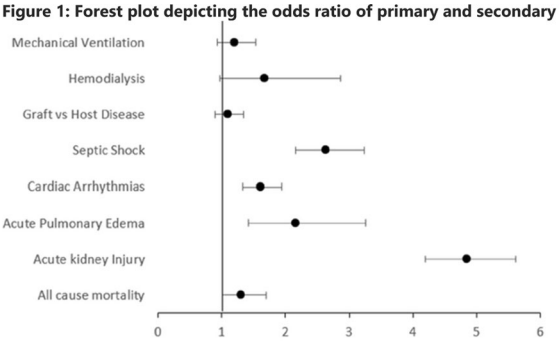
Background: Although patients with severe kidney dysfunction are usually deemed ineligible for allogeneic hematopoietic stem cell transplant (allo-HSCT), there is a paucity of data regarding the risks of adverse hospitalization outcomes among patients with mild to moderate chronic kidney disease (CKD) undergoing allo-HSCT.

Methods: The National Inpatient Sample Database was accessed, and data on hospitalizations for allo-HSCT patients >18 years of age were collected using the International Classification of Diseases 9th and 10th Revision (ICD-9 & ICD-10) codes. All hospitalizations for patients with severe or end-stage CKD were excluded. The data were then sub-classified into patients with mild-to-moderate CKD (CKD group) and patients without CKD (control group). Chi-square and independent student t-tests were performed to compare categorical and continuous variables, respectively. A multivariate logistic regression model was designed to adjust for potential confounding variables, including patient demographics and socio-economic status, admission type, co-morbidities, primary insurance, and hospital characteristics. The primary endpoint was all-cause mortality. Secondary endpoints included common hospitalization complications like acute kidney injury (AKI), acute pulmonary edema, cardiogenic shock, cardiac arrhythmias, graft-versus-host-disease (GVHD), septic shock, and the need for mechanical ventilation and hemodialysis (HD).

Results: The weighted data for 84,626 hospitalizations allo-HSCT was collected. Among these, 920 hospitalizations (1.1%) were for patients with early-to-moderate CKD. The patients with CKD were older, more likely to be male, and black. The prevalence of co-morbidities like coronary artery disease (CAD), chronic obstructive lung disease (COPD), congestive heart disease (CHF), diabetes (DM), hypertension (HTN), and obesity was also significantly higher in the CKD group compared to the control group. Multivariate logistic regression revealed that after adjusting for the potential confounders, patients with CKD had a higher risk of all-cause mortality: odds ratio (OR) = 1.31, 95% CI: 1.01-1.70; p = 0.04. CKD patients also had a statistically higher risk of developing AKI, acute pulmonary edema, cardiac arrhythmias, and septic shock. There was no statistical difference in the GVHD risk and the need for HD or mechanical ventilation. (Table 1 and Figure 1)

Conclusions: The result of our large retrospective study suggests mild-to-moderate CKD is an independent risk factor for adverse hospitalization outcomes, including death in patients undergoing allo-HSCT and should be taken into consideration, especially when making treatment decisions regarding the type and dosing of renal toxic therapies like conditioning chemotherapy and antibiotics to reduce the risk of complications.

Figure 1: Forest plot depicting the odds ratio of primary and secondary endpoints.



Disclosure: "Nothing to declare".

1 - Haematopoietic Stem Cells

P306

PROGNOSTIC IMPACT OF LOW SERUM MAGNESIUM LEVELS IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Emine Merve Savaş[1], Zeynep Arzu Yegin[1], Münevver İrem Kök[1], Hande Tuğba Karayel[1], Zübeyde Nur Özkurt[1], Merve Nazlı Bozer[1], Melike Çamoğlu[1], Özlem Gülbahar[1]

[1]Gazi University, Ankara, Turkey

Background: Magnesium (Mg) is an essential electrolyte which acts as a cofactor in many cellular reactions including the complex immunological network. A close relationship between intracellular Mg levels and cytotoxic T cell activation has been demonstrated. As T cells are responsible for most of the immunological reactions in the posttransplant period, we aimed to investigate the potential impact of serum Mg levels on transplant outcome.

Methods: A total of 340 patients [median age: 45(range 18-71) years; male/female: 210/130] who underwent allogeneic stem cell transplantation (alloHCT) were included in this retrospective study. Patient and transplant characteristics are given in Table 1. Serum Mg levels were recorded on days -28, -7, 0, +7. +14, +21, +30, +60 and +90.

Results: Age ($p = 0.003$), antithymocyte globulin as graft versus host disease (GvHD) propylaxis ($p = 0.002$), fungal infection ($p < 0.001$), acute GvHD ($p = 0.006$), graft rejection ($p = 0.025$) and relapse ($p < 0.001$) were found to have a significant impact on overall survival (OS). Age ($p = 0.011$), acute GVHD ($p = 0.001$) and Mg^{+14} levels ($p = 0.025$) predicted non relaps mortality (NRM) in multivariate analysis. Based on the optimum threshold of Mg^{+14} [1.33; $p = 0.018$; AUC: 0.581(0.515-0.648)], the study group was divided into two subgroups as low- and high-Mg^{+14}. The incidence of acute GVHD ($p = 0.002$), sinusoidal obstruction syndrome (SOS) ($p = 0.013$), engraftment syndrome (0.013), cytomegalovirus (CMV) reactivation ($p = 0.001$) and Epstein Barr virus reactivation ($p = 0.005$) was significantly lower in low-Mg^{+14} group. The probability of OS ($p = 0.002$) (Figure 1) and NRM ($p = 0.001$) was significantly higher in low-Mg^{+14} group. Serum Mg^{+14} levels were found to have a significant impact on the development of mucositis ($p = 0.027$), fungal infection ($p = 0.006$), engraftment syndrome ($p < 0.001$), SOS ($p = 0.001$), CMV reactivation ($p = 0.039$) and acute GvHD ($p < 0.001$).

Conclusions: Low serum Mg after alloHCT seems to provide a significant advantage for posttransplant outcome, NRM and OS via its possible role in the immunological microenvironment. Further studies are required to confirm the prognostic impact of Mg levels in alloHCT recipients.

Table 1: Patient and Transplant Characteristics

Diagnosis [n(%)]		**Pretransplant Disease Status [n(%)]**	
Acute myeloid leukemia	154 (45.3)	Complete remission	231(68.8)
Acute lymphoblastic leukemia	81(23.8)	Partial remission	16(4.8)
Myelodysplastic syndrome	31(9.1)	Stable disease	24(7.1)
Non Hodgkin lymphoma	31 (9.1)	Progressive disease	65(19.3)
Multiple myeloma	23(6.8)		
Others	20 (6.2)		
EBMT Score [n(%)]		**Donor Type** [n(%)]	
Low (0-3)	188(59.7)	MRD	228(67.1)
Intermediate (4)	61(19.3)	MMRD	9 (2.6)
High (> 4)	66(21)	MUD	36 (10.6)
ECOG [n(%)]		MMUD	40 (11.8)
0-1	318 (93.5)	Haploidentical	27 (7.9)
≥2	22 (6.5)		
Conditioning Regimen [n(%)]		**GvHD Prophylaxis I** [n(%)]	
Myeloablative	165(48.5)	CSA-MTX	199(58.5)
Reduced intensity	175(51.5)	CSA-MMF	141(41.5)
CD34$^+$ Cell Count (10^6/kg)		**GvHD Prophylaxis II** [n(%)]	
[median (range)]	4.56 (0.99-7.44)	ATG Based	33(9.7)
		PTCy Based	40(11.8)
SOS [n(%)]	42 (12.3)	**Neutrophil Engrafment** (days) [median (range)]	14 (9-43)
Acute GvHD [n(%)]	124 (36.5)	**Engraftment Syndrome** [n(%)]	30 (8.8)
Relapse [n(%)]	72 (21.2)	**Follow-up** (days) [median (range)]	874(5-4468)

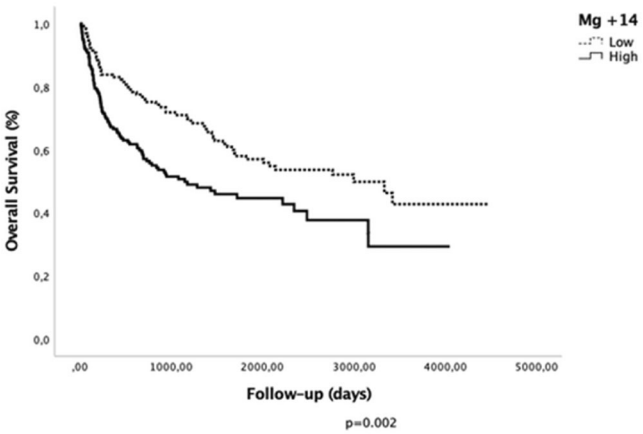


Figure 1: Overall survival is higher in low Mg^{+14} group **($p = 0.02$)**

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P307

5-AZACITIDINE MAINTENANCE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT FOR PATIENTS WITH HIGH RISK AML AND MDS

Bruna Puglisi[1], Francesco Saraceni[1], Selene Guerzoni[1], Ilaria Scortechini[1], Giorgia Mancini[1], Alessandro Fiorentini[1], Antonio Lotito[1], Francesca Romana Colaneri[1], Irene Federici[1], Attilio Olivieri[1]

[1]Institute, Ancona, Italy

Background: Disease relapse remains the main cause of failure of allogeneic hematopoietic stem cell transplant (HSCT) in patients with AML and MDS. Low-dose 5-azacitidine has been evaluated by different groups as a promising approach for maintenance therapy after HSCT, however a recent randomized trial failed to demonstrate an advantage in terms of relapse-free survival.

Methods: In this retrospective single-center analysis, we analyzed 93 patients diagnosed with high risk AML or MDS who received HSCT from 1st January 2016 to 30th June 2022. High risk disease was defined as follows: AML: adverse risk (ELN 2017), induction failure, second remission or beyond, active disease or

detectable MRD at the time of HSCT; MDS: blast count>5% or persistent disease by FISH in patients with -5 or -7 at the time of HSCT. 81 AML and 12 MDS patients were included in the analysis. Median age was 58 years (range 18-70). Donor was matched sibling (18%), matched unrelated (46%), haploidentical (34%), or cord blood (2%). Stem cell source was PBSC in 73% of the patients. Conditioning regimen was myeloablative (MAC) or reduced-intensity (RIC) in 64% and 36% of the patients, respectively. Since 2019 we implemented maintenance with 5-azacitidine as standard policy for all patients with high risk AML or MDS as previously defined. The scheduled treatment provided for 6 monthly courses of 5-azacitidine, at a dose of 35 mg/m^2 per day, for 5 days every 4 weeks. Since December 2020 the dose was increased to 50 mg/m^2, maintaining the dose of 35 mg/m^2 at the first cycle only. Patients were allowed to start maintenance beyond day 40 after HSCT, with confirmed CR, negative MRD and full donor chimerism, absence of active GVHD, absolute neutrophil count >1.0 x 10^9/L and platelet count >20 x 10^9/L.

Results: Maintenance with 5-azacitidine was administered to 15 patients. Median number of cycles were 6 (range 1-9). Median time of start of 5-azacitidine was 94 days since HSCT (range 54-280 days). Treatment was well tolerated; adverse events recorded were neutropenia (grade 4) in 4 patients and thrombocytopenia (grade 4) in 1 patient. Mild gastrointestinal side effects, such as nausea (grade 1), diarrhea (grade 2) or constipation were reported by 6 patients. No infections were observed. One patient developed acute GVHD (grade 3) and 1 patient developed moderate chronic GVHD. Two patients discontinued maintenance due to side effects. One patient relapsed and 3 patients developed MRD relapse during maintenance. Relapse incidence at 2 years was 21% in patients who received 5-azacitidine as compared to 38% in historical controls who did not receive maintenance ($p = 0.15$). Leukemia-free survival at 2 years was 78% and 62%, respectively ($p = 0.2$).

Conclusions: Maintenance with 5-azacitidine after HSCT is feasible and seems well tolerated even at the increased dose of 50 mg/m^2 for 5 days every 28 days. We believe that such schedule deserves further investigation; prospective studies are needed to identify the best strategy to prevent relapse after HSCT in patients with high risk AML and MDS.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P308

SECOND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA: RESULTS OF A TRANSPLANT CENTER WITH A LONG-FOLLOW UP COHORT

Irati Ormazabal Vélez[1], Angela Figuera Alvarez[2]

[1]Hospital Universitario de Navarra / Universidad Autónoma de Madrid, Iruña-Pamplona / Madrid, Spain, [2]Hospital Universitario La Princesa / Universidad Autónoma de Madrid, Madrid, Spain

Background: Disease relapse remains a major cause of post-allo-HCT mortality in acute lymphoblastic leukemia (ALL) patients. The survival of ALL patients who relapse after an allo-HCT is poor, with long-term leukaemia-free survival (LFS) < 10%. Although the optimal management of these patients is not clear, a second allo-HCT (HCT2) might be an option for durable remissions in a subset of patients.

Methods: Adult patients with ALL who underwent HCT2, identified from the Hospital Universitario de la Princesa (Madrid, Spain) database, were included in this retrospective study. Data were extracted from the transplantation database and from individual chart review.

Results: From a cohort of 141 HCT performed in consecutive ALL patients between 1983 and 2020, 14 patients (10%) underwent HCT2. The reason was ALL relapse in all of them. The median age at HCT2 was 29 years (range 16-58). The median time of relapse after HCT1 was 18 months (range 2-205) and the median time from HCT1 to HCT2 was de 26 months (range 6-208). Patients, disease and HCT characteristics are summarised in Table1. Ten patients were retransplanted from the same donor. Donor was changed for HCT2 in 4 patients (28.6%). First donor was UD in 3 of them and the second donor was haploidentical in 1 and a different UD in 2 patients. For the other patient first donor was MSD and the second haploidentical. For HCT2 conditioning intensity was reduced, being the most employed regimen FluMel140 (n = 9, 64.3%). Half of HCT2 GVHD prophylaxis regimens consisted in CSA alone.

Six patients developed acute GVHD grade 2 and only 1 grade 3-4. Out of 10 patients evaluable, 6 patients developed cGVHD, 3 of them classified as severe.

Death causes were relapse (n = 6, 43%), Sinusoidal obstructive syndrome (n = 3, 21.4%), infection (n = 1, 7%) and pulmonary toxicity (n = 1, 7%). Early mortality (< 100 days) occurred in six patients (43%), only in one of them because of relapse. Five of seven patients who had relapsed after HCT2 lived between 6 and 18 months.

With a median follow up of 14.5 months (range 0.2-207) the 1- and 3- year PFS and OS were 35.7% and 21.4%, and 50 and 28.6%, respectively. Three patients remain alive and in CR after >5 years after HCT2. All of them have developed severe chronic GVHD though they are free of systemic immunosuppressive treatment at last follow up. Their Karnofsky score is reported as 70, 80 and 100%.

Patients and disease characteristics	N (%)	HCT Characteristics	HCT1 N (%) HCT2 N (%)
Age		**HCT period**	
<40 years	8 (57%)	<2000	5 (35.7%) 3 (21.4%)
≥40 years	6 (43%)	2000-2009	6 (43%) 6 (43%)
		≥2010	3 (21.4%) 5 (35.7%)
Sex		**Donor**	
Female	7 (50%)	MSD	11 (78.6%) 10 (71.4%)
Male	7 (50%)	UD	3 (21.4%) 2 (14.3%)
		Haplo	0 (0%) 2 (14.3%)
Clinic presentation		**Graft source**	
CNS involvement	1 (7%)	Bone marrow	11 (78.6%) 3 (21.4%)
Extramedullary involvement	7 (50%)	Peripheral blood	3 (21.4%) 11 (78.6%)
Hyperleucocytosis	3 (21.4%)		
Diagnosis		**Conditioning regimen**	
B-ALL, Ph negative	9 (64.3%)	CyTBI	11 (78.6%) 0 (0%)
B-ALL Ph positive	1 (7.1%)	CyBu	3 (21.4%) 2 (14.3%)
T-ALL	4 (28.6%)	FluBu	0 (0%) 1 (7.1%)

Patients and disease characteristics	N (%)	HCT Characteristics	HCT1 N (%) HCT2 N (%)
		Other	0 (0%) 11 /78.6%)
Disease status at HCT2		**Conditioning intensity**	
≥2nd complete remission (CR2)	8 (57%)	MAC	14 (100%) 3 (21.4%)
Advanced disease (AD)	6 (43%)	RIC	0 (0%) 11 (78.6%)
MRD at HCT2		**GVHD prophylaxis**	
Positive	2 (14.3%)	CSA	2 (14.3%) 7 (50%)
Negative	2 (14.3%)	CSA + MTX	12 (85.7%) 2 (14.3%)
Unknown/not applicable (AD)	4/6 (71.4%)	CSA + MMF +Cy post	0 (0%) 2 (14.3%)
		Other	0 (0%) 1 (7.1%)
High risk genetics (Ph, MLL, etc.)		**HCT1 vs. HCT2 donor**	
No	6 (43%)	Same	10 (71.4%)
Yes	8 (57%)	Different	4 (28.6%)

Conclusions: Our cohort was consistent with HCT2 being a reasonable option for selected high risk patients as they can achieve durable remissions maintaining adequate performance status. Three of 14 patients (21%) are alive and in CR, with important sequelae. The high incidence of severe chronic GVHD associated to this procedure requires experienced and multidisciplinary approach to minimize impact in patients' quality of life.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P309

NO EVIDENCE FOR IMPROVED OVERALL SURVIVAL OR PROGRESSION-FREE SURVIVAL IN MULTIPLE MYELOMA PATIENTS AGED 70-75 UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION COMPARED TO A NON-TRANSPLANT STRATEGY

Eloísa Riva[1], Efsthathios Kastritis[2], Luuk Gras[3], Linda Koster[4], Denis Caillot[5], Alessandra Tucci[6], Francesco Lanza[7], Maurizio Musso[8], Anne Sirvent[9], Arpad Illes[10], Ron Ram[11], Francesca Bonifazi[12], Jean Henri Bourhis[13], Tsila Zuckerman[14], Shohei Mizuno[15], Maria Roussou[2], Meletios A. Dimopoulos[2], Hira S. Mian[16], Yoshiko Atsuta[17], John Snowden[18], Anna Sureda[19], Mahmoud Aljurf[20], Liesbeth C. de Wreede[21], Patrick J. Hayden[22], Donal McLornan[23], Dietger Niederwieser[24], Laurent Garderet[25]

[1]Hospital de Clinicas, Montevideo, Uruguay, [2]National and Kapodistrian University, Athens, Greece, [3]EBMT Statistical Unit, Leiden, Netherlands, [4]EBMT Leiden Study Unit, Leiden, Netherlands, [5]Hopital d'Enfants, CHU de Dijon, Dijon, France, [6]Spedali Civili, Brescia, Italy, [7]Unità Operativa di Ematologia, Ravenna, Italy, [8]Ospedale La Maddalena, Palermo, Italy, [9]CHU Lapeyronie, Montpellier, France, [10]University of Debrecen Clinical Center, Debrecen, Hungary, [11]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [12]Bologna University, S.Orsola-Malpighi Hospital, Bologna, Italy, [13]Gustave Roussy Cancer Campus, Villejuif, France, [14]Rambam Medical Center, Haifa, Israel, [15]Aichi Medical University School of Medicine, Nagakute, Japan, [16]McMaster University, Hamilton, Canada, [17]Japanese Data Center for Hematopoietic Cell Transplantation, Nagakute, Japan, [18]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, [19]Institut Català d'Oncologia-Hospitalet, Barcelona, Spain, [20]Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [21]Leiden University Medical Center, Leiden, Netherlands, [22]Trinity College Dublin, St. James's Hospital, Dublin, Ireland, [23]University College London Hospitals NHS Trust, London, United Kingdom, [24]University of Leipzig, Leipzig, Germany, [25]Hôpital Pitié Salpêtrière, Paris, France

Background: Randomized clinical trials have demonstrated autologous stem cell transplant (ASCT) increases response rate and survival up to 65 years in newly-diagnosed multiple myeloma (NDMM) patients, but data in patients older than 70 years are limited.

This collaborative project aimed to compare the results of transplant vs non-transplant strategies in MM patients aged 70-75 years, diagnosed between 2013-2020.

Methods: We selected patients from a prospectively maintained database from Kapodistrian University Hospital, Athens, Greece (non-transplant approach being a local policy in > 70 years), and patients from Mediterranean countries other than Greece undergoing a first ASCT, from the EBMT database. Inclusion criteria were MM diagnosed between 2013-2020, 70-75 years, alive and relapse-free at 6 months from diagnosis, Karnofsky score >60, and ≥ partial response (PR) at 6 months or at the time of ASCT. Tandem transplants were excluded.

Endpoints were overall survival (OS), non-relapse mortality (NRM), relapse incidence (RI), and progression-free survival (PFS). Baseline was 6 months from diagnosis. EBMT patients undergoing an ASCT after 6 months entered the risk set from the time of ASCT using left-truncated Cox proportional (cause specific) hazard models including disease stage and Karnofsky score at 6 months /ASCT, ISS and age at diagnosis, year of diagnosis, sex, MM classification, and abnormal cytogenetics (defined by the presence of at least one of the following: del17p, t (4; 14), and t (14; 16)).

Results: 113 patients from the non-transplant cohort, and 597 from the transplant cohort were included. The median age was 73.5 (IQR 71.5-74.5) years for the non-transplant cohort and 71.2 (70.6-72.2) for the transplant cohort. ISS 3 was reported in 42.5% and 28.0%, abnormal cytogenetics in 17.5% and 25.5%, and response rate ≥VGPR in 48.7% and 70.9 for non-transplanted and transplanted patients, respectively. The median time to ASCT was 7.1 months. Melphalan dose was 200 mg/m^2 in 35.4%, 140 mg/m^2 in 50.3%.

In univariable analyses OS and NRM did not significantly differ between the two cohorts whilst the transplant cohort had better PFS and RI.

In MVA the HR comparing transplant vs. non-transplant cohort was 1.20 (95% CI 0.66-2.16, $p = 0.55$) The difference in PFS between the two cohorts was not significant after including ISS at diagnosis in the model (HR transplant vs. non-transplant 0.71, 95% CI 0.47-1.07, $p = 0.11$). OS was worse for patients at PR at 6 months, compared to those in CR/VGPR (HR 1.95 95% CI 1.22-3.13; $p = 0.0005$), and for males (HR compared to females 2.07 95% CI 1.23-3.49; $p = 0.006$). Age was strongly associated to OS (HR per year older 1.19, 95% CI 1.02-1.38, $p = 0.03$). CR/VGPR response at 6 months or ASCT compared to PR was associated with superior PFS (HR 1.41, 95% CI 1.06-1.88, $p = 0.02$) and risk of relapse (HR 1.83, 95% CI 1.23-2.72); $p = 0.003$).

Conclusions: We did not find evidence for a benefit in OS and PFS because of ASCT in patients with NDMM between 70 – 75 years. Studying the impact of transplanting vs. not transplanting using different observational cohorts is difficult because of cohort-

specific differences which cannot always be accounted for in statistical analyses.

Disclosure: None.

1 - Haematopoietic Stem Cells

P310

THE EFFECTIVENESS OF A PREHABILITATION PHYSIOTHERAPY SERVICE FOR PATIENTS UNDERGOING HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) AND CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY (CAR-T)

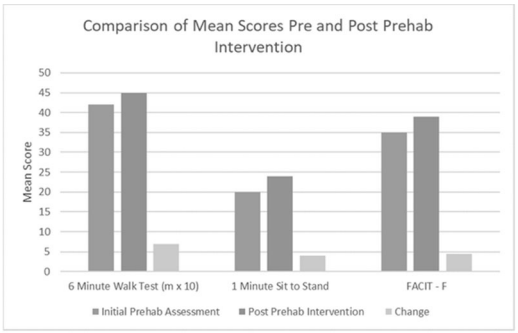
Evelyn Evans[1], Bronagh McGoldrick[1]

[1]Cardiff and Vale University Health Board, Cardiff, United Kingdom

Background: Prehabilitation (prehab) has been shown in cancer to improve cardiovascular fitness, maximise resilience to treatments and enhance patients' quality of life[6]. Physical activity can help reduce the risk of cancer recurrence and increase survival rates[1]. There is currently limited research into the benefits of prehab in HSCT/CAR-T patients. As part of a wider service at Cardiff and Vale University Health Board, we implemented a prehab pathway, hypothesising that prehab would improve cellular therapy patient outcomes. This abstract focuses on the physiotherapy outcomes of those who have undergone prehab and proceeded to cellular therapy to analyse its effectiveness.

Methods: Patients who were referred for HSCT/CART between April and December 2022 and attended prehab in this time were included in this study. On the initial prehab assessment the following outcome measures were collected; Clinical Frailty Score (CFS), Godin's Leisure Time Activity Questionnaire (Godin's), FACIT-F, EQ-5D-5L, 1-minute sit to stand (1MSTS), 6-minute walk test and the Short Physical Performance Battery. Selected outcome measures were used to record patients' pre-symptomatic illness baseline to compare to their presentation prior to commencing prehab. Post assessment, individualised treatment plans were set with the patient. They were followed up, in person or virtually, and reviewed on average 3 times over an 8-week period. Length of time for prehab varied from 1-25 weeks. All outcome measures were retested on admission for cellular therapy and results analysed.

Results: A total of 43 patients were included in the study, including 18 females and 25 males, aged from 26 to 73 years. The majority of patients (79%) had an increase in CFS from pre-illness to their initial prehab assessment, highlighting increased frailty in this patient group. 41/43 patients had a decline in physical activity from their pre-illness baseline to their prehab initial assessment. Prior to prehab patients were mostly classed as 'insufficiently active' and not meeting the WHO exercise guidelines for those living with chronic conditions[2]. Post prehab the results showed that patients' activity greatly increased (396%) with patients mostly meeting the 'active' criteria. Over half of patients (56%) improved on their 6-minute walk test with an overall mean increase of 69m. The minimal important difference (MID) for cancer patients is an improvement of 42m[3]. In the 1MSTS test, 59% of patients saw an increase in the number of repetitions. The mean increase in number of sit to stands completed increased by 4, MID was reported to be 2-3 in a study of COPD patients[4], suggesting patients lower limb muscle endurance increased. Our data collection showed the mean FACIT-F score increased by 26% with a mean score change of +4, indicating decreased fatigue levels with the completion of prehab. Previous studies have shown the MID for cancer patients is 3-5 points, indicating these scores could have a clinical significance[5].



	Age	CFS Pre-Illness	CFS Inital Prehab Assessment	Change in CFS	Godin's Pre-Illness	Godin's Prehab Inital Assessment	Godin's Post Prehab
Mean Score	57	2	3.5	-1.5	41	15	24
Mode Score	63	3	3	-1	41	6	21

Conclusions: Physiotherapy delivered through the prehab service is effective in increasing patient's fitness and has a positive impact on fatigue levels. Future data collection is planned in order to determine whether this improved fitness is associated with better long-term outcomes for these patients.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P311

LOW DOSE ALEMTUZUMAB FOR GRAFT VERSUS HOST DISEASE PROPHYLAXIS IN MATCHED SIBLING DONOR HEMATOPOIETIC CELL TRANSPLANTATION

Maria Liga[1], Dimitrios Tsokanas[1], Elefteria Sagiadinou[1], Evangelia Triantafyllou[1], Krisela Valera[1], Anastasia Christopoulou[1], Vassiliki Zacharioudaki[1], Alexandros Spyridonidis[1]

[1]University Hospital of Patras / BMT Unit, Patras, Greece

Background: Though a randomized study suggested the benefit of in vivo T-cell depletion (TCD) as Graft versus Host Disease (GvHD) prophylaxis in matched sibling donor (MSD) allogeneic hematopoietic cell transplantation (allo-HCT), its use remains controversial. Here we report our single center experience of the use of alemtuzumab in MSD.

Methods: We report on 84 consecutive patients who underwent MSD allo-HCT from October 2005 to November 2022 in our centre. Uniform GvHD prophylaxis was given that included in vivo TCD with alemtuzumab and cyclosporine post-transplant. As part of a de-escalation study, 2 patients received a total of 30 mg alemtuzumab, 9 patients 20 mg, 2 patients 15 mg and 71 patients received 10mg of alemtuzumab (5mg at day (d)-2 and d-1). The conditioning regimen and the details of patient's characteristics are shown in Table 1.

Results: From the total 84 patients, 40 had Acute Myeloid Leukemia, 20 Acute Lymphoplastic Leukemia, 7 Myelodysplastic Syndrome, 3 Chronic Myeloid Leukemia, 3 Non Hodgkin Lymphoma and 11 other diagnosis. Median age at transplantation was 41 years (range, 17-70), 49 were male and 35 were female patients. The stem cell source was granulocyte colony-stimulating mobilized peripheral blood stem cells in 82 patients and bone marrow in 2 patients. Two patients died before engraftment.

	Age	CFS Pre-Illness	CFS Inital Prehab Assessment	Change in CFS	Godin's Pre-Illness	Godin's Prehab Inital Assessment	Godin's Post Prehab
Mean Score	57	2	3.5	-1.5	41	15	24
Mode Score	63	3	3	-1	41	6	21

Eleven out of 82 (13.4%) evaluable patients developed acute GvHD grade 2-4 in a median of 35 days after allo-HCT (range, 25-91 days), while 6 patients (7.3%) developed acute GvHD-grade 3-4 after 32 days of allo-HCT (range, 25-51 days). Chronic GvHD developed 16 out of 77 (20.77%) evaluable patients in a median of 188 days (range, 108-785 days). Forty patients died. GvHD was the cause of death in two patients. Causes of death was relapse in 22 patients and non relapse mortality in 18 patients. 28 patients (33.3%) relapsed in a median of 225 days (range 27-975). With a median follow up of 598 days (range 3-4167 days), 52.3 % of patients are alive.

Table 1. Details of patient's characteristics

Characteristic	Number (%)
Age	
Median (range)	41 (17-70)
Sex	
Male	49/84 (58.34%)
Female	35/84 (41.67%)
Diagnosis	
Acute Myeloid Leukemia	40/84 (47.62%)
Acute Lymphoblastic Leukemia	20/84 (23.81%)
Myelodysplastic Syndrome	7/84 (8.33%)
CML	3/84 (3.57%)
NHL	3/84 (3.57%)
Other	11/84 (13%)
Disease Status at Transplantation	
CR-1	55/84 (65.48%)
≥CR-2	12/84 (14.29%)
PR	4/84 (4.76%)
Relapse / Refractory	10/84 (11.9%)
Conditioning Regimen	
BCNU/TT/Flu	10/84 (11.9%)
TBI/VP16/Cy	12/84 (14.28%)
Bu/Flu/TT	27/84 (32.1%)
Bu/Cy	13/84 (15.47%)
Other	22 (26.19%)
Engraftment (patients)	
WBC ≥ $1000x10^9$/L, day median (range)	14 (10-45)
PLT ≥ $20x10^9$/L, day median (range)	12 (6-20)
PLT ≥ $50x10^9$/L, day median (range)	13 (9-134)
Acute GvHD	17/82 (20.7%)
gr II-IV	11/82
gr III-IV	6/82
Chronic GvHD	16/77 (20.77%)
Limited	10/77
Extensive	6/77
Relapse	28/84
Day, median (range)	225 (27-975)
Transplant Related Mortality	18/84 (21.4%)
Day, median (range)	143 (18-947)
Overall Survival	44/84 (52.3%)
Day, median (range)	598 (3-4167)

Conclusions: We report results of in vivo T cell depletion with low dose alemtuzumab in MSD allo-HCT,

Clinical Trial Registry: NA

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P312

COMPARABLE OUTCOMES OF ALLOGENEIC PERIPHERAL BLOOD VERSUS BONE MARROW HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM A SIBLING DONOR FOR PEDIATRIC PATIENTS

Bo Kyung Kim[1], Eun Sun Song[1], Kyung Taek Hong[1], Jung Yoon Choi[1], Hyery Kim[2], Hyun Jin Park[1], Hyoung Jin Kang[1]

[1]Seoul National University College of Medicine, Seoul, Korea, Republic of, [2]University of Ulsan College of Medicine, Seoul, Korea, Republic of

Background: Traditionally, bone marrow (BM) have been a common stem cell source in pediatric hematopoietic stem cell transplantation (HSCT), however the use of peripheral blood stem cell (PBSC) has recently increased. With the advances of graft-versus-host disease (GVHD) prophylaxis, it is controversial whether bone marrow is still a better stem cell source than peripheral blood in sibling donor HSCT. Here, we compared the results of BM and PBSC transplantation in pediatric patients with malignant or non-malignant disease receiving a sibling HSCT by using a total of 7.5mg/kg of ATG.

Methods: From 2005 to 2020, we retrospectively reviewed children who received HSCT from a sibling donor at Seoul National University Children's Hospital. Of the 86 patients, 40 were transplanted with BM, 46 with PBSC. Fifty six patients had malignant diseases and 30 patients had non-malignant diseases. All conditioning regimens comprised anti-thymocyte globulin (ATG) (2.5mg/kg/day, once daily from days -4 to -2). Busulfan-based myeloablative conditioning regimens was administered in the patients with malignant diseases and about half of patients with non-malignant diseases. The other half of the patients with non-malignant diseases were given cyclophosphamide-based reduced intensity conditioning regimens.

Results: In all 86 patients, the median age at the time of HSCT was 11.4 years (range 0.7-24.6) and the patients were 47 male and 39 female. The median follow-up period was 57.9 (range, 0.9 to 228.6) months, and the corresponding values for those with BM and PBSC were 77 (range, 2.4 to 228.6) months and 48.7 (range, 0.9 to 213.2) months, respectively. Engraftment failure occurred in 1 patient with BM and no patient with PBSC. The cumulative incidence of acute graft-versus-host disease (GVHD) with grade II-IV was higher in PBSC (BM 2.5%, PBSC 26.1%, $p = 0.002$), but there was no significant difference in those of acute GVHD with grade III-IV (BM 0%, PBSC 6.5%, $p = 0.3703$) and extensive chronic GVHD (BM 2.5%, PBSC 11.6%, $p = 0.1004$). There were no significant differences in the treatment-related mortality (TRM) (BM 14.2%, PBSC 6.8%, $p = 0.453$), the 5-year event free survival (EFS) (BM 71.5%, PBSC 76.2%, $p = 0.874$) and overall survival (OS) rates (BM 80.8%, PBSC 80.3%, $p = 0.867$) between BM and PBSC in univariate analysis. In the multivariate analysis, which included all factors with a $P < .50$ in the univariate analysis, there was no significant prognostic factor for EFS or OS. There was no significant difference in relapse incidence between BM and PBSC among patients with

malignant diseases (BM 14.2%, PBSC 6.8%, $p = 0.453$). Furthermore, there were no significant differences in the TRM, the 5-year EFS and OS rates between malignant and non-malignant disease and also between busulfan-based myeloablative regimen and reduced intensity chemotherapy using cyclophosphamide.

Conclusions: In this study, we showed that there were no significant differences in EFS, OS TRM, and GVHD except for acute GVHD grade II-IV between BMT and PBSCT from sibling donors by using a total of 7.5mg/kg of ATG. Therefore, peripheral blood, which is less invasive for donors and less labor-intensive for doctors, also could be considered as an acceptable stem cell source of sibling donor HSCT in children.

Disclosure: I have no personal or financial interests to declare.

1 - Haematopoietic Stem Cells

P313

DAY + 120 CD4 OR CD 19 LYMPHOPENIA IS ASSOCIATED WITH INFERIOR SURVIVAL AND INCREASE NRM FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION

Samar Alfaqawi[1], Heba Madien[1], Mostafa Mohammed Saleh[1], Ahmed Kotb[1], Tusneem Elhassan[1], Taimoor Hussain[1], Harron Alfadhil[1], Ahmed Bin Salman[1], Momen Nassani[1], Yazeed Bujaifer[1], Mohamed Issam Sharif[1], Marwa Nassar[1], Riad Younis[1], Ahmad Alotaibi[1], Walid Rasheed[1], Marwan Shaheen[1], Alfadel Alshaibani[1], Ali Alahamri[1], Saud Alhayli[1], Mansour Alfayez[1], Abdelwahab Albabtain[1], Riad Elfakih[1], Feras Alfraih[1], Amr Hanbali[1], Fahad Alsharif[1], Naeem Chaudhri[1], Hazza Alzahrani[1], Fahad Almohareb[1], Mahmoud Aljurf[1], Syed O. Ahmed[1]

[1]Adult Hematology, Stem Cell Transplant and Cellular Therapy Section, Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Background: Immune reconstitution after allogeneic stem cell transplantation (SCT) is a complicated process. The timely recovery of donor-derived lymphocytes could impact long-term survival of patients after SCT. The variable lymphocyte subsets recovery is associated with late viral or fungal infections, occurrence of graft-versus-host disease (GVHD), and relapse. Studying the dynamics of immune balance in patients after SCT is an area of great interest to predict SCT outcomes. We studied the association between the kinetics of lymphocyte subsets at D + 120 and transplant outcome to clarify its clinical significance.

Methods: Transplant and clinical data were retrieved from patients' medical records at Adult Hematology, HSCT and cellular therapy section, Oncology center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. Patients aged ≥14 years old who underwent SCT between February 2014 and March 2018 were initially selected. Those who received second SCT and who died or experienced disease relapse before day 120 post SCT were excluded. Lymphocyte subsets in the peripheral blood of recruited patients were analyzed by quantitative flow-cytometry using antibodies against CD3, CD4, CD8, CD19, CD16 and CD56 on D + 120 post SCT. The relationships of lymphocyte subsets with SCT outcomes including chronic GVHD, relapse, NRM and survival were analyzed.

Results: The final cohort included 209 patients with median age was 26 (range: 14- 66) years, 113 males and 96 females. Primary diagnoses include malignant disorders in 157 (mainly acute leukemia, n = 128) and benign disorders in 52 patients (mainly SAA, n = 24). Donors were 185 identical matched siblings, others (15 haplo, 5 MUD, 1 cord, 1 twin, 2 single antigen mismatch). Median CD34 cell dose was 6.5×10^6/kg (range 0.95-11). Irradiation based conditioning was used in 60 patients and chemotherapy based conditioning were commonly BU/CY in 36 while FLU/CY in 24 patients. Cyclosporine with short-term methotrexate was mainly used in 136 patients for GVHD prophylaxis.

High proportion of patients were found at D + 120 to have low CD4 (52.9%), low CD19 (50.6%) while other subsets were within normal range CD3 (67.1%), CD8 (62.4%), CD + 16 + 56 (83.7%)

The median follow-up of surviving patients was 74.8 (range: 51.3 - 98.4) months. The 5-year overall survival (OS) was 56.4%, cumulative incidence of relapse (CIR) 29.1%, non-relapse mortality (NRM) 15.4% and chronic GVHD 56.1%

No association could be found between any lymphocyte subsets and incidence of chronic GVHD or relapse. However, low CD 19 counts and low CD4 counts were associated with poor OS ($p = 0.039$ and $p = 0.058$, respectively). This impact on OS was most likely due to an increase in NRM resulting from CD19 lymphopenia (2.7% vs 19%, $p = 0.005$) and CD4 lymphopenia (6.2% vs 25.8%, $p = 0.050$). No significance was found for analysis of CD3, CD8, CD16 and CD56 on survival rates.

Conclusions: The variable recovery of lymphocyte subsets at D + 120 post SCT for CD4 and CD19 could help for predicting transplant outcome. Further exploration of such variable dynamics of immune reconstitution post SCT is warranted in prospective large studies to clarify its clinical impact.

Clinical Trial Registry: Not applicable

Disclosure: No conflict of interest to disclose.

1 - Haematopoietic Stem Cells

P314

EFFECT OF AUTOLOGOUS STEM CELL TRANSPLANTATION ON SUBSEQUENT TREATMENT AFTER FIRST RELAPSE IN PATIENTS WITH MULTIPLE MYELOMA

Hee Jeong Cho[1], Jihyun Na[1], Juhyung Kim[1], Dong Won Baek[2], Ji Yeon Ham[2], Soon Hee Chang[1], Young Rok Do[3], Ji Woon Yea[4], Sang Kyun Sohn[1], Joon Ho Moon[1]

[1]Kyungpook National University Hospital, Daegu, Korea, Republic of, [2]Kyungpook National University Chilgok Hospital, Daegu, Korea, Republic of, [3]Keimyung University Dongsan Hospital, Daegu, Korea, Republic of, [4]Yeungam University Medical Center, Daegu, Korea, Republic of

Background: The selection of treatment regimen after first relapse in patients with multiple myeloma (MM) depends on many factors: response, response duration and toxicity of first treatment, the use of autologous stem cell transplantation (ASCT), etc. ASCT is still an effective option for patients treated with novel agents. But the factors affecting the treatment outcomes to subsequent therapy still need to be elucidated. Herein, we evaluated the treatment outcomes of second-line therapy and factors affecting the survival rates for patients MM.

Methods: We retrospectively reviewed medical records of 90 newly diagnosed MM (NDMM) patients who were transplant-eligible (age <70 years) and treated with proteasome inhibitor and/or immue-modulators. ASCT was considered as front-line options in NDMM patients. Second progression free survival (PFS2) was defined as the time from diagnosis to second objective disease progression, or death from any cause, whichever first. Overall survival (OS) was defined as the time from diagnosis to death from any cause or last follow-up.

Results: Among 90 patients, 51 patients were treated with ASCT (ASCT group) and 39 patients with chemotherapy only (No-ASCT group) as front-line therapy. Median age were 59 years (range 38-68 years), and 64 years (33-69 years) in ASCT and No-ASCT group, respectively. R-ISS risk and high risk cytogenetics by FISH (56.9% vs 48.7%) did not differ between ASCT and No-ASCT group. Major first-line regimen was VTD (82.4% vs 61.5%) and major second-line regimen was KRD (82.4% vs 69.2%) in ASCT and No-ASCT group, respectively. Final response to frontline therapy including ASCT were CR in 37 patients (72.8%), VGPR in 11 (21.6%), and PR in 3 (5.9%) in ASCT group; CR in 5 (12.8%), 5 (12.8%), and PR in 15 (38.5%) in No-ASCT group. PFS was significant different between ASCT (median 805 days) and No-ASCT group (median 442 days). PFS2 was median 1361 days (range 244 – 3659) and 1000 days (119 – 3002) in ASCT and No-ASCT group, respectively ($p = 0.014$). However, the OS rate did not differ between ASCT and No-ASCT group (median 1533 and 1147 days; $p = 0.146$). Time to relapse (TTR) with frontline therapy was related with OS and PFS2: median OS of 1808 and 580 days ($p < 0.001$) and median PFS2 of 1543 and 486 days ($p < 0.001$) in TTR > 1 year and TTR < 1 year, respectively. Second-line regimen did not affect OS and PFS2. In the multivariate analysis, ASCT significantly improved PFS2 (HR 0.49 [0.28-0.83]; $p = 0.008$) and trend toward OS (HR 0.53 [0.27-1.01]; $p = 0.055$).

Conclusions: Deeper response with ASCT as frontline therapy prolonged survival outcomes with regards to PFS2, and time to relapse more than 1 year with frontline therapy was related with prolonged OS and PFS2. The more effective triplelets with monoclonal antibody as well as ASCT might be needed to prolong OS rate.

Clinical Trial Registry: Not applicable

Disclosure: The authors declare nothing to disclose.

1 - Haematopoietic Stem Cells

P315

VIABILITY OF HAEMATOPOIETIC STEM CELLS – FROM LABORATORY TO BEDSIDE

Tanya Glatt[1,2], Khensani Ramadwa[1], Riana Cockeran[1]

[1]Sanbs, Johannesburg, South Africa, [2]University of Johannesburg, Johannesburg, South Africa

Background: A critical part of the haematopoietic stem cell (HSC) transplant process is ensuring that the infused HSCs are viable and will engraft. The stored HSCs are subjected to viability testing (CD45, CD34 flow cytometry and trypan blue (TB)), prior to commencing conditioning therapy. Viability testing is performed in the laboratory on vials that are stored under the same condition as the HSC graft product. The vials act as a surrogate of the actual HSC graft viability. The CD34 and CD45 flow cytometry viability is a more accurate test than TB viability testing; however, in our setting flow cytometry at the bedside is not logistically feasible and only bedside TB is performed. The true correlation between laboratory viability of the vial and bedside viability of the HSC graft needs to be assessed.

Methods: All reinfused HSC grafts between 1 October 2021 and 31 October 2022, where vial viability and bedside viability were performed, were included. The viable cells using

(i) vial CD34, CD45 flow cytometry,
(ii) vial TB results and
(iii) TB results of the HSC product, were analysed for acceptability.

Acceptable viability was defined as: viable CD45 cells ≥ 50% of total, viable CD34 cells ≥ 70% of total and viable cells determined by TB ≥ 50% of total.

Exclusion criteria: HSC grafts for which vial viability and/ or bedside viability were not performed / available.

Results: During this 13 month period 55 HSC grafts (out of 102) fulfilled inclusion criteria. All 55 HSC grafts showed acceptable vial viability and bedside viability. The average viability for CD34 was 99.4%, CD45 was 60.4%, vial TB was 80.5% and product TB was 84.7%. Statistical analysis was performed using a two-tailed paired student t-test. CD45 vial viability significantly underestimated the bedside TB viability in all 55 HSCs ($p < 0.001$) and vial TB viability was on average 4% lower than the bedside TB viability.

Conclusions: The results of this study show that vial viability underestimates HSC product viability. In South Africa, vial viability is an acceptable surrogate marker for true HSC product viability, however care should be taken as this could underrepresent the viability of the product HSC.

Clinical Trial Registry: Not Applicable

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P316

CRP/ALBUMIN RATIO MAY PREDICT SURVIVAL AND NON RELAPSE MORTALITY IN AML/MDS PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Şeyma Yildiz[1], Zeynep Arzu Yeğin[1], Gonca Gül Gündem[1], Sema Yaşar[1], Seda Çiçek[1], Zübeyde Nur Özkurt[1], Münci Yağci[1]

[1]Gazi University, Ankara, Turkey

Background: The ratio of C-reactive protein to albumin (CAR) has been shown to be a feasible predictor for prognosis in patients with solid tumors and acute myeloid leukemia (AML) who are not eligible for allogeneic hematopoietic stem cell transplantation (alloHCT). As the potential prognostic role of CAR has not been evaluated in alloHCT recipients, we aimed to investigate the predictive impact of pretransplant CAR on transplant outcome in AML and myelodysplastic syndrome (MDS) patients undergoing alloHCT.

Methods: A total of 263 alloHCT recipients [median age: 45 (18-71) years; male/female: 150/113] were included in this retrospective study. Patient and transplant characteristics are summarized in Table 1. The CAR was calculated using CRP and albumin concentrations at diagnosis and pretransplant period.

Results: Primary diagnosis was AML in 221 patients (84%) and MDS in 42 patients (16%). Median follow-up period was 682 (4-5910) days. Pretransplant CAR was shown to have a significant impact on overall survival (OS) in univariate analysis [$p = 0.018$, HR: 1.119 (1.020-1.227)]. Based on the optimum cutoff value of pretransplant CAR, which was found to be 0.2645 [$p < 0.001$, AUC: 0.656 (0.581-0.731)], the study population was divided into two subgroups such as low-CAR and high-CAR. The probability of OS was significantly lower in high-CAR group compared to low-CAR group [26.2% vs 31.1%, $p < 0.001$]. The probability of non relapse mortality (NRM) was significantly higher in high-CAR group ($p = 0.032$). The frequency of posttransplant early complications including sepsis ($p = 0.013$), nephrotoxicity ($p = 0.012$) and dialysis requirement ($p = 0.003$) were significantly higher in high-CAR group. EBMT score ($p = 0.012$), development of sepsis in the first 30 days ($p = 0.003$), type of the conditioning regimen ($p = 0.018$)

and posttransplant relapse ($p = 0.003$) had significant impact on OS in multivariate analysis.

Table 1. Patient and Transplant Characteristics.

Age (years) [median (range)]	45 (18-71)	**BKV Associated Hemorrhagic Cystitis** [n(%)]	20 (7.6)
Gender (male/ female) [n(%)]	150/113	**Sepsis** [n(%)]	13 (4.9)
Primary Diagnosis [n(%)]		**Invasive Fungal Infection** [n(%)]	21 (8)
Acute myeloid leukemia	221 (84)		
Myelodysplastic syndrome	42 (16)		
Pretransplant Disease Status [n(%)] (n = 231)		**SOS** [n(%)]	28 (10.6)
Complete remission	149 (64.5)		
Partial remission	53 (22.9)		
Stable disease	14 (6.1)		
Progressive disease	15 (6.5)		
ECOG [n(%)] (n = 259)		**Hepatotoxicity** [n(%)]	88 (33.5)
0-1	204 (78.8)		
≥2	55 (21.2)		
HCT-CI [n(%)] (n = 217)		**Nephrotoxicity** [n(%)]	28 (10.6)
Low (0)	105 (48.4)		
Intermediate (1-2)	81 (37.3)		
High (≥ 3)	31 (14.3)		
EBMT Score [n(%)] (n = 195)		**Cardiotoxicity** [n(%)]	21 (8)
Low (0-3)	138 (70.8)		
Intermediate (4)	28 (14.3)		
High (> 4)	29 (14.9)		
Donor Type [n(%)] (n = 256)		**Acute GvHD** [n(%)]	95 (36.1)
MRD	187 (73.1)		
MMRD	10 (3.9)		
MUD	23 (9)		
MMUD	18 (7)		
Haploidentical	18 (7)		
Graft Source [n(%)] (n = 261)		**Chronic GvHD** [n(%)]	11 (4.2)
Bone marrow	5 (1.9)		
Peripheral blood**Conditioning Regimen** [n(%)] (n = 238)	256 (98.1)	**Graft Failure** [n(%)]	19 (7.2)
Myeloablative	163 (68.5)		
Reduced intensity	75 (31.5)		
Infused CD34$^+$ Cell Count (10^6/kg) [median (range)]	4.35 (1.24-6.19)	**CRP at Diagnosis** (mg/L) [median (range)]	27.8 (1-485)
Neutrophil Engrafment (days) [median (range)]	15 (9-32)	**CRP at Pretransplant Evaluation** (mg/L) [median (range)]	11.35 (1-322)
	14 (0-45)		
Platelet Engraftment (days) [median (range)]		**Albumin at Diagnosis** (g/dL) [median (range)]	4 (2.3-5.3)
Neutropenic Fever [n(%)]	134 (51)	**Albumin at Pretransplant Evaluation** (g/dL) [median (range)]	3.9 (2-5.5)
CMV Reactivation [n(%)]	94 (35.7)	**Follow-up** (days) [median (range)]	682 (4-5910)

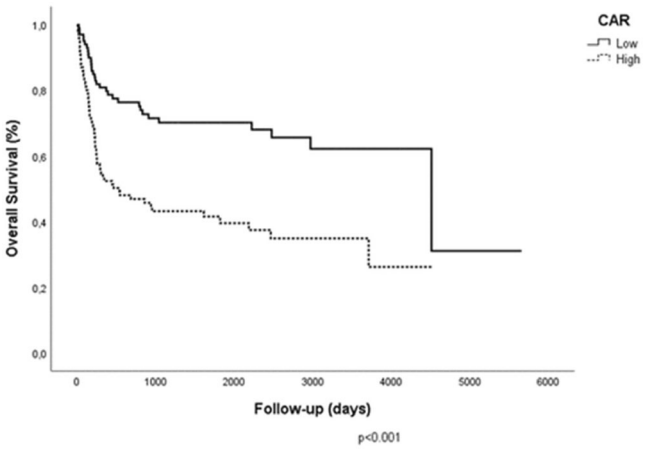


Figure 1: The Probability of Overall Survival is Better in Low-CAR Group ($p < 0.001$)

Conclusions: Pretransplant CAR may be considered as a simple and cost effective marker to predict transplant outcome and NRM in alloHCT recipients. The prognostic role of CAR should be confirmed in further studies to be used in clinical practice.

Disclosure: The authors report no conflicts of interest in this study.

1 - Haematopoietic Stem Cells

P317

THE ADDITION OF THIOTEPA TO HAPLO HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR THE TREATMENT OF ACUTE LEUKEMIA WITH EXTRAMEDULLARY LESIONS IS SAFE AND EFFECTIVE

Wei Zhao[1], Min Xiong[1], Yanli Zhao[1]

[1]Beijing Ludaopei Hospital, Beijing, China

Background: The relapse rate following allogeneic hematopoietic stem cell transplantation(allo-HSCT) for acute leukemia with extra-medullary lesions is still high even with high-intensity conditioning. How to improve prognosis and increase the rate of long-term survival is currently a major focus but is challenging to accomplish.

Methods: We performed a retrospective analysis of 36 patients with acute leukemia with extramedullary lesions who received haplo-HSCT at the Beijing Lu Daopei Hospital between August 2019 and March 2022. Fourteen of 36 (38.9%) patients received a conditioning regimen with busulfan/ cyclophosphamide (Bu/Cy) and the remaining 22 (61.1%) patients received total body irradiation/ cyclophosphamide (TBI/Cy). All patients also received thiotepa (5mg/kg, -3 days to -2 days) as part of their conditioning

regimen. Overall survival (OS), disease-free survival (DFS), and transplant-related mortality (TRM) were evaluated.

Results: A total of 36 patients were identified, 11 with acute myeloid leukemia, and 25 with acute lymphoblastic leukemia (16 with B-cell acute lymphoma and 9 with T acute lymphoma). There were 25 males and 11 females. The median age was 6.5 years (0.7-58). Poor prognosis and stratification factors analyzed included 12 (33.3%) patients with high leukocyte onset, 24 (66.7%) with poor molecular genetic prognosis, and 19 (52.8%) with poor cytogenetic prognosis. There were 16 (44.4%) patients with central nervous system leukemia, 26 (72.2%) with extramedullary infiltration. Disease status at time of transplantation was first complete remission (CR1) in 6 (16.7%) patients, ≥ CR2 in 22 (61.1%) patients, and no-remission (NR) in 8 (22.2%) patients. The median concentration of mononuclear cells (MNCs) of the reinfused graft was 8.64 $\times 10^8$/kg (5.88-26.68) and CD34+ was 5.52 $\times 10^6$/kg (2.98-10.03). The stem cell engraftment rate was 100%. Among patients who underwent an engraftment evaluation had neutrophils at a median of day +17 (10-23), and platelets on day +10 (7-60) days. The most common non-hematologic adverse reactions were gastrointestinal symptoms and oral mucositis. There was 1 case of grade III-IV infection, 1 case of grade III hemorrhagic cystitis. No allergic or rash adverse reaction were observed. The infection rates of Epstein-Barr (EB) and cytomegalovirus (CMV) after transplantation were 13.9% and 55.5%, respectively. Ten (27.8%) patients had grade III-IV acute graft versus host disease (aGVHD) and 2 (5.5%) patients had extensive chronic graft versus host disease (cGVHD). The median follow-up time was 549 days (range: 97-819 days), Up to the cutoff date of Nov. 30, a total of 9 (27.8%) patients died, including 7 who died of GVHD, and two that died of intracranial hemorrhage. Logical regression analysis showed that every 1$\times 10^8$/kg increase in MNCs was associated with a 0.49-fold increase in the risk of death [OR 95%CI 1.49 (1.01-2.19)]. The 1-year OS and DFS rates were 83.3%, and TRM was 19.4%. There was no significant difference in OS among the CR1, ≥CR2, and no-remission (NR) subgroups ($P > 0.05$).

Conclusions: During the follow-up period, the cumulative recurrence rate of enrolled patients was 5.5%, and there was no extramedullary recurrence after hematopoietic stem cell transplantation. We conclude that conditioning regimens that include thiotepa are feasible for patients with acute leukemia with extramedullary lesions.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P318

ROLE OF INTERFERON-GAMMA IN POST-ALLOGENEIC HSCT COMPLICATIONS AND IN PATIENTS WITH IMPAIRED HAEMATOPOIETIC STEM CELL PROLIFERATION AT DIAGNOSIS: PROSPECTIVE CLINICAL STUDY DESIGN

Régis Peffault de Latour[1,2], Pietro Merli[3], Emmanuel Monnet[4], Teresa Urbanowska[4], Franco Locatelli[5]

[1]French Reference Center for Aplastic Anemia and PNH Hematology-Bone Marrow Transplantation, Hôpital Saint-Louis AP-HP, Paris, France, [2]Université Paris Diderot, Paris, France, [3]Bambino Gesù Children's Hospital, Rome, Italy, [4]Swedish Orphan Biovitrum AG, Basel, Switzerland, [5]Catholic University of the Sacred Heart, Rome, Italy

Background: Allogeneic HSCT is associated with a risk of graft failure (GF), which, in most cases, is hypothesised as resulting from residual host immune cells becoming activated in the presence of an immune–genetic disparity between donor and recipient immune cells. Activated immune cells produce interferon-γ (IFNγ), which has been reported to have a deleterious effect on haematopoietic stem cell proliferation in preclinical studies. A systematic and specific elevation in IFNγ levels has been observed prior to GF in patients undergoing allogeneic HSCT for various conditions. This study is assessing the relationship between 1) the levels and activity of IFNγ and the risk of GF, and occurrence of GvHD, in patients receiving HSCT, and 2) levels and activity of IFNγ in patients with impaired haematopoietic stem cell proliferation (IHSCP; e.g., acquired severe aplastic anaemia [SAA]) at diagnosis).

Methods: Initially, ~200 patients were planned to be enrolled across Europe in this prospective clinical study, including a minimum of 20 patients with GF. The maximum 15 patients with IHSCP were enrolled, alongside healthy controls sourced from outside the study. Eligible patients aged >1 year had pre-transplant IHSCP or were undergoing HSCT for underlying non-malignant haematological disease or malignant disease with a higher risk of GF, and had at least one of the following: a non-malignant disease and received reduced intensity or non-myeloablative conditioning, or received a graft from bone marrow; ex vivo T-cell–depleted graft; graft from mismatched unrelated or haploidentical donor; or graft from umbilical cord blood. Patients with haemophagocytic lymphohistiocytosis or a body weight <10 kg were excluded. In the HSCT cohort, hospital records data collection was performed for HSCT outcomes and blood samples analysed regularly for IFNγ levels and activity (**Table**). An additional single blood sample was collected at the time of suspected primary or secondary GF or GvHD diagnosis. In the IHSCP cohort, a single blood sample was taken at the time of diagnosis. Patients undergoing HSCT were followed up via hospital record data collection until Day 100 post-HSCT. Serum levels of IFNγ and CXCL9, a chemokine that is almost exclusively produced by IFNγ receptor activation, were measured pre- and post-HSCT. Absolute neutrophil and platelet counts were also assessed in patients undergoing HSCT, and ferritin and chimerism data recorded, when collected per site routine practice. All endpoints are exploratory.

IFNγ activity assessment (blood sampling) and hospital record data collection	Patients undergoing allogeneic HSCT		Patients with impaired haematopoietic stem cell proliferation
Pre-transplant	Day -7		At diagnosis
At transplant	Day 0		
Post-transplant (up to Day 42)	**Mandatory**	• Days 1, 3, 5, 9, 13, 17, 21, 28, 31 and 38 • At time of suspected primary or secondary GF or GvHD diagnosis	
	Recommended	• Days 7, 11, 15, 19, 24, 35 and 42	
Follow-up (Days 42–100)	• At time of suspected primary or secondary GF or GvHD diagnosis • Day 100 (hospital records data collection only)		

Results: This study enrolled 86 patients undergoing HSCT (31 with non-malignant disease; 55 with malignant disease) and 15 patients with IHSCP (14/15 had SAA). GF was observed in 5 patients and GvHD in 39 patients. The relationship between the IFNγ pathway and the risk of GF and occurrence of GvHD is being assessed. Levels of IFNγ and CXCL9 will be compared between patients with IHSCP at diagnosis and in healthy controls.

Conclusions: Understanding the relationship between the IFNγ pathway and the risk of GF and occurrence of GvHD in patients receiving HSCT, and IFNγ pathway activity in patients with IHSCP, will allow deciphering of the role of IFNγ in haematopeitic stem cell proliferation in the absence and presence of competing immune signals.

Clinical Trial Registry: Clinicaltrials.gov identifier: NCT04494061

Disclosure: RPDLT is a consultant to Alexion, Amgen, MSD, Novartis and Pfizer, and has received research grants from Alexion, Amgen, Novartis and Pfizer. PM is a consultant for Sobi and Jazz Pharmaceutical. TU and EM are employees of Sobi. FL is a consultant to Sobi, Amgen, Novartis, Bellicum Pharmaceutical, Neovi, Miltenyi, Medac, Jazz Pharmaceutical and Takeda.

1 - Haematopoietic Stem Cells

P319

THE CRYOPRESERVATION MEDIA USED FOR PRESERVING CD34 + STEM CELLS INFLUENCES THE CELL COUNT, SURVIVAL AND APOPTOSIS OF THESE CELLS POST-THAWING

Rebecca Axelsson Robertson[1], Pablo Giusti Coitinho[1], Lyda M Osorio Fernandez[1]

[1]Karolinska University Hospital, Stockholm, Sweden

Background: New strategies for improving cryopreservation (CP) outcome on CD34+ stem cells are focusing on the mitigation of cell stress response to CP and reduction of post-thaw CP-induced delayed onset cell death (CIDOCD). Immediate assessment of viability with 7-aminoactinomycin D (7AAD) post-thawing does not measure the CP effect on stress-induced cell damage that occurs hours later. We therefore use a CD34 + /Annexin/7AAD-based flow cytometry method to measure post-thaw viability and apoptosis in stem cells graft that have been cryopreserved with different CP solutions approved for clinical use, as a strategy to evaluate different cryopreservation methods.

Methods: CD34+ cell and CD3 + T-cell counts, viability and apoptosis were analyzed directly and 18 hours post-thaw, in stem cells grafts cryopreserved in the following different cryopreservation media: (a) Heparin + 2.5% human albumin (HSA) + 5% DMSO, (b) CryoStor CS10 (10% DMSO) and (c) Plasmalyte A + 5% HSA + 10% DMSO. Each sample was split in two and compared with cryopreservation in our routine cryomedia, human plasma + 10% DMSO.

Results: (1) Utilization of Plasmalyte/10% DMSO based cryomedia yielded an increase both in CD34 + /7AAD- cell counts ($p < 0.05$) and survival ($p < 0.05$) compared to Plasma/10% DMSO directly post-thaw.

(2) Utilization of CryoStor CS10 media resulted in a decrease of total Annexin + /7AAD-, CD34 + /Annexin + /7AAD- and CD3 + / Annexin + /7AAD- apoptotic cells compared to Plasma/10% DMSO 18 hours post-thaw ($p < 0.01$, $p < 0.05$ and $p < 0.01$ respectively).

(3) Heparin/5% DMSO based cryomedia showed similar results as plasma/10% DMSO cryomedia direct post-thaw but yielded an increase in CD34 + /Annexin + /7AAD- apoptotic cells 18 hours post-thaw ($p < 0.05$).

Conclusions: In conclusion, an apoptosis-based flow cytometric assay is a useful approach to analyze CD34+ cell viability and apoptosis in stem cells graft with the aim of improving stem cell cryopreservation methods.

Clinical Trial Registry: NA

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P320

SHARED TRANSPLANT

Ana Lario[1], Pilar Herrera[1], Gemma Moreno[1], María García[2], Anabelle Chinea[1], Alejandro Luna[1], Jose Valentín García Gutiérrez[1], María Luisa Palacios[1], Milagros Sánchez[2], Ana María Espuela[2], Begoña Hinojo[1], Francisco Javier Peñalver[2], Francisco Javier López[1]

[1]Hospital Universitario Ramón y Cajal, Madrid, Spain, [2]Hospital Universitario Fundación Alcorcón, Alcorcón, Spain

Background: The "shared transplant" is a program already implemented in several Spanish centers, whose fundamental objectives are to improve the emotional well-being of the patient and reduce the waiting list in the transplant center, without affecting the safety of the procedure.

Methods: Hematopoietic stem cell transplantation is a complex procedure, not available in the portfolio of services of all hospitals in the Community of Madrid. With the previous objectives, and to articulate patient-centered care, a "shared transplant" program was implemented between the Ramón y Cajal University Hospital, as transplant center, and the Alcorcón Foundation University Hospital, as patient origin center, being the phases of the process distributed as follows:

Transplant center: pre-transplant, obtaining hematopoietic progenitors, conditioning and infusion of hematopoietic progenitors (day 0).
Center of origin: post-transplant, from day +1 of the infusion, that is divided into 2 parts, admission and post-transplant consultation.

A timeline was established for the launch, containing the implementation of work procedures, staff training and infrastructure adaptation in the satellite center. Prior to the start of the piloting, an audit was carried out with a favorable result.

This program included patients diagnosed with lymphoma or multiple myeloma, who have undergone autologous hematopoietic stem cell transplantation (autologous HSCT). A control panel of quality indicators was designed to monitor the process.

Results: In the period between October 2021 and December 2022, a total of 7 autologous HSCT have been carried out within this program. Of the 7 patients, 3 are lymphomas (1 T lymphoma and 2 follicular lymphomas) and the other 4 are multiple myelomas. Conditions received were: BEAM for lymphomas and MEL200 for multiple myelomas. Of the 7 patients, 1 of them could not be transferred to the center of origin due to an episode of fever on day +1, the rest were transferred without incident. The average number of days for leukocyte grafting was 17 days and for platelet grafting 15.7 days, similar to those of the transplant center. No patient has presented bacteremia associated with a central venous catheter. The average number of days of admission was 21.7, similar to those of the transplant center. Of the 7 patients, 1 died of colon adenocarcinoma, 1 is in the progression of his follicular lymphoma, and the rest are under follow-up with no evidence of disease progression.

Conclusions: The "shared transplant" is a safe procedure, which facilitates access to a transplant to a greater number of people, being a formula to consider for some patient profiles, which allows comprehensive patient care from their center of origin, also contributing optimal use of resources in transplant centers. Our objective is to continue increasing the number of patients included in this program, and, if possible, extend it to other centers.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P321

PRETRANSPLANT MYELOID AND IMMUNE SUPPRESSION (PMIS) FOR THALASSEMIA PATIENTS RECEIVING MATCHED RELATED DONOR ALLOGRAFT

Eman Khattab[1], Mayada Abu Shanap[1], Hasan Hashem[1], Iyad Sultan[1], Rawad Rihani[1]

[1]King Huseein Cancer Center, Amman, Jordan

Background: Allogeneic stem, cell transplantation (allo-HSCT) is the only curative treatment for patients with thalassemia major. Patients with thalassemia,especially high risk patients, have a higher incidence of transplant related complications and graft failure. Many modifications were done to the transplant protocol to improve their survival and thalassemia free survival.

Methods: This is a retrospective chart review of patients who received PMIS for thalassemia patients receiving matched related donor allografts, according to our new guidelines which were in effect since Oct2020. Accordingly, these patients received two cycles of Fludarabine in combination with dexamethasone over 5 days, four weeks apart in association with hydroxyurea, followed by Fludarabine based reduced toxicity conditioning (RTC) for high risk thalassemia patients (age more than 14 years or class 3 thalassemia), or myeloablative conditioning (MAC) for low risk patients.

Results: Fourteen patients received PMIS since Oct2020 (10 patients received RTC), all were given anti-PCP and antiviral prophylaxis. The median age at transplant was 15.7 (range, 2.25-26.5 years), median ferritin 1045(324-7300 ng/ml); median liver span15.5 (9.5-19.5 cm); median absolute lymphocyte count prior to transplant 500 (range, 200-2100). None of the patients had significant liver fibrosis as confirmed by pre-transplant biopsy. The median time of neutrophil and platelets engraftment was on days 16 (range, 13-21) and 20 (range,14-34), respectively. After a median follow up of 192 days (range, 58-681), all patients except 2 patients have full donor chimerism (above 95% donor cells), and 2 have stable mixed chimerism. There were no signs of acute graft vs host disease (GVHD), and only one patient developed chronic GVHD. Eight patients developed molecular CMV reactivation but with no clinical manifestations. One patient developed BK cystitis that was treated conservatively.

Conclusions: Applying pre-transplant immunosuppressants and hydroxyurea thalassemia patients receiving MRD allografts was not associated with significant toxicity. This approach may improve the transplant outcome, especially for high risk group. Viral reactivation needs close monitoring.

Disclosure: I have no conflict of interest.

1 - Haematopoietic Stem Cells

P322

THE ROLE OF SECOND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION OVER THE YEARS: SINGLE-CENTER EXPERIENCE

Cristina García Herce[1], Ángela Figuera[1], Rafael de la Cámara[1], Adrián Alegre[1], Beatriz Aguado[1]

[1]La Princesa University Hospital, Madrid, Spain

Background: Allogeneic Hematopoietic stem cell transplantation (allo-HSCT) is the only potential long-term curative option for patients affected by advanced hematological diseases, but sometimes with serious complications such as graft failure and disease relapse. Some of those patients can be considered for second allo-HSCT.

Methods: We retrospectively reviewed 52 patients who received a second allogeneic HSCT between January 1991 and June 2022. Patients were divided into 2 groups depending on the period of time the second transplant was performed.

Results: We included 52 patients (table 1). Median age and gender distribution were similar in all the two groups. In the group of 1991-2006 (N = 19), the indication for second allo-HSCT was mostly by graft failure originated during the first year. All of them received bone marrow (BM) graft at first allo-HSCT. Chronic myeloid leukemia (CML) was the most frequent diagnosis, and all 19 patients had the same donor. Only 9 received myeloablative intensity regimen.

In the most current group, there were more patients with relapse and advanced disease: 4 acute myeloid leukemia (AML) without response and 1 multiple myeloma (MM) with partial response. Besides, 7 of 33 received auto-HSCT previously and 2 of 5 acute lymphoblastic leukemia (ALL) received antibody treatment (1 Blinatumuab; 1 Inotuzumab-ozogamicin). Median interval between first and second allo-HSCT was longer than the other group. Among patients with relapse after 1 year, 10 (30.3%) had extramedullary relapse. Same donor was selected in most patients, but there were more haploidentical and unrelated donors. All of the 33 patients received peripheral blood graft at second allo-HSCT. Moreover, 2 of 19 received a third allo-HSCT with different donor: 1 unrelated donor, 1 with haploidentical donor.

We observed higher indicence of acute and chronic graft-versus-host disease after the second allo-HSC. The 2 patients who did not receive any inmunosuppressive treatment had poor outcome. Median follow-up was 7.4 (range 1.3-149.2) months in the first period, and 14.9 (range 4.3-44.3) months in the most current group. 13 patients (68.4%) died in the first group and 23 (69.7%) died during the last period. The development of veno-occlusive disease (VOD) was high especially in the first group (intravenous busulfan era).

Table 1. Patient and transplantation characteristics at the second allogeneic HSCT.

Period of time	1991-2006 (N = 19)	2007-2022 (N = 33)
Age, years (range)	31.8 (28.4-42.5)	40.7 (27.9-49.9)
Sex, males (%)	9 (47.4)	17 (51.5)
Time between first HSCT and second HSCT, years (range)	1.5 (0.6-4.1)	2 (0.8-5)
- <1 year, n (%)/ > 1 year, n (%)	9 (47.4) / 10 (52.6)	11 (33.3) / 22 (66.7)
Indication for second HSCT, n (%)		
- Relapse / Graft failure	11 (57.9) / 8 (42.1)	29 (87.9) / 4 (12.1)
Disease, n (%)		
- ALM	5 (26.3)	13 (39.4)
- ALL	3 (15.8)	5 (15.6)
- MDS/CMML	1 (5.3)	3 (9.1)
- CML	9 (47.4)	1 (3)
- HL	0 (0)	1 (3)
- NHL	0 (0)	4 (12.2)

Period of time	1991-2006 (N = 19)	2007-2022 (N = 33)
- MM	0 (0)	2 (6.1)
- Other	1 (5.3)	4 (12.1)
Disease status, n (%)		
- Complete remission / Other	16 (84.2) / 3 (15.8)	28 (84.8) / 5 (15.2)
Acute GvHD grade II-IV after first HSCT, n (%)		
- Yes / No / Unknown	3 (15.8) / 14 (73.7) / 2 (10.5)	5 (15.2) / 28 (84.8) /0 (0)
Chronic GvHD grade II-IV after first HSCT, n (%)		
- Yes / No / Unknown	3 (15.8) / 14 (73.7) / 2 (10.5)	4 (12.2) / 29 (87.9) / 0 (0)
Donor, n (%)		
- Same / Other	19 (100) / 0 (0)	27 (81.8) / 6 (18.2)
Type of donor, n (%)		
- HLA-identical	15 (78.9)	14 (42.4)
- Haploidentical	2 (10.5)	7 (21.2)
- MUD	2 (10.5)	8 (24.2)
- MMUD	0 (0)	4 (12.1)
Second graft progenitor source, n (%)		
- BM / PB	6 (31.6) / 13 (68.4)	0 (0) / 33 (100)
Intensity of conditioning, n (%)		
- MAC / RIC	9 (47.4) / 10 (52.6)	24 (72.7) / 11 (33.3)
Immunosuppression, n (%)		
- CsA + MTX	4 (21)	6 (18.2)
- CsA + MMF	3 (15.8)	1 (3)
- CsA	12 (63.2)	18 (54.5)
- Cyclophosphamide + CsA + MMF	0 (0)	5 (15.2)
- ATG+ CsA	0 (0)	1 (3)
- None	0 (0)	2 (6.1)
Acute GvHD grade II-IV after second HSCT, n (%)		
- Yes / No / Unknown	8 (42.1) / 11 (57.9) / 0 (0)	17 (51.5) / 16 (48.5) / 0 (0)
Chronic GvHD grade II-IV after second HSCT, n (%)		
- Yes / No / Unknown	5 (26.3) / 15 (73.8) / 0 (0)	7 (21.2) / 26 (78.8) / 0 (0)
VOD, n (%)	6 (31.6)	5 (15.2)

Abbreviations: *AML*, acute myeloid leukemia; *ALL*, acute lymphoblastic leukemia, *MDS*, myelodysplastic syndrome; *CML*, chronic myeloid leukemia; *HL*, Hodgkin lymphoma; *NHL*, non-Hodgkin lymphoma; *MM*, multiple myeloma; *GvHD*, graft-versus-host disease; *MUD*, matched Unrelated donor; *MMUD*, Missmatched unrelated donor; *BM*, bone marrow; *PB*, peripheral blood; *MAC*, myeloablative conditioning; *RIC*, reduced-intensity conditioning; Csa, cyclosporine A; *MTX*, methotrexate; *MMF*, mycophenolate mofetil; *ATG*, antithymocyte globulin; *VOD*, veno-occlusive disease.

Conclusions: Second allogeneic transplantation can be a curative option for aggressive diseases, especially when relapsing after the first one. Even in the era of new therapies (tyrosine kinase inhibitors, immunotherapy such as bispecific antibodies and chimeric antigen receptor-T cells) it still may play a role in some selected patients.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P323

PRECLINICAL VALIDATION OF FULLY-AUTOMATED WASHING OF THAWED PERIPHERAL BLOOD STEM CELLS (PBSC) WITH SUCCINYLATED GELATINE

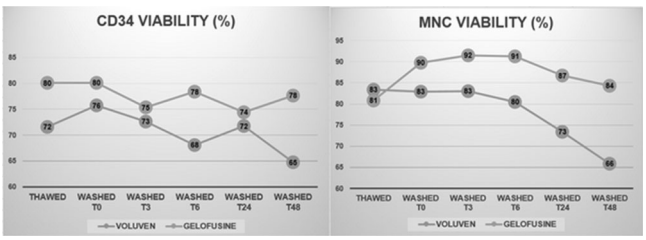
Serena Urbani[1], Irene Sodi[1], Rita Antonini[1], Lucia Bianchi[1], Valeria Calossi[1], Carmela De Sanzo[1], Francesca Felicioni[1], Valentina Fulgido[1], Gaetano Mobilio[1], Michela Santosuosso[1], Riccardo Saccardi[1]

[1]Cell Therapy and Transfusion Medicine Unit, Careggi University Hospital, Firenze, Italy

Background: Clinical-grade, fully automated washing of thawed cellular products through Sepax 2 S-100 device (Biosafe, *Cytiva*, CH) and low-molecular weight Hydroxyethyl-starch (HES) was previously reported. Marketing authorization of HES solutions for infusion was recently suspended by EU Commission. We report here the pre-clinical validation process of a 4% w/v solution of succinylated gelatine (Gelofusine, B Braun) as washing solution to be used in a clinical setting.

Methods: Six frozen Peripheral Blood Stem Cells (PBSC) Units, which had lost the indication for clinical use, were selected for this study. All units were cryopreserved in 2 equal bags: one bag was thawed in a 37°C water bath, washed by SmartWash Protocol using HES (Voluven, Fresenius Kabi) as washing and resuspension solution; the second bag was processed with the same protocol, but using Gelofusine as washing and resuspension solution. Immediately after thawing, an aliquot from each bag was obtained to evaluate Total Nucleated Cells (TNC), Mononuclear Cells (MNCs) and $CD34^+$ cells; other aliquots were taken just after washing and then after 3, 6, 24, and 48 hours from the end of the procedure, respectively. At each time point, cell count and viability were assessed by Flow-Cytometry standardized technique; at + 3 hours time point CFU assay was also carried out. Bags content was visually monitored to detect the occurrence of either aggregates or cellular debris.

Results: All procedures were successfully carried out and data stored in a dedicated database. Recovery and viability of products washed with Gelofusine were shown to be equal of better than those processed with HES. In particular, MNC viability was significantly higher in Gelofusine-treated samples beyond 3 hours from the end of the procedure, despite a decreasing trend up to 48 hours. CFU count at +3 hours was significantly higher in the units washed and resuspended with Gelofusine (11,6 10E6) respect to the ones washed and resuspended with Voluven (7,8 10E6, $p < 0.05$). No visually detectable aggregates or cellular debris were shown at any time points.



Conclusions: In a preclinical setting we found that washing of thawed PBSC by Gelofusine is safe and reliable in the setting of the SmartWash protocol, which is a fully automated procedure in a closed system. Cell viability was stable within 6 hours from the end of the washing procedure and slowly decreased up to 48 hours. Clonogenic test at +3 hours confirmed the Flow-Cytometry result. The results were compared with the

same protocol and HES, showing a slight superiority of Gelofusine in most of tests. A trial aimed to validate the clinical use of Gelofusine as washing solution is currently ongoing, therefore maintaining such established methodology of fully automated processing in the clinical setting of Stem Cells Transplantation.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P324

PEDIATRIC ALLOGENEIC STEM CELL TRANSPLANTATION: A REPORT OF 30 YEARS OF A SINGLE CENTER'S EXPERIENCE

Charline Pegon[1], Emmanuelle Rochette[1], Victoria Greze[1], Bruno Pereira[1], Etienne Merlin[1], Christophe Piguet[2], François Deméocq[1], Justyna Kanold[1]

[1]CHU Clermont Ferrand, Clermont Ferrand, France, [2]CHU Limoges, Limoges, France

Background: Determine that the observed changes were consistent with European trends in pediatric allogeneic HSCT, in therapeutic indications with a predominance for acute leukemias and with an expansion for non-malignant disorders. Bone marrow remains a major stem cell source and myeloablative conditioning remains also a major preparative regimen. However, new conditioning regimens were adopted with an increase in transplants with unrelated donors. The changes and trends observed in adults are not always those experienced in pediatric patients.

Methods: Retrospective observational study, included 207 patients who underwent their first allo-HSCT before 20 years, between May 1985 and December 2019 in a dedicated pediatric transplant unit of Clermont Ferrand. Patient characteristics, type of transplant, transplant-related mortality, overall survival were assessed according to the definitions of the EBMT.

Results: Leukemias were the main indication for allo-HSCT (60%), followed by non-malignant diseases (23%), with a significant increase ($p = 0.009$). BM remained the main source of stem cells but the use of PBSC increased significantly ($p = 0.001$), while the percentage of CB graft remained stable. The number of allo-HSCTs with unrelated donor increased significantly ($p = 0.004$), but family HLA identical donors still widely used. Five-year OS and EFS following allo-HSCT were 50.6% and 47.4%. A non-significant decrease in TRM was observed and a non-significant improvement in OS.

Conclusions: Importance of analyzing changes that occurred in a single center over time to show how general trends have impacted HSCT on a real-life level.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P325

RENAL OUTCOME AND POSSIBLE ASSOCIATIONS IN SICKLE CELL PATIENTS WITH STEM CELL TRASPLANT IN OUR CENTER: A RETROSPECTIVE STUDY

Jose Manuel Marco Sanchez[1], Paula Elisa Melero Guardia[1], Eduardo Rodriguez Pascual[1], Marina García Morin[1], Eduardo Bardón Cancho[1], Cristina Beléndez[1], Elena Carceller Ortega[1], Belén Huguet Rodríguez[1], Cristina Mata Fernandez[1], Jorge Huerta Aragonés[1], Carmen Garrido Colino[1], Olalla Alvarez[1], Daniel Barraca Núñez[1], Debora Claramunt[1], Ana Belén Martínez[1], Pablo González Navarro[1], Elena Cela de Julián[1]

[1]Hospital Universitario Gregorio Marañon, Madrid, Spain

Background: Transplant-associated kidney injury in sickle cell disease (SCD) patients includes vascular (thrombotic microangiopathy), glomerular (proteinuria, glomerulopathies), and/or tubulointerstitial abnormalities. The incidence varies widely between 10–73%, depending on the stage of kidney disease at baseline and type of transplantation (HSCT). Risk factors for CKD post-HSCT are: myeloablative conditioning regimen, medication-induced kidney injury (calcineurin inhibitors, antifungal and antivirals drugs), hypertension (HTA), graft-versus-host disease (GvHD), older age, female gender, hepatic sinusoidal obstruction syndrome (SOS) and sepsis.

Methods: A single retrospective center study in children with SCD, who underwent allogeneic HSCT from an HLA-identical sibling donor and bone marrow source, between may 2010 and september 2022. We analyzed the incidence and characteristics of post-HSCT renal complications, acute kidney injury (AKI) and CKD during the first 12 months post-infusion. We also analyzed the global event-free survival of post-HSCT renal complications and overall survival.

Until June 2015 we used a myeloablative conditioning regimen: busulfan, cyclophosphamide and alemtuzumab. Afterwards, we used myeloablative reduced toxicity conditioning: thiotepa, treosulfan, fludarabine and ATG. GvHD prophylaxis used until February 2019 was CsA and MTX, later tacrolimus and mycophenolate mofetile (MMF). We also initiate hydroxyurea 30 mg/kg and transfusion regimen (MTR) 3 months prior to transplant, to maintain $<100.000/mm^3$ reticulocytes.

Data are presented as percentages. *Pearson's Chi-squared* and *Fisher's exact* tests were used for the analysis of the variables, univariate logistic regression with *odds ratio* for predisposition studies and *Survminer* to represent Kaplan-Meier survival curves.

Results: 51 allo-HCST in 50 patients, median age 6.0 years (p25 2; p75 13), 26 males (52%) and 24 males (48%). 80% and 25% with hydroxyurea and MTR > 6 months pre transplant, respectively. 14% had previous SCD nephopathy (elevated B2-microglobulin, enuresis, tubulopathy or renal hyperechogenicity by ultrasound); 1 with focal and segmental glomerulonephritis. 20% previously treated with nephrotoxic drugs (iron chelation).

9.8% developed AKI in first month (25% stage 1, 50% s2, 25% s3). Statistically significant decrease on AKI was observed with RIC compared to myeloablative conditioning (**p0.006**).

41% developed post-HSCT nephropathy (1 SHU; 1 BK hemorrhagic cystitis; remaining 90% CKD related to infections and nephrotoxic drugs, mostly G2A1 stages). Use of pre (**p0.07**) and post-HSCT (**p0.08**) nephrotoxic drugs almost had statistically significant predisposition to develop post-trasplant CKD. No statistically significant predisposition was established with gender host ($p > 0.9$), conditioning regimen (p0.5), type of GvHD prophylaxis (p0.9), previous sickle nephropathy (p0.4), pre-HSCT CKD (p0.4), acute (p0.2) or chronic (p0.4) GvHD, SOS (p0.4) or HTA. No statistically significant decrease on AKI or CKD pos-HSCT was observed between administration >6 months prior to transplant of hydroxyurea and MTR, compared with 3 months.

Global event-free survival of post-HSCT renal complications for each time point were: 98% at month 1, 67% at month 3, 65% at month 6 and 59% at month 12. Overall survival were 98% at the end of follow-up (12.33 years).

Conclusions: Renal disease contributes significantly to the morbidity and mortality of SCD. AKI generally occurs in the first three months after transplantation, what agrees with our study, and have a poor outcome with myeloablative conditioning.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P326

ESTABLISHING A PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION PROGRAM IN A LIMITED-RESOURCES COUNTRY: A SUCCESSFUL JOURNEY IN A UNIVERSITY CENTER

Nayera HK Elsherif[1], Sara Makkeyah[1], Safa Matbouly[1], Nihal Hussein Aly[1], Alaa Taha Mousa[1], Noura Bahaa[1], Fatma SE Ebeid[1]

[1]Ain Shams University, Cairo, Egypt

Background: Establishing a hematopoietic stem cell transplant (HSCT) program in developing countries carries many obstacles, of which the scarcity of resources and the manpower expertise may lead to high operating and maintenance costs.

Methods: Our objective is to describe our 1-year experience in starting up a Pediatric HSCT program at Ain Shams University in Cairo, Egypt, balancing high quality concurrently with lowering the costs.

Roadmap: Our team started with the training of 3 physicians in 2 prestigious Centers in UK as well as training one Nurse in the biggest HSCT center in Egypt. In Apr 2021, the initial team began by holding BMT meetings to increase the knowledge and skills for young doctors and nurses and development of standard operating procedures as well as increasing awareness among the Pediatric department as regards the indications for transplant. A team was assigned including two Chief consultants as a clinical director and co-director with another two consultants, three senior fellows, two registrars, three nurses and a head nurse, two nutritionists, and one clinical pharmacist. a We collaborated with the stem cell laboratory and the transfusion center. To ensure providing the best services, national and international connections were developed for consultations and shared experiences.

Results: The program started by performing low-risk transplants. Fifteen children underwent transplants, four autologous and 11 allogeneic transplantations (10 matched siblings and one matched related family donor). In addition, two patients received immunosuppressive therapy (IST) for severe aplastic anemia. The main diagnoses for allogeneic transplantation were aplastic anemia (33.3%), β-thalassemia major (20%), one patient with ALL, one with AML and one with HLH. Three patients received autologous SCT for neuroblastoma and one for refractory Hodgkin disease. Seven patients maintained full chimerism after a year follow-up, four suffered acute GVHD and two had VOD with no reported deaths

Conclusions: Establishment of a pediatric HSCT service at a lower cost in resource limited settings is achievable.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P327

HIGH RATE OF COMPLETE HEMATOPOIETIC RECOVERY FOLLOWING CD34 + SELECTED STEM CELL BOOST IN ALLO-HSCT RECIPIENTS WITH PERSISTENT POOR GRAFT FUNCTION

Nerea Castillo[1], Jesus Fernandez-Sojo[1], Elena Valdivia[1], Carmen Azqueta[1], Lluis Martorell[1], Nuria Rubio[1], Ana Garcia-Buendia[1], Monica Linares[1], Gonzalo Ferrer[1], Nadia Garcia-Muñoz[1], Cristina Diaz-de-Heredia[2], Luz Uria[2], M. Isabel Benitez[2], Laura Fox[2], Irene Garcia-Cadenas[3], Alberto Mussetti[4], Ivan Lopez-Torija[3], Joaquin Delgadillo[1], Sergio Querol[1]

[1]Blood and Tissue Bank, Barcelona, Spain, [2]Hospital Vall Hebron, Barcelona, Spain, [3]Hospital Sant Pau, Barcelona, Spain, [4]Institut Catala Oncologia, Barcelona, Spain

Background: Poor graft function (PGF) following allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is a life-threatening complication characterized by bilineage or trilineage blood cell deficiency and hypoplastic marrow with full donor myeloid and lymphoid chimerism in the absence of other explanations. Outcomes of patients with PGF have been very poor, and there are no standardized approaches to treatment.

Methods: We retrospectively investigated the usefulness of a CD34 + SCB without conditioning to treat PGF in children and adult patients who received allo-HSCT for the treatment of malignant and non-malignant diseases. PGF was defined as the need for granulocyte colony stimulating factor (G-CSF) and/or packed red blood cell or platelet transfusion support with full bone marrow donor chimerism. The main outcome of interest was durable complete recovery (CR) of hematopoiesis that was defined as recovery of peripheral blood counts without recurrent need for G-CSF or transfusion support. An additional outcome of interest of the study was overall survival (OS).

Results: A total of 25 patients (13 children and 12 adults) who underwent an allo-HSCT from 2009 to 2021 were included. Median (range) age was 17.8 years (2.4-68) and 15 (60%) patients were male. Underlying diseases were acute lymphoblastic leukemia (n = 5, 20%), acute myeloid leukemia (n = 4, 16%), chronic lymphoproliferative diseases (n = 4, 16%), myelodysplastic syndrome (n = 4, 16%), chronic myeloid leukemia (n = 1, 4%), inherited disorders (n = 2, 8%), bone marrow failure (n = 4, 16%) and primary immunodeficiency (n = 1, 4%). Recipients received grafts from matched related (n = 9, 36%), matched unrelated (n = 4, 16%), mismatched unrelated (n = 5, 20%) and haploidentical donors (n = 7, 28%). In case of an HLA mismatched donor, patients were screened for anti-HLA donor-specific antibodies prior to stem cell transplantation and were all negative. Twelve (48%) patients received myeloablative, 11 (44%), reduced intensity and 2 (8%) intermediate intensity conditioning. Median (range) CD34+ cell dose infused for HSCT was 3.96 x 10^6 /kg (1.01-11.1). Median (range) time of PGF diagnosis from HSCT was 6 months (1.8-12). At the time of PGF diagnosis 8 (32%) patients showed 2 cytopenias and 17 (68%) 3 cytopenias. Median (range) whole blood donor chimerism before the CD34 + SCB infusion was 97.5% (range, 95% to 100%), and all patients had hypocellular bone marrow. With the aim to treat PGF, the whole cohort received CD34 + SCB without previous conditioning. G-CSF–mobilized peripheral blood stem cells were collected from the origin donor used for the initial transplant. Median (range) of CD34 + SCB cell dose was 5.66 x 10^6 /kg (1.03-20.1) and were infused at a median (range) of 5.8 months (1.5-31.7) after HSCT Of total of patients, 6 (24%) received CD34 + SCB with co-infusion of 2 doses of Wharton jelly-derived mesenchymal stem cells at 1 x 10^6/ kg. None adverse events caused by cells infusion were observed. The probability of CR at 60 days was 64% (95%CI 39-78%). With a median (range) follow-up for survivors of 47 months (11.4-158). the overall survival at 2 years was 48% (95% CI: 32-72%).

Conclusions: CD34 + SCB infusion is safe and can provide durable trilineage hematopoietic responses contribute to long-term survival in adult and pediatric patients diagnosed with PGF following allo-HSCT.

Clinical Trial Registry: No.

Disclosure: Authors declare no disclosure of conflict of interest.

1 - Haematopoietic Stem Cells

P328

DESCRIPTION OF THE ACTIVITY OF BONE MARROW TRANSPLANTATION IN A COLOMBIAN BMT UNIT: A SINGLE CENTER EXPERIENCE

Jorge Cuervo-Sierra[1], German Velasquez[1], Sebastian Hoyos-Gutierrez[1], Juan Felipe Jaramillo-Alvarez[2], Jurany Marin-Montoya[1], Maira Mesa-Giraldo[1], Maria Camila Villegas-Osorio[1], Luisa Fernanda Castro-Quintero[1], Deisy J. Giraldo-Gomez[1], Luis Buitrago[3], Willian Castellanos[3]

[1]Clinica Somer Rionegro-BMT Unit, Rionegro, Colombia, [2]Clinica Somer Rionegro, Rionegro, Colombia, [3]Hematology, Medellin, Colombia

Background: There are still no sufficient data about activity of BMT in latin america, the statistics stem mainly of european or North american studies.

We describe the activity in Bone marrow transplantation developed during the years 2017 to 2022 for demographical purposes.

Methods: Retrospective and observational study between january 2017 and november 2022.

Results: We made 205 bone marrow transplantations including 124 autologous, 27 allogenic and 54 haploidentical. All transplants were made using stem cells from peripheral blood after mobilization with G CSF. Only autoimmune diseases (Systemic Sclerosis) used Cyclophosphamide for mobilization. The main indications for BMT were multiple mieloma (63 pts), acute leukemias 60 (31 ALL, 27 AML), Lymphomas 62 (46 Non hodgkin and 16 hodgkin), 7 myeloproliferative syndromes (5 Chronic Myeloid Leukemia, 2 Myelofibrosis), 3 myelodisplasic syndromes, 2 mycosis fungoides, 2 systemic sclerosis, 6 aplastic anemias. The mean age was 43,85 (range 17-73 yo), 54,64% were male (n:112) and 45,36% (n:93) female. The 34% of celular products were cryopreserved and 66% were refrigerated after its obtaining. The median CD34 obtained was 7,551 /kg (range 1,471 – 13,998). The main conditioning regimens were BEAM and Melphalan in autologous setting. The 81,86% of patients had at least one episode of neutrophenic fever during the process of BMT. The infections during the first 30 days were bacterial (87,5 %), viral (6,94%) and fungal(5,55%). The bacterias isolated included E coli (37,87%), staphylococo epidermidis (13,63%), klebsiella pneumoniae (7,53%), streptococo species (13,63%), pseudomonas (3,03%). Between the viruses, the SARS COV2 represented the 4,16% (n:3) and Influenza A (1,38%). The fungal infections with microbiological isolation presented in 4 cases (3 candidemia and 1 disseminated fusarium) reaching just the 5,55% of the total of infections. This rate of fungal infections in our population was inferior to the classical pattern of fungal infections in BMT described in literature.

Within the early complications after BMT the most frequent were mucositis (48,29%), infections (13,17%), acute GVHD (9,87% of allogenic BMT and 3,9% of total BMT) and primary graft failure (4,55%). The median time for the myeloid recovery was 15,5 days (range 8-30 days). Almost all patients needed at least one transfussion post trasplantation mainly of platelets.

Between the total population (n:205) just 27 patients died representing a 13,17% mortality rate.

The survival mean was 227,26 days (range 7-1670 days)

Conclusions: The results of our BMT Unit revealed a similar rate of succes and a low rate of fatal complications between the allogenic and haploidentical BMT.

We need more efforts to join the data of most centers of latin america for obtain real statistic that let us to learn more and improve our work.

Disclosure: nothing to declare.

1 - Haematopoietic Stem Cells

P329

PLERIXAFOR IN AUTOLOGOUS STEM CELL TRANSPLANTATION: DOES IT AFFECT ENGRAFTMENT KINETICS?

Istemi Serin[1], Omur Gokmen Sevindik[2], Berrin Balik Aydin[2], Elif Melek[2], Yasa Gul Mutlu[2], Hulya Bilgen[2], Huseyin Bekoz[2], Leylagul Kaynar[2]

[1]University of Health Sciences, Istanbul, Turkey, [2]Istanbul Medipol University, Istanbul, Turkey

Background: In current mobilization regimens, granulocyte colony-stimulating factor (G-CSF) is used frequently in autologous stem cell transplantation (ASCT), with or without chemotherapy, and forms the basis of mobilization. Plerixafor is preferred in cases where the use of a single G-CSF is insufficient, especially in cases with severe treatment burden and stem cell toxicity due to the treatments utilized before transplantation. Plerixafor increases stem cell mobilization by reversibly binding to the chemokine receptor CXCR4. In our study, we aimed to examine the results of mobilization with plerixafor and G-CSF in our patient group and to reveal their effects on engraftment kinetics.

Methods: All ASCT cases performed in the Adult Bone Marrow Transplantation Unit of Istanbul Medipol University between January 2014 and January 2022 were included in the study. In addition to demographic data of the patients such as age and gender, primary diagnosis, pre-transplant treatment preferences, radiotherapy exposure, lenalidomide usage, mobilization subtypes (chemo-mobilization + G-CSF or G-CSF only ± plerixafor), CD34+ stem cell amounts collected, neutrophil and platelet engraftment status; data such as febrile neutropenia and presence of fungal infection were recorded. Plerixafor was implemented in accordance with the just-in-time usage principles when necessary.

Results: Plerixafor-mobilized patients received more radiotherapy in their previous treatment compared to those without plerixafor ($p = 0.006$). While there was no difference in terms of neutrophil or platelet engraftment failure between patients mobilized with and without plerixafor, it was observed that mean neutrophil and platelet engraftment took longer time in plerixafor-mobilized patients (neutrophil: 12 ± 4.1 vs. 10.2 ± 2.7 days; platelet: 21.6 ± 13.9 vs. 14.2 ± 5.9 days; $p = 0.008$ and $p = 0.002$). The number of febrile neutropenia attacks was found to be statistically significantly higher in plerixafor-mobilized patients ($p = 0.04$). Chemo-mobilized patients with plerixafor had significantly more radiotherapy in their treatment history than those without plerixafor ($p = 0.009$). In this patient subgroup, plerixafor-mobilized patients experienced more febrile neutropenia attacks ($p = 0.04$). While there was no significant difference in terms of engraftment failure, the mean time to both neutrophil and platelet engraftment was longer in patients mobilized with plerixafor (neutrophil: 12.44 ± 4.62 vs. 9.97 ± 2.68; platelet: 21.14 ± 14.04 vs. 13.91 ± 5.65; $p = 0.008$ and $p = 0.01$). In the subgroup of patients with MM, there was no difference in terms of neutrophil or platelet engraftment failure between patients mobilized with or without plerixafor, and the mean time to

platelet engraftment was found to be longer in patients mobilized with plerixafor (18,6 ± 8,01 vs. 12,89 ± 4,01, p = 0.05).

Conclusions: In conclusion, there was no difference in terms of neutrophil or platelet engraftment failure between plerixafor-mobilized patients and others in whole patient group. The time to neutrophil and platelet engraftment was longer in plerixafor-mobilized patients. While there was no significant difference in terms of engraftment failure in chemo-mobilized patients and others, the time to both neutrophil and platelet engraftment was longer in patients with plerixafor. Chemo-mobilized patients with plerixafor received significantly more radiotherapy, but this difference was not observed in G-CSF-mobilized patients.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P330

HEMATOPOIETIC STEM CELL TRANSPLANTS AND TREATMENT OF SEVERE BLOOD DISORDERS: ROLE OF PROVIDERS IN MEDICAL TOURISM

Deepika Khanna[1], Damiano Rondelli[1]

[1]University of Illinois Chicago, Chicago, United States

Background: Hematopoietic stem cell transplants (HSCT) are rapidly becoming the treatment of choice for blood disorders and malignancies, as the procedure is considered curative. However, this treatment is not widely available across the globe and more highly concentrated in high income countries. This creates a global health issue in low and middle income countries (LMICs) where the prevalence of hemoglobinopathies and cancer mortality are higher. The few transplant centers that are established in LMICs have substantially lower costs with similar patient outcomes, offering an opportunity for traveling patients to receive low cost and high quality tertiary care while strengthening LMIC health systems. Medical tourism involves providing international patients with medical services, but little data is present on the role of medical tourism in regard to HSCT services. Over the last 10 years, the University of Illinois at Chicago Blood & Marrow Transplant program has established an international network (GlobalBMT) of LMIC centers, that includes hospitals in Nepal, India, Nigeria, Tanzania, Bolivia, Cuba, Argentina, and Ukraine. This project involves each hospital of the GlobalBMT network to: 1. qualitatively assess the current role of medical providers in international care of HSCT patients and 2. quantitatively and qualitatively assess the current policies of medical institutions for sending and accepting international transplant candidates.

Methods: This is a mixed-methods cross-sectional study with a quantitative component (questionnaire) and a qualitative component (interview). A questionnaire was disseminated to 12 medical providers in 8 countries, who either refer or accept international HSCT patients, to assess the demographics, volume, and frequency of international referrals. We also conducted semi-structured virtual interviews with willing healthcare providers to qualitatively assess the current infrastructure in medical tourism for international HSCT candidates, as well as elicit ways in which this structure can be improved.

Results: Here we will report on the results of the mixed-methods cross-sectional study that was conducted within the GlobalBMT network. In the setting of this research project, we suggest a need for a formalized provider-to-provider framework in the sphere of medical tourism for HSCT patients to be sent outside of their home countries to receive a HSCT, diminishing the impact of third party brokers and misinformation. Our data have uncovered themes in the existing structure of third-party agents searching for a profit, difficulty connecting with home physicians to coordinate care, and limited information for patients on the procedure.

Conclusions: The data collected in this project provide an example of existing structures in medical tourism for HSCT in some LMICs. Gaps in center-to-center patient information, role of middle-men directly contacting patient families, or lack of advanced medical care in LMICs, are some of the relevant findings that based on this initial study could be exploited in a large multicenter international registry study.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P331

MACROPHAGE ACTIVATION SYNDROME AND TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY: A RETROSPECTIVE/PROSPECTIVE SINGLE CENTER STUDY

Roberto Bono[1], Giuseppe Sapienza[1], Stefania Tringali[1], Lucia Sbriglio[1], Giulia Maria Camarda[2], Luca Castagna[1]

[1]A.O.O.R Villa Sofia-Cervello, Palermo, Italy, [2]A.O.U.P 'Paolo Giaccone', Palermo, Italy

Background: Transplant-associated thrombotic microangiopathy (TA-TMA) can associated to high mortality after allogeneic stem cell transplantation (allo-SCT). TA-TMA is characterized by non-immune hemolytic anemia, platelet consumption, and mainly by multi-organ damage due to microvascular occlusion. Macrophage Activation Syndrome (MAS) is another life-threatening syndrome, associated or not to infections or graft versus host disease (GVHD). Diagnosis is difficult leading to variable incidence.

The first aim of this study was to determine the incidence and their outcome of these 2 post-allo-SCT complications.

Methods: All consecutive patients receiving an allo-SCT since September 2021 were included. Even if this is a retrospective study, clinical and biological variables were collected prospectively. Patients were monitored every day for hypertension detection, and one time per week LDH, proteinuria as measured by routine dipstick, and ferritin levels. Renal function was controlled every day starting from day 0. Abnormal values were monitored more frequently.

Diagnostic criteria used for TA-TMA were those proposed by Jodele et al. (except for sC5b-9) complex including LDH above normal, presence of schistocytes, thrombocytopenia, anemia, hypertension, proteinuria above 30mg/dL. Every patient with probable TA-MAT was screened for direct Coombs test.

Diagnostic criteria for MAS were ferritin >10.000 ng/ml and at least one other criterion such as fever, cytopenia, LDH levels, evidence of hemophagocytosis in bone marrow, triglycerides.

Results: Since September 2021 to October 2022, 43 patients received first allo-SCT. The median follow-up was 3.3 months (0.2-10.8). Median age was 50 years (range 19-71). For the whole population, the cumulative incidence (CI) of grade 2-4 acute graft versus host disease (aGVHD) was 14%, CI NRM at 3 months was 10%. The CI of relapse at 3 months was 7%. Overall, 100-day CI of TA-MAT and MAS was 25%. 100-day CI TA-MAT was 11% (4/36). The median time to diagnosis was 21 (range 16-25). In these patients, TA-MAT was considered primary in 1 patient and secondary to active infections in 3 patients. 2 patients were treated with Eculizumab with complete regression. No patients died from TA-MAT.

100-day CI of MAS was 14% (5/36). The median time to diagnosis was 17.6 days (range 14-22 days). The median ferritin levels were 22.390 ng/ml (8.898- >33.510 ng/ml). Other symptoms/signs associated to hyperferritin were fever, diarrhea, increase bilirubin, and triglycerides increase. 2 patients were treated with steroids and iv immunoglobulins, achieving a complete response. No patients died from MAS.

Conclusions: In this retrospective single center analysis, the CI of TA-MAT and MAS was 11% and 14% respectively. Overall, 44% of these patients were treated. Although the incidence can be considered similar to that reported in other studies, the impact on early outcome of TA-MAT and MAS in our cohort was null. It can hypothezed that systematic prospective monitoring for these 2 complications could lead to early identification and treatment initiation. Furthermore, in this cohort, the good prognosis could be related to fact that no patients had concomitant GVHD diagnosis.

Disclosure: no disclosures.

1 - Haematopoietic Stem Cells

P332

A SUCCESSFUL OUTCOME OF DONOR-SPECIFIC ANTIBODIES MITIGATION IN HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Sreejith Ramachandrakurup[1], Beki James[2]

[1]Leeds Teaching Hospitals and NHS Trust, Leeds, United Kingdom, [2]Leeds Teaching Hospitals, Leeds, United Kingdom

Background: Donor-specific antibodies are HLA-type antibodies present in the recipient and directed against antigens in the intended donor. They have significant implications in haematopoietic stem cell transplant (HSCT) as they are associated with graft failure and rejection, especially when directed against haploidentical first-degree relatives (1) when there is a high rate of primary graft failure. The aetiological factors for producing such antibodies include environmental triggers, pregnancy, blood transfusion, and stem cell transplantation (2). There is no consensus on the optimal management of patients with donor-specific antibodies.

Methods: We report our experience of DSA in two siblings transplanted for congenital agranulocytosis in our tertiary care stem cell transplant unit.

Results: Case 1:

AA initially presented as a neonate with hypocalcaemia and hypomagnesemia. At 5 months, he represented with meningitis, ventriculitis and agranulocytosis. He was referred for HSCT, but developed a second life-threatening infection with a large cavitating lesion in the right upper lobe requiring lung resection, prolonged antibiotics and antifungals, and daily infusions of granulocytes. Genetic testing showed only a heterozygous PRF1 gene mutation. His only donor option was his haploidentical father. However, during the workup for HSCT, high titre DSA were detected. Given the urgency of SCT and lack of alternative donors, he was conditioned with ATG (day -4to-2 to), two cycles of plasma exchange (day -3,-2) and a dose of rituximab (day -2). He was then infused with alpha beta-depleted CD34 cells and had a final plasma exchange on day+1. Sequential HLA monitoring showed a continuous decline in Ab. We electively added a CD34-selected stem cell boost at day+16. He engrafted neutrophils and platelets on day+18.

Case 2:

IA, is the younger sibling of AA. Her neonatal period was similarly complicated by hypocalcaemia, hypomagnesemia and a severe progressive agranulocytopenia unresponsive to GCSF. While being worked up for HSCT, she became septic with a large retropharyngeal abscess requiring drainage, antibiotics and multiple infusions of granulocytes in the paediatric intensive care unit. Her haploidentical father was her only donor option. Again, she had a high titre DSA at 23 252MFI. A similar mitigation plan of plasma exchange (given on alternate days) with rituximab and IVIG was employed, with a steady fall in DSA. However, she developed a line infection, and full conditioning could not be started. Her DSA remained <5000MFI, and so as soon as clinically improved, she started conditioning with ATG fludarabine, treosulfan and thiotepa. On the day of alpha beta-depleted peripheral blood cell infusion, she has a sacrificial dose of antigen-positive platelets to mop up residual antibodies. Her neutrophils engrafted on day+15 and platelets on day+21. Both children remain well with 100% and 99% donor chimerism, respectively.

Conclusions: Plasma exchange and IVIG (with antigen-positive platelets in case 2) to remove antibodies, with rituximab and ATG to deplete B and T cells, respectively proved effective in our experience. Both patients had a successful transplant outcome.

Clinical Trial Registry: nil

Disclosure: nil.

1 - Haematopoietic Stem Cells

P333

HLA LOSS RELAPSE DETECTION APPLYING NGS-BASED HLA TYPING: PRELIMINARY RESULTS OF A PROSPECTIVE STUDY

Marta Canelo-Vilaseca[1], Mireia Morgades[1], Christelle Ferrà[1], Maria José Jiménez[1], Elsie Vera-Santiesteban[2], Silvia Mantecón-Ferrer[2], Laura Monday[2], Marta Peña[3], Alberto Mussetti[3], M. Luz Uria-Oficialdegui[4], Maria Isabel Benitez[4], Laura Alonso[4], Cristina Díaz de Heredia[4], Núria Nogués[2], Francesc Rudilla[2], Maria José Herrero-Mata[2], Elena Gómez-Massa[2]

[1]Institut Català d'Oncologia de Badalona, Hospital Universitari Germans Trias I Pujol, Josep Carreras Leukemia Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain, [2]Banc de Sang i Teixits, Barcelona, Spain, [3]Institut Català d'Oncologia, Hospital Duran i Reynals, Barcelona, Spain, [4]Pediatric Hospital Vall d'Hebrón, Barcelona, Spain

Background: Mismatched hematopoietic stem cell transplant (HSCT), specially haploidentical HSCT, is now increasing its use as a treatment modality in hematological malignancies. Nonetheless, relapse is a common cause of treatment failure. HLA loss relapse (HLA-LR) consist of de novo genomic loss of mismatched HLA molecules in re-emerging leukemic cells. In contrast to classical relapse, HLA-LR has usually a later onset and donor lymphocyte infusion (DLI) is no effective as a rescue therapy. Thus, assessing the mechanism of relapse is crucial for guiding therapeutic decisions. The aim of this study is to evaluate the prognostic value and clinical utility of the HLA-LR detection during post-HSCT monitoring by next-generation sequencing (NGS)-based HLA typing.

Methods: Multicenter prospective study which includes 23 selected patients with hematological malignancies and high risk of relapse who undergo a mismatched (≥ 1 HLA incompatibility) HSCT. Post-transplant monitoring was conducted monthly during the first 6 months and every 3 months until 2 years by assessing

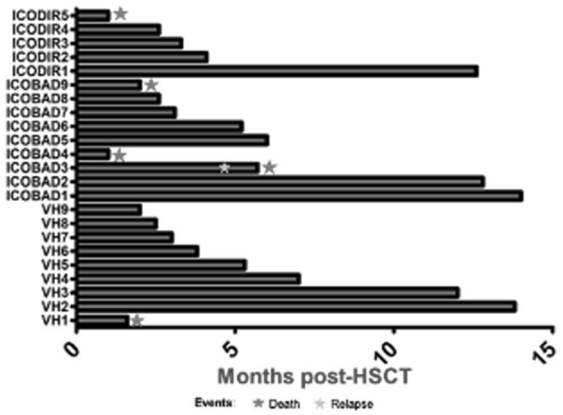
lineage-specific chimerism (also in enriched blasts population when possible) through short tandem repeat (STR) (AmpFLSTR™ Identifiler PCR amplification kit, Applied Biosystems). Samples were obtained from peripheral blood and bone marrow (in some time points). Previously to the beginning of this study, NGS-based HLA typing was optimized and validated for the classification of relapse (classical vs HLA-LR) showing good accuracy, high sensitivity (1.5% in all HLA genes) and complete HLA gene and allele coverage. When mixed chimerism was detected or in case of suspicion of relapse, NGS-based HLA typing was performed in order to detect the presence of patient-specific allele(s). Moreover, in one patient who experienced relapse we retrospectively used NGS chimerism assay NGStrack® (GenDx) in the two samples pre-relapse.

Results: Twenty-three patients were included between July 2021 and October 2022 with a median follow-up of 3.8 months (0.9-12.4). Baseline characteristics are summarized in *Table 1*. At the moment of the present study, only one patient experienced relapse [at 4 months post-HSCT, non-related donor 9/10 (mismatch in HLA-C and DPB1)]. Complete chimerism was observed in the rest of patients. Using NGS-based HLA typing, relapse was classified as classical since recipient-specific HLA alleles were detected in CD34+ enriched cells. Chimerism assessed by STR in CD34+ was 83%D – 17%R in the moment of relapse and 100%D in the previous samples (month 2 and 3 post-HSCT). NGS chimerism detect 99.3%D – 0.7%R at month 2 and 98.56%D – 1.44%R at month 3. The patient received azacytidine but died from an infectious cause and disease progression.

Patients' and HSCT's characteristics [N = 23]		
Age (years)	Median [range]	27 [5–74]
Gender	Male	15 (65%)
Disease	AML / ALL / MDS / CMML	7 (30%) / 12 (52%) / 3 (13%) / 1 (4%)
Status disease allo-HSCT	CR / MRD positive / Molecular relapse	17 (74%) / 3 (13%) / 3 (13%)
Relapses pre-HSCT	≥ 1 / 2 / ≥ 3	13 (56%) / 3 (13%) / 2 (9%)
Stem cells source	PB / BM	19 (83%) / 4 (17%)
Type of donor	Haplo / MUD / MRD	10 (43%) / 10 (43%) / 3 (13%)
HLA compatibility	5/10 / 9/10 / 10/10 (with 10/12)	13/21 (62%) / 7/21 (33%) / 1/21 (5%)
Conditioning	Myeloablative / Non myeloablative / reduced intensity conditioning	17 (74%) / 2 (9%) / 4 (17%)
TNC x 10^8/Kg	Median [range]	4.64 [2.60-12]
CD34 x 10^6/Kg	Median [range]	6.01 [2.36-7.94]
GVHD prophylaxis	CNI + others	6 (26%)
	PT-Cy based	17 (74%)
Events post-HSCT		
Acute GVHD	Any grade / Grade 1-2 / Grade 3-4	17/23 (74%) / 9/17 (53%) / 8/17 (47%)
Relapse	Any type / Classical relapse / HLA-loss relapse	1/23 (4%) / 1/23 / 0/23
Death		5/23 (22%)
Cause of death	Infection / GVHD	4/5 (80%) / 1/5 (20%)

HSCT hematopoietic stem cell transplant; *AML* acute myeloid leukemia; *ALL* acute lymphoid leukemia; *MDS* Myelodysplastic syndrome; *CMML* Chronic myelomonocytic leukemia; *CR* complete response; *MRD* positive: minimal residual disease; *PB* peripheral blood; *BM* bone marrow; *MUD* matched unrelated donor; *MRD* matched related donor; *TNC* total nucleated cell; *CNI* calcineurin inhibitors; *PT-Cy* posttransplant cyclophosphamide; *GVHD* graft versus host disease.

Figure 1. Flowchart of the follow-up's patients included in the study.



Conclusions: Chimerism plus NGS-based HLA typing allowed us to differ classical relapses from HLA-LR; although no HLA-LR were detected in the present study. NGS chimerism could be useful for predicting relapse as it is more sensitive than STR. In the patient who relapsed, loss of chimerism by NGS was detected two months earlier than with the STR-assessed chimerism. Limitations of the study are the small number of patients included and the short follow-up period. Nonetheless, the study is still open to clarify the use of chimerism plus NGS-based HLA typing in clinical practice.

Disclosure: *Nothing to declare.*

1 - Haematopoietic Stem Cells

P334

HSCT ACTIVITY IN A SINGLE CENTER OF BANGLADESH

Abu Saleh[1], Quazi Haq[1], Masba Chowdhury[1]

[1]Evercare Hospital, Dhaka, Bangladesh

Background: Hematopoietic stem cell transplantation (HSCT) offers a potentially curative treatment option for a number of otherwise fatal hematological diseases. In Bangladesh first HSCT took place at Dhaka medical college hospital in 2014, which is a government hospital. In private sector, Evercare Hospital Dhaka (former Apollo Hospitals Dhaka) made the first move to establish HSCT in 2016. We are reporting here the outcome of all transplants done at our center.

Methods: Data were analyzed retrospectively for all patients who underwent HSCT from March, 2016 to September, 2022.

Results: Out of sixty-eight transplant procedure at our center, 26 were allogeneic (including 10 haplo-identical) and 42 were autologous transplants. Most common indication for autologous transplant was multiple myeloma, and for allogeneic transplant was acute myeloid leukemia. Median age of autologous and allogeneic patient's cohort was 39 years and 30 years respectively. For all patient peripheral blood stem cell was used. Conditioning for auto transplant consisted melphalan and BEAM. Both myeloablative and reduced intensity conditioning regimen including total body irradiation (TBI), used in allogeneic patients. Median time of neutrophil engraftment for autologous and allogeneic transplants was 11 days and 14 days respectively. Major early complications were infections, mucositis, and acute graft versus host disease.

Transplant related mortality (TRM) at 100 days was 15.38% with non-relapse mortality 7.6% in allogeneic patients. No patient died

within 100 days of autologous transplantation. Major cause of death was disease relapse and sepsis. 74 % of autologous and 69 % of allogeneic patients are in complete remission. Disease relapsed in 26% and 23% of autologous and allogeneic patients respectively. Disease free survival is is 85% in autologous and 70 % in allogeneic transplants at a median follow up of 12 months.

Conclusions: So far 68 transplants have been carried out till date, which is the largest number of HSCT performed at a single center in Bangladesh. Even during covid pandemic 35 HSCT procedure took place at our center successfully. Our overall results are comparable to many international published reports. Considering rapidly increasing hematologic malignancies in a densely populated country like Bangladesh, more transplant centers needs to be established.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P335

EFFECT OF PHARMACOKINETICS AND PHARMACOGENOMICS IN ADULTS WITH ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION CONDITIONED WITH BUSULFAN

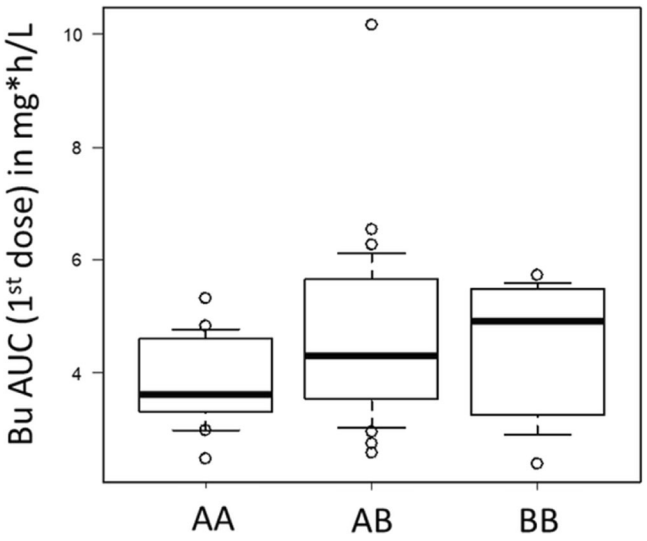
Claire Seydoux[1], Chakradhara Rao Satyanarayana Uppugunduri[2,3], Michael Medinger[1], Tiago Nava[2,3], Joerg Halter[1], Dominik Heim[1], Yves Chalandon[4], Urs Schanz[5], Gayathri Nair[5], Nathan Cantoni[6], Jakob Passweg[1], Marc Ansari[2,3]

[1]Division of Hematology, University Hospital of Basel, Basel, Switzerland and University Basel, Basel, Switzerland, [2]Division of Pediatric Oncology and Hematology, University Geneva Hospitals, Geneva, Switzerland, [3]Cansearch Research Platform for Pediatric Oncology and Hematology, Gynecology and Obstetrics, University of Geneva, Geneva, Switzerland, [4]Division of Hematology, Bone Marrow Transplant Unit, University Hospital of Geneva, University of Geneva, Geneva, Switzerland, Stem-/Immune- Cell-Transplant Unit, University Hospital of Zurich, Zurich, Switzerland, [6]Division of Oncology, Hematology and Transfusion Medicine, Kantonsspital Aarau, Aarau, Switzerland

Background: Busulfan (Bu) combined with cyclophosphamide (Cy) is commonly used as a myeloablative conditioning regimen for allogeneic hematopoietic cell transplantation (allo-HCT). There is inter-individual variability of Bu pharmacokinetics (PK) and hence in toxicity and efficacy. The introduction of therapeutic drug monitoring (TDM) of Bu has decreased toxicity of the regimen. Hepatic metabolism of Bu is mediated through Glutathione-S-Transferases (GSTs), mainly *GSTA1*. Patients with *GSTA1**A variants are considered normal metabolizers and *GSTA1**B corresponds to poor metabolism, defined by the nucleotide changes at -52 or -69 locus in *GSTA1* promoter region.

Methods: The aim of the study was to explore the correlation between *GSTA1* polymorphisms and Bu-PK in 60 adult patients receiving an allo-HCT in the BuCyBu clinical study (ClinicalTrials.gov I, ID NCT01779882) comparing the sequence BuCy to CyBu. DNA samples prior to conditioning were genotyped for candidate variants at -52 (rs3957356) and -69 (rs3957357) loci in the *GSTA1 promoter*.

Results: Thirty-three % of patients were *GSTA1**A*A, 49% *GSTA1**A*B and 18% *GSTA1**B*B. In *GSTA1**A*A patients, median Bu-AUC was 3.6 +/− 0.7 mg*h/L, in *GSTA1**A*B 4.5 +/− 1.6 and in *GSTA1**B*B 4.9 +/− 1.4 (AUC 35% higher than *GSTA1**A*A, $p = 0.03$, with a similar significant correlation with Bu-clearance ($p = 0.04$). The correlation of *GSTA1* polymorphism with AUC remained significant in multivariate linear regression analysis. There was a trend for lower non-relapse mortality (NRM) in patients with low AUC. We could not demonstrate a correlation of *GSTA1* polymorphisms with NRM, acute graft-versus-host disease (aGvHD) in this small cohort, but there is a trend of higher aGvHD incidence in *GSTA1**B*B patients.



Conclusions: PG adds to TDM in terms of safety and effectiveness in intensive chemotherapy regimens.

Clinical Trial Registry: ClinicalTrials.gov I, ID NCT01779882

Disclosure: Conflict of interest : none.

Funding source: Baxter SA, Robapharm / Pierre Fabre SA and CANSEARCH research laboratory

1 - Haematopoietic Stem Cells

P336

SUCCESSFUL TREATMENT WITH GRANULOCYTE TRANSFUSION AND EARLY NEUTROPHIL ENGRAFTMENT IN ALLOGENEIC TRANSPLANT PATIENTS WITH FEBRILE NEUTROPENIA; DOES GRANULOCYTE TRANSFUSION SHORTEN THE NEUTROPHIL ENGRAFTMENT TIME?

Ali Unal[1], Şaziye Esra Tubay[1], Muzaffer Keklik[1], Neslihan Mandacı Şanlı[1], Gülşah Akyol[1]

[1]Erciyes University, Kayseri, Turkey

Background: Febrile Neutropenia is very severe and urgent complication after bone marrow transplantation before engraftment. Infection delays engraftments in these periods. In this study we evaluated the effect and outcome of granulocyte transfusion on febrile neutropenia and neutrophil engraftment in patients receiving allogeneic transplantation.

Methods: Between 2015–2021, thirty-six patients receiving allogeneic bone marrow transplantation (BMT) were treated with granulocyte transfusion at the time of febrile neutropenia before engraftment. Twenty-four patients with AML andtwelves patients with ALL underwent allogeneic transplantation. Twenty-seven of them transplanted from match sibling donors, two from unrelated donor, and sevenfrom mismatch relatives (haploidentical transplantation). They had febrile neutropenia after transplantation, before engraftment. They were given antimicrobial therapy.

Granulocyte was collected from unrelated and same blood groups donors. We gave Granulocyte transfusion for three days. Mean infused granulocyte counts were 3 x 10^10 (1.2 - 4.8x10^10). Before the granulocyte transfusion, on the 12th – 19th days of transplantation, neutrophil counts were 0.02-0.09 x 10^3/dl.

Results: Twenty-four hours after granulocyte transfusion, mean neutrophil counts were 0.7x10^3/dl (0.4-1.2 x 10^3/dl). Neutrophil counts were 2.2 x 10^3/dl, (1.7-2.6 x 10^3/dl) after 48 hours. After 72 hours, neutrophil counts were 3.2 x 10^3/dl. (2.0- 4.6 x 10^3/dl). After 4th days of granulocyte transfusion, 28 patients' were more than 0.5 x 10^3/dl.), and 8patients' neutrophil counts were less than 0.5 x 10^3/dl).

Conclusions: Granulocyte transfusions during the febrile neutropenia in allogeneic transplant patients, helped to better-overcome febrile neutropenia periods. In addition, granulocytes transfusion also did shorten the neutrophil engraftments time. Increased cytokine (G-CSF-GM-CSF-IL3) levels at transfused neutrophils can also affect on shortening of the neutrophil engraftment periods.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P337

OUTCOMES OF ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) IN PAEDIATRIC PATIENTS WITH MALIGNANT DISEASES IN ARGENTINA: IMPACT OF HLA MISMATCH

Silvia Mariana Pizzi[1], Cintia Yanina Marcos[1], Valeria Santidrián[1], Mariana Roizen[1], Germán Carli[1], Analia Juliá[1], Raquel Staciuk[1]

[1]Hospital de Pediatría "Prof. Dr. Juan P. Garrahan", Ciudad Autónoma de Buenos Aires, Argentina

Background: HLA matching is associated with better survival and reduced post-transplant complications including graft-versus-host disease (GVHD). Despite the increasing number of volunteer donors available worldwide, the chance of having a 10 out of 10 matched available unrelated donor (MUD) ranges from 30-79%, depending on patient ethnic background. However, in most cases a 9/10 single HLA-mismatched donor (mMUD) might be available. Objective: This retrospective analysis aims to evaluate the outcomes of 9/10 vs 10/10 HSCT in paediatric patients.

Methods: Retrospective cohort of 67 patients (p) with malignant diseases (ALL, AML, MDS, JMML and CML). The HSCT were performed between January-2014 and December-2020 in a single institution. All p and donors were HLA class I and class II typed using Sequencing technology. Data was obtained by reviewing medical records. Analyzed variables included patient and donors characteristics, transplantation procedure and outcomes.

Results: 39 p (64% male, median age: 7.6 years) received an allele-mismatched unrelated graft and 28 p (64% male, median age: 8.9 years) a full matched HSCT. 36 p were transplanted with class I mismatched donor (16 HLA-A, 16 HLA-B and 4 HLA-C) and 3 p with one HLA-DQ mismatched donor. The SC source was Bone marrow for 62% of the 9/10 UD group and 43% for the 10/10 HSCT group. All patients received myeloablative conditioning with rabbit anti-thymocyte globulin. GVHD prophylaxis consisted of Calcineurin inhibitor combined with methotrexate, except for 1 p (in the mMUD group) who combined Cyclosporine (CsA) with prednisolone and 1 p (in the MUD group) who received CsA with mycofenolate mofetil. The incidence of acute GVHD grades III–IV was similar between both groups (10%). For chronic GVHD the incidence was 28% in 9/10 HSCT vs 35% in p with MUD ($p = 0.5$). Graft failure occurred in 3 p in the mMUD group and in 2 p in the MUD group. Relapse was similar for both the mMUD and the MUD group: 20% vs 21%. TRM in the two groups was: 36% (9/10 HSCT) vs 21% (10/10 HSCT) ($p = 0.2$). The overall survival was 46% in patients with allele-level mismatched donors compared with 54% in patients with a MUD ($p = 0.54$).

Conclusions: Compared to MUD, HLA allele mMUD transplants had a slightly (but not significant) increased risk of TRM. There were no differences between both groups regarding GVHD or relapse. A comparative analysis between mismatches at allele I and II could not be performed because most of the 9/10 transplants were HLA class I allele mismatched.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P338

RESULTS OF ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR RELAPSED AND REFRACTORY ACUTE LEUKEMIA: SINGLE CENTER EXPERIENCE

Irina Kostareva[1], Timur Aliev[1], Nara Stepanyan[1], Yuriy Lozovan[1], Nataliya Burlaka[1], Karina Sergeenko[1], Konstantin Mitrakov[1], Tatyana Potemkina[1], Ramil Fatkhullin[1], Mariya Malova[1], Anna Yelfimova[1], Elena Machneva[1], Meri Shervashidze[1], Nataliya Batmanova[1], Timur Valiev[1], Kirill Kirgizov[1], Svetlana Varfolomeeva[1]

[1]Lev Durnov Research Institute of Pediatric Oncology and Hematology of N.N. Blokhin National Medical Research Centre of Oncology, Moscow, Russian Federation

Background: Allogenic hematopoietic stem cell transplantation (alloHSCT) is effective option for treatment of relapsed/refractory (R/R) acute leukemia. Modern approaches required to improve results of alloHSCT for R/R acute leukemias. We aimed to present our experience of alloHSCT for children with R/R acute leukemias.

Methods: Fifty-one patients were included. Pts. received alloHSCT between January 2021 and October 2022. Median age – 8.7 y.o. (5 months – 17 y.o). M/F = 31/20. Diagnosis: ALL – 32 pts, AML – 17 pts, ABiL – 2 pts. Twenty-six pts. were in second CR, other pts – in first (high risk AML and refractory ALL). All pts. received alloHSCT in CR. Donors: haploidentical – 22 (43.1%), match related donor (MRD) – 19 (37.2%), matched unrelated donor (MUD) – 10 (19.6%). Graft source: BM – 14, PBSC – 37. Graft manipulation: haploidentical – 16 pts. underwent TCRαβ/CD19-depletion and 6 – PtCy. Conditioning regimens: ALL – TBI-based (12 Gy) in 26 pts, busulphan-based in 6 pts; AML/ABiL – treosulfan/thio (n = 10) or treosulfan/melphalan (n = 9) based. Pts. with TCRαβ/CD19-depleted grafts did not received based immunosuppressive therapy (IST) for "graft versus host" disease (GvHD) prevention (only abatacept/tocilizumab). Pts. with MUD/MRD received combined IST with abatacept and calcineurin blockers. Pts. with PtCy received additionally ruxolotinib.

Results: All pts. engrafted with the median engraftment day 13 (9 – 24) after alloHSCT. Seven pts. relapsed (4 are alive now). At the median follow-up period of 13 months (2 – 23 months) the following survival rates received. ALL OS – 78.1%, RFS – 73.4%; AML OS – 70.6%, RFS – 67.5%. GvHD 1-4 gr. rate was 72.5%, GvHD 3-4 gr. – 5.3%. Chronic GvHD developed in 7 children, 5 patients are currently receiving treatment. Infectious

complications: febrile neutropenia – 96%, viral reactivation – 47.3%, mucositis – 78.4%, cystitis – 12.3%. TRM was 6% (GvHD, toxicity). Late mortalities: relapses. No significant difference was found in toxicity and GvHD incidence between haploidentical and MUD alloHSCT.

Conclusions: Our study showed efficacy and tolerability of alloHSCT for R/R acute leukemias treatment. Both TCRαβ/CD19-depletion and PtCy alloHSCT were effective and safe in our study. Most of unsatisfactory results have been associated with relapses. Future studies required to estimate long-time follow-up.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P339

MANAGEMENT OF ADULT PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION IN AN OUT-PATIENT SETTING, THE EXPERIENCE OF THE VENEZUELAN PUBLIC TRANSPLANT CENTER "DR. ABRAHAM SUMOZA"

Laura Saavedra[1], Marcos Hernandez[1]

[1]Dr Abraham Sumoza, Valencia, Venezuela

Background: Due to the high number of patients requiring an auto stem cell transplanst (ASCT) and the lack of resources, there was a need to create an outpatient program that could increase the number of patients treated.

Methods: a retrospective study of all the ASCT performed in the outpatient setting in one year. The criteria to decide which patient was going to be treated as an outpatient were the distance between their houses and the hospital, the conditions of the house, and if they had the means of transport to go to the hospital.

Results: out of the 13 ASCT performed in adults, 6 met the inclusion criteria; 2 with a diagnosis of non-hodgkin lymphoma and received a conditioning regimen with BCNU, ARA-C, etoposide, and melphalan (beam), the rest with a diagnosis of multiple myeloma that received high doses of Melphalan, all patients attended daily to the hospital to receive mobilization drug, conditioning regimen, only three patients stayed in the hospital the night after finishing the high doses of melphalan but were discharged the next morning, all received oral acyclovir and levofloxacin as prophylaxis after the infusion of stem cells, all of which were refrigerated. Every other day the patients attended the hospital by their own means of transport for follow-up. Only 2 patients had to be admitted to the hospital due to fever, one who lived the farthest from the hospital, and the other one had received BEAM, however, both cases responded quickly to first-line antibiotics and were discharged within 5 days. The rest of the patients did not present any major complications besides mucositis and gastrointestinal mild discomfort. All patients lived on average 9 km away from the hospital, all attended by car tothe hospital, and lived in houses with access to electricity, running water, and one bathroom at least, and the care was provided by their relatives. Only 2 patients required admission to the hospital due to fever but no germs were isolated in the cultures and both responded to first-line treatment, with the rest of the patients only complaining of gastrointestinal symptoms. The reason only three patients stayed in the hospital was that the melphalan

infusion and cryotherapy finished late at night, so they were allowed to stay until the next morning, and none of those patients developed an infection.

The strategy used in our center is different from others because the patients remain in their houses which is an uncontrolled environment, and there was no medical or nurse staff who could evaluate the patients at their homes.

Conclusions: This strategy has proven to be effective, safe, and affordable for patients and it will continue to be implemented by our center.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P340

NON TBI BASED T CELL REPLETE HAPLO-IDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH POST TRANSPLANT CYCLOPHOSPHAMIDE – EARLY EXPERIENCE FROM A NEWLY ESTABLISHED CENTER IN INDIA

Divya Doval[1], Dharma Choudhary[1]

[1]Sanar International Hospital, Gurugram, India

Background: Hematopoietic stem cell transplantation (HSCT) is the only curative treatment for various severe hematological disorders. However, only 25% of patients have an HLA-matched sibling donor and the prohibitive cost of unrelated donors makes it unaffordable in developing countries. Haploidentical related donors are readily available as an alternate source of stem cells. TBI based regimes have been commonly used in Haplo HSCT in the past.

We report herein early experience of haplo-HSCT using non TBI based T-cell replete graft with post transplant Cyclophosphamide (PTCy) in patients with hematological disorders.

Methods: This is a retrospective, single-center study investigating outcomes of haplo-HSCT in 10 consecutive patients with hematological disorders that underwent transplant between July 2022 and December 2022 in a newly established bone marrow transplant unit. The detailed characteristics of the patients and transplant are summarised below.

A total of 10 patients underwent haploidentical HSCT with a median age of 23.5 years (3-54 years) of which five were female and 5 were male. Diagnosis ofthese patients were Acute lymphoblastic leukemia in 4 patients, 2 had Acute myeloid leukemia, 2 had Severe aplastic anemia, one had refractory T-NHL and one had Thalassemia major. The disease status at the tme of transplant was CR1 in 3 patients, CR2 in 3, 3 patients were transfusion dependent and one had refractory disease. PBSC collection was done for all 10 patients. In none of the transplants there was a female donor to male recipient infusion. Donor–recipient CMV status was positive for all transplants. Conditioning chemotherapy was Thio/Flu/Bu3 in 6 patients, Flu/Cy/Mel +/- Thymo in 2 patients, Flu/Bu/Thymo in 1 and Flu/Bu/Cy/Thymo in 1 patient. Nine patients received PTCy-Tac-MMF as GvHD prophylaxis and one patient got PTCy-CSA-MMF.

Results: The median follow-up period of study was 48 days (range,7-169 days). The overall survival (OS) and disease-free survival (DFS) were 70 % and 70%, respectively. There was no graft failure. The incidence of grades 2 to 4 acute graft-versus-host disease (GVHD) was 10 %, chronic GVHD was 10%. One patient developed CMV colitis and CMV reactivation was noted in 40 %. Two patients developed BK virus related haemorrhagic cystitis. All 3 patients that expired before engraftment due to sepsis within 10 days of stem cell transplant. Further details of the results are given in table 2.

Table 2. Results

	All patients(n = 10)
CD 34 cell dose Median(range)	15.55 (6.46-23.78)
Neutrophil engraftment(days) Median (range)	14 (13-20)
Platelet engraftment (days) Median (range)	21 (15-90)
Primary graft failure	0
Secondary graft failure	0
Acute GvHD	1
Chronic GvHD	1
CMV reactivation	4
Haemorrhagic cystitis	2
Blood c/s positive sepsis	3
Expired	3
Rejected	0
DFS	70%
OS	70%

Conclusions: T cell replete haploidentical stem cell transplant using a non TBI based regime is a feasible option in patients with no available HLA matched donor. Long term follow up is required for better understanding of the outcome of these patients.

Disclosure: Nothing to declare.

1 - Haematopoietic Stem Cells

P341

SUCCESSFUL HAPLO-IDENTICAL HSCT FOR HODGKIN LYMPHOMA AFTER 4TH RELAPSE

Abu Jafar Saleh[1], Dr. Menoti Paul Mukti[1], Masba Uddin Chowdhury[1], Quazi Smita Haq[1]

[1]Evercare Hospital Dhaka, Dhaka, Bangladesh

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment option for patients with relapsed/refractory(R/R) Hodgkin lymphoma (HL), that relapse after autologous hematopoietic stem cell transplantation (Auto-HSCT). Haplo-identical hematopoietic stem cell transplantation (haplo-HSCT) is a promising treatment modality, especially for whom, suitable matched sibling or unrelated donor is unavailable.

Methods: We are reporting a case of 20-years-old male, diagnosed as nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). Following diagnosis, he received 6 cycles of R-CHOP, 2 cycles of GDP followed by autologous transplantation with BEAM conditioning. Then he had relapse after 16 months of achieving a PET negative complete remission with auto-HSCT. At this stage, he was started treatment with immune checkpoint inhibitor (ICI), nivolumab and remained refractory to it even after 12 cycles necessitating an urgent allo-HSCT. Haplo-identical transplant was the only feasible alternative for this patient in the absence of a matched sibling donor. So he underwent a successful haplo-HSCT using Fludarabine/Melphalan/Thiotepa/ ATG based RIC regimen following two cycles of Obinituzumab-GDP combination salvage therapy at Evercare Hospital Dhaka. Post-transplant immunosuppressive was given with cyclosporin/ MMF/PTCy (post-transplant-cyclophosphamide) to prevent GvHD.

Results: The patient developed chronic gut GvHD after six months of transplant which improved with intravenous methyl-prednisolone. During a follow up period of 12 months, this patient is doing well in a state of complete remission.

Conclusions: This case highlights the challenges involved in treating a patient with R/R Hodgkin lymphoma, who relapsed from several chemotherapy regimens, as well as after auto-HSCT. He did not even achieve response to immune checkpoint inhibitor (ICI), nivolumab. This report creates huge scope for haplo-identical transplantation in difficult-to-treat R/R HL patients lacking HLA identical donor.

Disclosure: There are no present or potential conflicts of interest.

23 - Haemoglobinopathy

P342

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC SICKLE CELL DISEASE WITHIN THE POST-TRANSPLANT CYCLOPHOSPHAMIDE ERA

Lisa Oostenbrink[1], Frans Smiers[1], Anja Jansen-Hoogendijk[1], Marco Schilham[1], Arjan Lankester[1], Alexander Mohseny[1]

[1]Leiden University Medical Center, Leiden, Netherlands

Background: Hematopoietic stem cell transplantation (HSCT) delivers an unequaled curative potential for patients with sickle cell disease (SCD). HSCT outcomes are excellent for SCD patients transplanted by using HLA-matched donors, however these are not available for the majority of patients. The use of HLA-mismatched (un)related donors is historically associated with a higher incidence of transplant-related complications and mortality mainly related to graft-versus-host-disease (GVHD). The use of post-transplant cyclophosphamide (PT-CY) has been reported to effectively prevent GVHD and improve HSCT outcome with mismatched donors in patients with malignant and non-malignant diseases.

Methods: We here report our experience with the PT-CY approach in mismatched related and unrelated donor HSCT in pediatric SCD patients treated with a fludarabine-treosulfan-thiotepa -reduced toxicity- conditioning regimen in combination with individualized ATG. We compared these outcomes with those of patients treated by HLA matched donors (HLA-identical related or 10/10 matched unrelated) without PT-CY treatment. Thirty-five children (age 2-18 years, with a mean age of 10 years at HSCT) treated by thirty-six transplantations (n = 6 HLA-identical sibling donors; n = 8 10/10 matched unrelated donors; n = 13 9/10 mismatched unrelated donors; n = 1 9/10 mismatched other related donor; n = 4 8/10 mismatched unrelated donors and n = 4 haplo-identical mismatched related donors), who received a non-depleted bone marrow graft between May 2018 and October 2022 were included with a mean follow-up time of 26 months (range 2-50 months in the matched group and 6-56 months in the PT-CY mismatched group).

Results: Main outcomes, including overall survival (OS), event free survival (EFS) and GvHD were not inferior in the mismatched PT-CY group as compared to the matched group (OS 92,9% and EFS 92,9% in the matched group vs OS 100% and EFS 95,5% in the PT-Cy group; aGVHD grade II-IV 14% and extensive cGVHD 14% in the matched group vs aGvHD grade II-IV 5% and extensive cGVHD 0% in the PT-Cy group). Despite slightly delayed neutrophil engraftment, T- and NK-cell recovery and more viral reactivations in the PT-CY group, this did not result into more infectious complications.

Conclusions: We conclude that in the absence of an HLA-identical family or a matched unrelated donor, HSCT by using a mismatched unrelated or haploidentical related donor in the context of individualized ATG plus PT-CY can be considered as an equally safe and effective treatment option for pediatric SCD patients.

Disclosure: Nothing to declare.

23 - Haemoglobinopathy

P343

HLA ALLELE AND HAPLOTYPE FREQUENCIES IN SICKLE CELL DISEASE AND THALASSEMIA PATIENTS: A JOINT STUDY ON BEHALF OF EUROCORD AND SFGM-TC

Graziana Maria Scigliuolo[1,2], Barbara Cappelli[1,2], Wahid Boukouaci[3], Marie Robin[4,5], Stéphanie Nguyen[5,6], Nicole Raus[5], Nathalie Dhedin[7], Regis Peffault de Latour[8], Christine Devalck[9], Jean-Hugues Dalle[10], Pierre Quartier dit Maire[11], Olivier Hermine[12], Marie Ouachée Chardin[13], Xavier Poiré[14], Bénédicte Brichard[15], Catherine Paillard[16], Yves Beguin[17], Dominique Plantaz[18], Benedicte Bruno[19], Ibrahim Yakoub-Agha[20], Jean-Henri Bourhis[21], Fernanda Volt[2], Monica Rivera Franco[2], Hanadi Rafii[2], Chantal Kenzey[2], Ching-Lien Wu[3], Jihène Bouassida[3], Vanderson Rocha[2,22], Annalisa Ruggeri[2,23], Ryad Tamouza[2,3], Eliane Gluckman[2,1]

[1]Monacord, Centre Scientifique de Monaco, Monaco, Monaco, [2]Eurocord, Hopital Saint Louis, APHP, IRSL EA3518, Université de Paris Cité, Paris, France, [3]Laboratoire Neuro-Psychiatrie Translationnelle, INSERM U955, IMRB, et APHP, Hôpital Henri Mondor, Créteil, France, [4]Service d'Hématologie-Greffe, Hôpital Saint-Louis, APHP, Université de Paris-Cité, Paris, France, [5]Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC), Pierre-Bénite, France, [6]Hématologie clinique, CHU Pitié Salpêtrière, Paris, France, [7]Service d'Hématologie Adolescents Jeunes Adultes, Hôpital Saint Louis, APHP, Paris, France, [8]Service d'Hématologie-Greffe, Hôpital Saint-Louis, APHP, Université de Paris Cité, Paris, France, Université Libre de Bruxelles, Bruxelles, Belgium, [10]Hôpital Robert Debré, GH-APHP -Nord Université de Paris, Paris, France, [11]AP-HP, Hôpital Necker-Enfants-Malades, Paris, France, [12]AP-HP, Hôpital Necker, University of Paris, Paris, France, [13]Institute of Pediatric Hematology and Oncology (IHOPe), Lyon, France, [14]Section of Hematology, Cliniques Universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium, Cliniques Universitaires Saint Luc, Brussels, Belgium, Hopital de Hautepierre, Strasbourg, France, Division of Hematology, University of Liège, Liège, Belgium, University Hospital Grenoble, Grenoble, France, [19]Service de Pédiatrie - Unité d'Hémato-Oncologie, CHRU de Lille - Hôpital Jeanne de Flandre, Lille, France, [20]CHU de Lille, Univ Lille, INSERM U1286, Infinite, Lille, France, [21]Institut Gustave-Roussy, Service d'Hématologie, Villejuif, France, Hospital das Clínicas, São Paulo University, Sao Paulo, Brazil, [23]Hematology and Bone Marrow Transplant Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

Background: The biological implications of the human leukocyte antigen (HLA) haplotypes in complications after hematopoietic stem cell transplant (HCT) in patients with hemoglobinopathies are not well defined. Thus, the aim of this study was to analyze the HLA haplotype frequencies in patients transplanted for hemoglobinopathies in order to identify the most common haplotypes. This information might give a better overview of the probability of finding unrelated HLA matched donors for these patients in worldwide donor registries.

Methods: Eurocord/EBMT and Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) databases were retrospectively screened to obtain the HLA alleles and haplotypes of patients undergoing an HLA-matched sibling donor HCT, with any graft source, from 2000 to 2019. HLA genotypes of patients with sickle cell disease (SCD, N = 282) or thalassemia (N = 60), transplanted in EBMT centers in French speaking countries were collected.

For this preliminary study, low-resolution typing of HLA-A, -B, and -DRB1 was considered to standardize the data, even if high-resolution typing and HLA-C were available for some patients. Descriptive statistics was performed using Microsoft Excel, SPSS v.28 and R v.3.5.3. The public Easy-HLA website was used to generate HLA haplotypes according to HLA alleles.

Results: SCD patients:

Four hundred five different HLA-A-B-DRB1 haplotypes were identified among 564 total haplotypes of 282 SCD patients. The five most frequent were: HLA- A*34-B*44-DRB1*15 (n = 9, 1.59%), HLA- A*30-B*14-DRB1*15 (n = 8, 1.42%), HLA- A*36-B*53-DRB1*11 (n = 7, 1.24%), HLA- A*66-B*58-DRB1*13 (n = 7, 1.24%), and HLA-A*66-B*58-DRB1*15 (n = 7, 1.24%).

The distribution of HLA-A, -B, and -DRB1 alleles per se revealed that HLA-A*02, HLA-B*15, and HLA-DRB1*15 were the most frequent alleles in the studied population.

Thalassemia patients:

One hundred and eight different HLA-A-B-DRB1 haplotypes were identified among 120 total haplotypes of 60 thalassemia patients. The three most frequent were: A*01-B*08-DRB1*03, A*24-B*35-DRB1*11, and A*30-B*13-DRB1*07; all of which were observed three times, with a frequency of 2.5%. The most frequent HLA alleles were A*02, B*44, and DRB1*11.

The five most frequent HLA haplotypes in SCD patients greatly differed from the ones observed in thalassemia patients; none of them coincided. This difference could be attributed to the different ancestries of the two subpopulations that reflect the origin and evolution of the underlying genetic defects.

Conclusions: Our study shows that the genetic diversity of the HLA system in sickle cell disease population poses practical challenges to find HLA-matched unrelated donors for these patients. Less diversity was observed in patients with thalassemia consistent with these patients' ancestries.

This study underlines the importance of increasing the recruitment of potential donors of African descent in cord blood banks and hematopoietic stem cell donor registries.

Disclosure: Nothing to declare.

23 - Haemoglobinopathy

P344

FEASIBILITY AND SAFETY OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN SICKLE CELL DISEASE PATIENTS WITH ADVANCED KIDENY AND LIVER DISEASE

Israa Saib[1,2,3], Bader Alahmari[1,2,3], Ahmed Alaskar[1,2,3], Ayman Hejazi[1,2,3], Giamal Gmati[1,2,3], Hend Salama[1,2,3], Abdulrahman Al raiza[1,2,3], AS Al Saleh[1,2,3], Ayman Ibrahim[1,2,3], Mohammed Bakkar[1,2,3], Abdul Rauf Ghouri[1,2,3], Tahani Alanazi[1,2,3], Rasha Taher[1,2,3], Inaam Shehabeddine[1,2,3], Suha Alkhraisat[1,2,3], Amani Alharbi[1,2,3], Isam Mahasneh[1,2,3], Maybelle Ballili[1,2,3], Ahmed Alharbi[1,2,3], Somaya Aljohani[1,2,3], Zied Aljubour[1,2,3], Mazen Ahmed[1,2,3], Husam Alsadi[1,2,3], Mohsen Alzahrani[1,2,3]

[1]King Abdulaziz Medical City, Riyadh, Saudi Arabia, [2]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, [3]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Background: Sickle cell disease (SCD) can lead to different organs damage with variable degree of severity. Patients with

advanced organ damage such as end stage renal disease (ESRD) on dialysis or liver cirrhosis or severe cholestasis are at increasing risk of mortality. Allogeneic Hematologic Cell Transplant (AlloHCT) is a curative option for patients with severe SCD including patients with sickle hepatopathy or nephropathy. However, most of these patients are excluded from AlloHCT because of increased risk of transplant related mortality (TRM) and morbidities (e.g. VOD, liver decompensation, PRES, HTN). Additionally it is challenging to manage transplant medications pre and post-transplant. We aim from this study to demonstrate safety and efficacy of chemotherapy free non-myeloablative regimen in patients with ESRD and advanced liver disease secondary to SCD.

Methods: Following IRB approval, we conducted a retrospective analysis of adult SCD patients with underlying sickle nephropathy or hepatopathy that underwent AlloHCT from January 2015 to February 2022 at our center. Treatment protocol: the conditioning regimen was non-myeloablative with Alemtuzumab (1mg/kg) divided over 5 days on day -7 to -3 and total body irradiation 300cGy on day -2 or -1. Peripherally mobilized stem cells from HLA matched related donor targeting $10x10^6$/kg of CD34 cells were used. For graft versus host disease (GVHD) prophylaxis; Sirolimus was started on day -1 until one year post transplant. Prophylactic antimicrobial were used as per reported guidelines. Additional measure for these patients were applied to reduce toxicities and prevent complications.

Primary objective: Day 100 and one year TRM. Secondary objective: One year overall survival (OS) and event free survival (EFS): defined as graft failure, disease relapse or death.

Results: A total of 12 patients were included, 6 patients had sickle cell nephropathy requiring hemodialysis or peritoneal dialysis and 6 patients with liver cirrhosis or severe cholestasis. Other causes of renal failure and chronic liver disease were excluded by referral and work up by appropriate services. Median age was 29.5 years. Transplant procedure was tolerated very well and all patients had successful engraftment. Duration of hospitalization was 39 days similar to our historical result for other patients. There was 2 ICU admissions for short period. PRES and high BP was observed in 2 patients with ESRD. No patients with liver disease developed VOD or liver decompensation.

Day 100 and one year TRM was zero%. One year OS and ES was 100%. All patients with liver disease improved their liver function tests with baseline direct bilirubin 199.3 umol/L and 1 year post transplant 14.7 umol/L. Patients with ESRD stabilize their kidney function and one patient underwent kidney transplant 18 months post AlloHCT. Other patients are considered for kidney transplant.

Table 1 list baseline laboratory data and follow up values after 1 year

Number of patients	12
Gender	F 7 / M 5
Age (median) years	29.5 (14 – 41)
Sickle hepatopathy (Cirrhosis/Severe cholestasis)	5
Sickle nephropathy (ESRD on dialysis)	5
Other indications	• Recurrent VOCs: 5 patients • ACS: 1 patient • Silent stroke: 2 patients • AVN: 2 patients • Pulmonary HTN: 1 patient
Median follow up post-transplant	26.3 months (64.7-11)
ANC engraftment	18.5 days (16-27)
Platelet engraftment	28.5 days (13-51)
Duration of hospitalization	39 days (32-58)
Hemoglobin g/L	• Pre transplant: 55.5 g/L • 1 year post: 135.5 g/L
Hemoglobin S %	• Pre transplant: 37.1 % • 1 year post: 34.4 %
T Bilirubin (for patients with sickle hepatopathy)	• Pre transplant: 309 umol/L • 1 year post: 17 umol/L
D Bilirubin (for patients with sickle hepatopathy)	• Pre transplant: 199.3 umol/L • 1 year post: 14.5 umol/L
1 year chimerism (median)	• Whole 89% • Myeloid 99% • Lymphoid 37.5%
Graft failure	0
1 year EFS	100%
1 year survival	100%
Complications	• CMV infection: 3 patients • PRESS syndrome: 2 patient • VZV infection: 2 • Poor engraftment: 2 patients

Conclusions: In SCD with end organ damage either nephropathy or hepatopathy, a non-myeloablative conditioning regimen before AlloHCT is safe and well tolerated. This is the only transplant protocol suitable for these patients. Longer follow up and further expansion of this cohort is needed.

Disclosure: Nothing to disclose related to this study.

23 - Haemoglobinopathy

P345

THE EFFECT OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PEDIATRIC PATIENTS WITH BETA-MAJOR THALASSEMIA

AmirAli Hamidieh[1], Leila Jafari[1], Homa Kashani[2], Parisa Naji[1], Yalda Karamlou[1], Leila Hejazipour[1], Hamideh Kaykani[1], Fatemeh Hematyar[1], Maryam Behfar[1]

[1]Pediatric Cell and Gene Therapy Research Center, Gene, Cell and Tissue Research Institute, Tehran University of Medical Science, Tehran, Iran, Islamic Republic of, Institute for Environmental Research, Tehran University of Medical Science, Tehran, Iran, Islamic Republic of

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is the only definitive curative option for β-major thalassemia patients (β-MT) in most countries of the world. However, HSCT has considerable complications in these patients. Posterior reversible encephalopathy syndrome (PRES) is a pervasive neurological complication which typically ensues HSCT. Some studies indicate that the adoption of immunosuppressive drugs and calcineurin inhibitors (CNI) for graft-versus-host-disease (GvHD) prophylaxis might be a major determinant in post-HSCT neurological complications. Since β-MT patients are prone to higher GVHD incidence compared to other hematologic and non-hematologic disorders, they need to partake long-term or high dose immunosuppression therapy with CNI after HSCT; hence, these patients must be evaluated for PRES after HSCT.

Methods: In our study, we included 89 (53 males and 36 females) β-MT pediatric patients who underwent HSCT between March 2013 and August 2015 in our Center. The mean age of patients at the time of HSCT was 8.4 (range,3-14) years. Nine patients had β-MT class I (10.1%), 53 patients had β-MT class II (59.6%) and the remaining patients had β-MT class III ($n = 27$, 30.3%). All patients transplanted with full HLA-matched donor; 69 (77.5%) patients were transplanted with HLA-matched sibling, 13

(14.6%) from other related and 7 (7.9%) patients received cells from an unrelated donor. The graft source was peripheral blood stem cells in 60 patients, whereas only 25 and 4 patients received bone marrow and cord blood stem cells, respectively. All of the patients received myeloablative conditioning regimens (MAC) depending on the β-MT class based on Busulfan, Cyclophosphamide with and without Rabbit ATG. Cyclosporine and Methotrexate were also used as a GVHD prophylaxis. Brain imaging using magnetic resonance imaging (MRI) was performed on individuals who were suspected to have developed seizure and PRES. Patients were followed for 5 years.

Results: In tandem, based on our findings, engraftment occurred in all patients. On average, neutrophils and platelet engraftment transpired (occurred) in 89 patients, 10 and 15 days after HSCT, respectively. The clinical imaging findings in 10 pediatric patients, which represent 11.2% of the cohort, corroborated the diagnosis of PRES.

In the group that developed PRES, 8 out of 10 had β-MT-III and in the non-PRES group, 19 out of 79 patients had β-MT-III. Additionally, acute graft versus host disease (aGVHD) occurred in 100% and 53% of patients in the PRES and non-PRES group, respectively. Statistical analysis showed a significant difference between aGVHD and PRES occurrence (P value < 0.004). Additionally, 3 (30%) and 15 (19%) of patients manifested symptoms of chronic GVHD (cGVHD). No significant correlation existed between cGVHD and PRES (P value = 0.68). The results of the Kaplan-Meier analysis revealed that the 5-year overall survival (OS) was 45% in the PRES group versus 92% in the non-PRES group was statistically significant between the two groups (P value < 0.0001).

Conclusions: The main point of our study was correlation between β-MT-III and PRES development. Additionally, aGVHD was significant risk factor for PRES development. It is better to revise the PRES term nomenclature because of it sometimes can be associated with poor prognosis after HSCT.

Disclosure: Nothing.

23 - Haemoglobinopathy

P346

ALEMTUZUMAB REVERSES SECONDARY GRAFT REJECTION IN ALLOGENEIC STEM CELL TRANSPLANTATION IN PATIENTS WITH SICKLE CELL DISEASE

Erfan Nur[1,2], Elisabeth Dovern[1], Adetola A. Kassim[3], Bart J. Biemond[1], Daniel Dexter[4], Adam Gassas[4], Leena Karnik[4], Josu de la Fuente[4]

[1]Amsterdam University Medical Centers, location AMC, Amsterdam, Netherlands, [2]Sanquin Research and Landsteiner Laboratory, Amsterdam, Netherlands, [3]Vanderbilt University School of Medicine, Nashville, United States, [4]St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is the only established curative treatment for sickle cell disease (SCD). Graft rejection is a frequent complication of HSCT in SCD patients, especially in the setting of non-myeloablative conditionings and alternative donor (e.g. haploidentical) transplantation. Graft rejection, mediated by host immune cells attacking donor stem cells, is a severe complication associated with impaired autologous reconstitution, clonal hematopoiesis and development of myeloid malignancies (J Clin Med. 2022 Jun 2;11(11):3160). Options to treat graft failure are limited, with no consensus in the literature for its management. Earlier strategies to reverse impending graft rejection, such as adding other immunosuppressive drugs, have proven disappointing, especially when the process is advanced. Donor lymphocyte infusions have shown limited efficacy and have an increased risk of graft-vs-host disease limiting its use in non-malignant diseases. The anti-CD52 monoclonal antibody alemtuzumab induces lymphodepletion, thereby eliminating the proliferating recipient-derived lymphocytes and providing an opportunity for donor-derived stem cells to thrive and produce donor-derived blood cells, including lymphocytes, when there is a low and decreasing donor T-cell chimerism but still a donor-majority myeloid chimerism (marrow stem cell compartment). We hypothesized that lymphodepletion with alemtuzumab can reverse the immunologic mediated graft rejection following HSCT for SCD.

Methods: We describe 6 patients transplanted between July 2016 and February 2022 with progressive graft rejection who were treated with alemtuzumab as rescue therapy. Graft rejection was recognized as decreasing donor chimerism mostly with the recurrence of cytopenia's after initial engraftment.

Results: Patient 1, who had undergone a non-myeloablative haploidentical bone marrow transplant (haploBMT), developed decreasing blood counts and donor T-cell chimerism at Day +87. Alemtuzumab 1mg/kg was started at Day +150, following which donor T-cell chimerism and donor-derived blood counts gradually increased. Immunosuppression was successfully discontinued at Day +496. Patient 2, who received haploBMT and developed decreasing donor T-cell and myeloid chimerism with donor myeloid chimerism of 20% at the time of alemtuzumab administration, did not respond to alemtuzumab and soon developed secondary graft failure with autologous reconstitution. Patient 3 demonstrated a gradual decrease of donor chimerism and graft function starting at Day +67 following a myeloablative matched sibling donor (MSD) BMT. Treatment with alemtuzumab resulted in a robust increase in donor chimerisms and normalization of donor-derived blood counts. Patients 4 and 5, who had undergone non-myeloablative (alemtuzumab/TBI) MSD transplantations, demonstrated rapidly emerging cytopenia's with low donor T-cell chimerism, though robust myeloid chimerism. Alemtuzumab rescue (1mg/kg) led to prompt reversal of graft rejection. Patient 6, non-myeloablative HSCT, had a gradual decrease of both myeloid and T-cell donor chimerism. Alemtuzumab rescue at day +188 resulted in stabilization of donor myeloid chimerism at around 55%. There were no CMV or EBV reactivations or other infectious complications in the patients after alemtuzumab treatment.

Conclusions: Alemtuzumab can reverse the immune mediated graft rejection after HSCT in patients with SCD. A relatively high donor myeloid chimerism seems to be a prerequisite for a successful reversal of graft rejection by alemtuzumab. This approach needs to be evaluated in a larger cohort of patients.

Disclosure: Nothing to declare.

23 - Haemoglobinopathy

P347

NON-MYELOABLATIVE HAPLOIDENTICAL BMT WITH PTCY FOR CHILDREN AND ADULTS WITH SICKLE CELL DISEASES: THE BRAZILIAN EXPERIENCE

Carmem Bonfim[1], Belinda Simoes[2], Roseane V. Gouveia[3], Roberto Luiz Silva[4], Lauro Augusto C. Leite[4], Juliana Folloni Fernandes[5], Julia Lopes Garcia[5], Victor Gottardello Zecchin[6], Maria Lucia Lee[6], Cilmara Kuwahara[7], Alessandra Araujo Gomes[4], Celso Arrais Rodrigues[8], Samantha Nichele[9], Gisele

Loth[1], Valeria Cortze Ginani[10,11], Joao Vitor Feliciano[12], Alberto Cardoso Martins Lima[13], Luiz Guilherme Darrigo Jr.[2], Josu De La Fuente[14], Adetola Kassim[15], Adriana Seber[11]

[1]Federal University of Parana, Curitiba, Brazil, [2]Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, Brazil, [3]Hospital Sao Camilo, Sao Paulo, Brazil, [4]Hospital 9 de Julho, Sao Paulo, Brazil, [5]Instituto de Tratamento do Cancer Infantil (ITACI), Sao Paulo, Brazil, [6]BP - Beneficiencia Portuguesa Sao Paulo, Sao Paulo, Brazil, [7]Hospital Pequeno Príncipe, Curitiba, Brazil, [8]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [9]Hospital Nossa Senhora das Graças, Curitiba, Brazil, [10]Pediatric Oncology Institute, Federal University of Sao Paulo, Sao Paulo, Brazil, [11]Hospital Samaritano, Sao Paulo, Brazil, [12]Hospital de Base Sao Jose do Rio Preto, Sao Jose do Rio Preto, Brazil, [13]Immunogenetic Laboratory, Federal University of Parana, Curitiba, Brazil, [14]Imperial College Healthcare NHS Trust, St Mary's Hospital, London, United Kingdom, [15]Vanderbilt-Meharry Sickle Cell Disease Center of Excellence, Vanderbilt University School of Medicine, Nashville, United States

Background: Haploidentical (haplo)donors have expanded the donor pool for patients with sickle cell disease. Non-myeloablative conditioning regimen can further allow patients with established comorbidities to receive this curative treatment. The optimal conditioning regimen is yet to be determined in the non-myeloablative haploidentical setting. In 2013, a multi-institutional Vanderbilt Global Haploidentical Learning Collaborative to optimize haplo-BMT for SCD was established. Brazilian group joined the consortium in 2019. Two conditioning regimens were defined, with thiotepa (THIO) and without Thiotepa with an increased 4 Gy TBI dose (TBI-only) (Bolaños-Maede et al. *Lancet Haematol* 2019). In Brazil, THIO, is not available in the public system. The study aimed to evaluate outcomes after haplo-BMT using both conditioning regimens.

Methods: The THIO regimen consisted of thymoglobulin 4.5 mg/kg, thiotepa 10 mg/kg, fludarabine (FLU)150 mg/m^2, cyclophosphamide 29mg/kg, and TBI2Gy. The TBI-only regimen included TBI to 4 Gy, no Thiotepa. Graft-versus-host disease (GVHD) prophylaxis consisted of post-transplantation cyclophosphamide (PTCy)100 mg/kg, mycophenolate mofetil, and sirolimus. Primary(PGF) and secondary graft failure(SGF) were defined as whole blood donor chimerism <5% at day 28 or after initial engraftment, respectively. Endpoints were event-free survival (considering GF and death as events), overall survival, and graft rejection rates.

Results: Between November 2019 and August 2022, 33 patients were enrolled. Median age was 13.5 years (3.1-37). Median donor age was 39 years (13-58). Major indications for transplant were stroke 18/33 (54%), ACS/VOC 22/33 (66%). The conditioning regimen was THIO in 25 (73.5%), TBI in 8(24%). Thirty-two were at risk for CMV reactivation, 11/33 patients reactivated CMV, and ABO incompatibility was present in 9/33. Two had donor-specific antibodies (DSA), both were desensitized; one had a PGF and the other is alive and engrafted. After a median follow-up of 382 days 29/34 patients are alive. Five patients died (15%), 1 after TBI-only and 4 after THIO regimen.

Six graft failures, 6/8 (75%), were observed in the TBI-only cohort (PGF:1 and SGF:5), five are alive with autologous, recovery while one patient died after a 2nd haplo-BMT.

For THIO-regimen, 28-day neutrophil engraftment was 92% (95%CI 66.2-98.3); Median:20 days. Graft failure occurred in 6/25 (24%; PGF:1; SGF:5).

For THIO-regimen 1-year OS and EFS were 80.9% (95%CI 55.9-92.6) and 56.9% (95%CI 0.319-0.757), respectively. In univariate analysis, only age <14 years was associated with a better EFS($p = 0{,}005$). All 18 patients with sustained engraftment have full donor chimerism at last follow-up.

Table 1. Demographie and characteristics (N = 33)

Variable	THIO N = 25	TBI only N = 8*
Age at transplant, median (range)	12.6 (3.1-37)	17.3 (11.8-32.5)
Pretransplant		
Hydroxyurea 30 mg/kg	22/25	4/8
Hypertransfusion	22/25	7/8
HbS < 30%	22/25	7/8
SCD genotype SS	25/25	8/8
Major Transplant Indications		
Stroke	15/25	3/8
TIA	1/25	2/8
ACS/VOC	18/25	4/8
CMV at risk#	23/25	8/8
Stem Cell Source Bone Marrow	25/25	8/8
TNC infused, med (range)	6.97x10^8/kg (3.45-14,28)	3.4x10^8/kg (2,64-8,95)
CD34 infused, med (range)	4.8x10^6/kg (1.15-28.1)	3.1x10^6/kg (1.11-9.4)
CMV reactivation	6/25	5/8
Graft failure, n(%)	6/25 (24%)	6/8 (75%)
Deaths	4/25	1/8
Causes of death	1 pseudomonas infection, 1 bacterial sepsis, 1 aGVHD, 1 CNS bleeding and sepsis	Bacterial infection and sepsis after 2nd. transplant
Comments	#Only 2 cases with patient and donor CMV negative, both in THIO group. In all TBI-only group, patients and donors were CMV+	*1 TBI 400 cGy – single dose 2 patients, one rejected and one engrafted; TBI 200 cGy twice: 6 patients, 5 rejected, one engrafted

Conclusions: Although small numbers, we could not reproduce data previously published with TBI based approach, though there were differences in TBI dosing. However, not all patients were able to perform strict pretransplant recommendations. Though we do not have this data, we would expect that at least 30% of patients would be alloimmunized(Kelly B et al. *Transfusion* 2020), known risk factor for transplant outcome. Outcomes with THIO-regimen were comparable with the consortium's data (Kassim et al, ASH 2022 #398), though there were differences in supportive care practices across sites. These data demonstrate that conditioning regimens must be validated and locally adapted for country realities, considering patient characteristics, drug and TBI availability.

Disclosure: Nothing to declare.

23 - Haemoglobinopathy

P348

HAPLOIDENTICAL RELATED DONOR PERIPHERAL BLOOD STEM CELL TRANSPLANT FOR THALASSEMIA MAJOR WITH POST TRANSLANT CYCLOPHOSPHAMIDE AND THIOTEPA, FLUADARABNE AND TREOSULFAN OR BUSULFAN CONDITIONING

Satya Prakash Yadav[1], Dhwanee Thakkar[1], K Upasana[1], Sunisha Arora[1], Rachit Khandewal[1], Neha Rastogi[1]

390

[1]Medanta The Medicity, Gurgaon, India

Background: Reduced toxicity regimens – Thiotepa, Treosulfan, Fludarabine (TTF) and Thiotepa, Busulfan, Fludarabine (TBF) have been used for matched donor hematopoietic stem cell transplant (HSCT) for Thalassemia major. However, data regarding using these conditioning regimen in haploidentical related donor HSCT with post-transplant cyclophosphamide (PTCy) in thalassemia is lacking. Here, we report the outcomes of the same in children with thalassemia major.

Methods: Medical records of all children who underwent haploidentical related donor PBSCT with PTCy for Thalassemia Major from January 2017 to October 2022 were retrospectively analyzed. Patients received either TTF or TBF conditioning along with Anti-Thymocyte Globulin (ATG) after an informed written consent. Total doses were-Fludarabine-160mg/m^2, Thiotepa-10mg/kg and Rabbit ATG(Thymoglobulin)- 4.5mg/kg. Dose of Busulfan was 3.2mg/kg/day for 4 days and Treosulfan-14g/m^2/day for 3 days. Graft vs. host disease (GVHD) prophylaxis was with PTCy 50 mg/kg on day+3 &4 and Cyclosporine and mycophenolate mofetil. Children with donor specific antibody were desensitized as per John Hopkins protocol. Pre transplant immune suppression (PTIS) was given to all children with anti-HLA antibodies.

Results: Our cohort comprised of 16 children, 9 received TTF regimen and 7 received TBF regimen. Median age was 2 years (range 1-14 years). Male: Female was 2:1. Donors were parents in all cases (mother: father ratio was 1:1). PTIS was administered to 7 children (43%). Desensitization was done for 2 children with donor specific antibodies. All children received peripheral blood stem cell as graft with median CD34 cell dose of 8 million/kg (range 4-25 million/kg). One child died before engraftment on day+10 due to pulmonary hemorrhage. Another child had primary rejection followed by autologous recovery. Remaining 14 engrafted. Neutrophil engraftment was seen on median of 12 days (range 11-20) and platelet engraftment was seen on median 14 days (range-12-21). Acute GVHD was seen in 5 children (grade III-IV in 2) and chronic GVHD was seen in 3 children (extensive-1). CMV reactivation was seen in 50% children and BK virus reactivation was seen in 25% children. No child developed veno-occlusive disease. One child died on day+68 due to steroid refractory acute GVHD with massive gastrointestinal bleeding. Overall, 12 children are fully donor and one child has stable mixed chimerism. Overall, 14 children (88%) are alive at median follow up of 180 days. Thalassemia free survival of this cohort is 81%. Overall survival for TBF regimen was 86% and for TTF was 89%.

Conclusions: Haploidentical related donor PBSCT with myeloablative conditioning (TBF or TTF) with PTCy for children with Thalassemia major is highly effective and safe.

Disclosure: Nothing to declare.

25 - Immunodeficiency Diseases and Macrophages

P349

OUTCOME OF HSCT ON WITH AB-T CELL DEPLETION IN A COHORT OF INBORN ERRORS OF IMMUNITY WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Aishat Idarmacheva[1], Alexandra Laberko[1], Elvira Sultanova[1], Varvara Brilliantova[1], Alexey Maschan[1], Larisa Shelikhova[1], Dmitry Balashov[1], Michael Maschan[1]

[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: Hemophagocytic lymphohistiocytosis (HLH) is a primary syndrome in patients with familial HLH (FHLH), but it may also occur in various inborn errors of immunity (IEI), and allogenic hematopoietic stem cell transplantation (HSCT) is curative for both. We analyzed the HSCT outcomes in patients with different IEI with HLH.

Methods: From 2012 to 2020, 312 patients with various IEI underwent 1st HSCT in our center. 44 of them had HLH prior to HSCT and were divided into 2 groups: «FHLH» with defined genetic variant or typical clinical picture of FHLH in 24(UNC13D/STXBP2 n = 11, Chediak-Higashi syndrome n = 2, Griscelli syndrome n = 1, undefined HLH n = 10), and «Other HLH» in 20(XIAP deficiency n = 9, PAMI syndrome n = 2, STAT1-GOF n = 1, undefined IEI n = 8). Active HLH disease at HSCT was present in 4 of FHLH and 5 of other HLH. Pre-HSCT infections occurred in both groups, whilst inflammatory bowel diseases(n = 11), immune cytopenia (n = 7), arthritis (n = 5) and vasculitis (n = 3) were observed only in the other HLH. The median time from HLH onset to HSCT was 0.64(0.04-3.95) and 0.39(0.18-11.93) years, respectively, p = 0.12. The median age at HSCT was 2 years in both groups. HSCT was performed from matched unrelated (FHLH-14 and other-8), mismatched related donors (FHLH-6 and other-10) or HLA-identical siblings(FHLH-4 and other-2). Conditioning regimens included one(FHLH-9 and other-3) or two(FHLH-14 and other-17) alkylators and serotherapy. Peripheral blood with TCRαβ + /CD19+ graft depletion(FHLH-22 and other-19) or native bone marrow(FHLH-2 and other-1) were used. Post-HSCT graft failure(GF- non-engraftment/graft rejection), lack of HLH disease control with mixed chimerism or death were considered as events.

Results: The median time of follow-up was 6.85(1.91-10.6) in FHLH and 4.25(2.4-10) years in other HLH, p = 0.012. All, but one patient engrafted in both groups (median time of neutrophil engraftment was 12.5(9-33) and 14(9-33) days, respectively). No significant differences in rates of acute and chronic graft-versus-host-disease and viral reactivations were seen between the groups. GF rate in FHLH was 0.08 (95%CI 0.02-0.31) vs 0.25 (95% CI 0.12-0.53) in other HLH, p = 0.12; the median time of GF was 0.1 and 0.15 years, respectively. Overall survival was 0.92(95%CI 0.8-1) in FHLH and 0.85(95%CI 0.69-1) in other HLH, p = 0.5, and event-free survival (EFS) 0.83(95%CI 0.68-0.98) and 0.65(95%CI 0.44-0.85), p = 0.17 respectively. In the FHLH group, 2 patients died after 1st HSCT, 2 patients developed GF (doing well after 2nd HSCT). Among the other HLH group, 1 patient died, 1 has no disease control with mixed chimerism and 5 developed GF and received 2nd HSCT (2 died, 1 developed GF, 1 developed mixed chimerism and recurrence of colitis, and 1 is doing well). Among 11 patients with mixed chimerism at last FU, only 2 (both with XIAP deficiency) had no post-HSCT control of prior disease.

Conclusions: Patients developing HLH in non-FHLH IEI in comparison to FHLH syndromes appeared inferior, EFS with increased risks of GF and lack of disease control in mixed chimerism (seen in XIAP deficiency), although the difference did not reach statistical significance. Underlying disease factors in non-FHLH IEI developing HLH need to be investigated in greater detail to develop improved peri-transplant therapy in these patients.

Disclosure: Nothing to disclose.

25 - Immunodeficiency Diseases and Macrophages

P350

HAPLOIDENTICAL STEM CELL TRANSPLANTATION WITH EX-VIVO T-DEPLETION IN PRIMARY IMMUNODEFICIENCY AND IMMUNE REGULATORY SYNDROMES: A MULTICENTER EXPERIENCE

Stefano Giardino[1], Ursula Holzer[2], Ladislav Król[3,4], Francesca Bagnasco[1], Gianluca Dell'Orso[1], Filomena Pierri[1], Michaela Döring[2], Federica Sabatini[1], Jacek Toporski[5], Dominik Turkiewicz[3,4], Peter Lang[2], Maura Faraci[1]

[1]IRCCS Istituto G. Gaslini, Genova, Italy, [2]University of Tubingen, Tuebingen, Germany, [3]Skåne University Hospital, Lund, Sweden, [4]Lund University, Clinical Sciences, Lund, Sweden, [5]Karolinska University Hospital, Stockholm, Sweden

Background: Allogeneic hematopoietic stem cell transplantation from haploidentical donor(haplo-HSCT) represents the alternative treatment for patients with Primary Immunodeficiency Disorders (PIDD) and Primary Immune Regulatory Disorders (PIRD) lacking a full-matched donor. In the last decade advanced T-depletion approaches have been introduced, but few data regarding outcomes of haplo-HSCT with graft manipulation are currently reported.

The aim of this multicentric retrospective study is to report the outcome of a large cohort of PIDD/PIRD patients who underwent T-depleted haplo-HSCT and to compare different graft manipulation approaches.

Methods: Haplo-HSCTs performed in patients with PID or PIRD in 3 pediatric centers (Genoa-Italy, Tuebingen-Germany, Lund-Sweden) were eligible. Clinical and biological information about the disease and details on transplant procedures and outcomes were collected retrospectively. Diagnosis group, pre-HSCT status, conditioning regimen (CR) and graft manipulation approaches have been considered as main variables for the outcome. A part of the patients' data included in this study was previously published in different contexts.

Results: Fourty-eight haplo-HSCTs performed in 41 patients were included in the study, 7 patients received 2 haplo-HSCTs. The median age at transplant was 2.5 years (0.1-21.6). **Table 1** summarized the transplants features.

Table 1. Characteristics of the 48 haplo-HSCTs

Characteristics	n	%
Diagnosis		
• PIDD #	32	*66.7*
• PIRD ##	16	*33.3*
Haploplatform		
• TCR ab + /CD19+ negative selection	34	*70.8*
• CD3 + /CD19+ negative selection	13	*27.1*
• CD34 + positive selection	1	*2.1*
Karnofsky/Lansky at Haplo		
• ≤50	7	*14.6*
• ≥ 60	41	*85.4*
Conditioning regimens		
• Flu-based*	19	*39.6*
• Bus-based	4	*8.3*
• Treo-based**	20	*41.7*
• *No conditioning*	*5*	*10.4*
Radiotherapy		
• Yes	8	*16.7*
∘ *TLI / 4 Gy*	*6*	
∘ *TBI 4 Gy*	*2*	
• No	40	*83.3*
Serotherapy		
• ATG§	31	*64.6*
∘ *Early(before day -6)*	*6*	
∘ *Late(after day -6)*	*22*	
∘ *Not available*	*3*	
• OKT3	8	*16.6*
• Alemtuzumab	3	*6.3*
• None	6	*12.5*
Rituximab		
• YES	28	*58.3*
∘ *375 mg/m2 D + 1*	*9*	
∘ *200 mg/m2 D -1*	*18*	
∘ *missing*	*1*	
• NO	18	*37.5*
• *missing*	*2*	*4.2*
GvHD prophylaxis post-HSCT		
• No prophylaxis	31	*64.6*
• Prophylaxis	17	*35.4*
∘ *MMF*	*12*	
∘ *CyA*	*2*	
∘ *FK506*	*1*	
∘ *PT-Cy*	*2*	

 # IL2-R, IFNG R2, MHCII, RFXANK, RAG-1, DCLRE1C (ARTEMIS), WAS, HAX-1, IL7RA (n 2), IL2RG (n 3), IL7RA, PNP, IL7RA, HAX-1, ADA, IFNGR1, WAS (n 2), ARPC1B (n 2), RAG1, TACI (n 2), RMRP

LRBA (n 2), LYST, NSF2, CYBB, TACI + CASP10 + CARD11, GATA2 (n 2), SAMD9L, CASP10 (n 2), MVK (n 3), CARD11, UNC13D

** Flu-Mel-TT N = 13, Flu-Mel N = 1, Fly-Cy N = 1, Flu-TT N = 1, Flu alone N = 2, Flu-VP16 N = 1*

***Treosulfan (+Thiotepa, +Fludarabine); Treosulfan + ciclofosfamyde;Treosulfan + Fludarabine*

§ATG-Fresenius N = 23, ATG Thymoglobuline N = 5, ATG not specified N = 4

TCR-ab$^+$/CD19$^+$-depletion was the graft manipulation approach in the most of haplo-HSCT(n = 34, 70.8%), while CD3$^+$/CD19$^+$-depletion was performed in the remaining(n = 13, 27.1%). In the majority of haplo-HSCTs, the CR was reduce-intensity fludarabine-based(n = 19, 39.6%)or myeloablative treosulfan-based(n = 20, 41.7%). Radiotherapy (TBI 200-400 cGy/TLI 400 cGy) was part of CR in 8 transplants (16.7%).

Among 40 haplo-HSCTs evaluable (83.3%), engraftment occurred in 37(92.5%) and 34 HSCTs(70.1%) for neutrophils and platelets, respectively, after a median of 13 days (9-27; 10-41) for both. Rejection have been diagnosed in 11(22.9%) haplo-HSCTs(5 primary, 6 secondary). Among the 42 evaluable HSCTs for acute GvHD, 13 (30.9%) were complicated by acute-GvHD [n = 10 grade I-II (23.8%) and n = 3 grade III (7.1%)]. Chronic GvHD occurred in 6/39(15.4%) HSCTs (extensive in 3, 7.7%).

At a median follow-up of 3.0 years (IQR 0.8-6.7) after haplo-HSCTs, 29 patients are alive, 2 lost and 10 dead, resulting in a 3-years-overall survival probability of 74.5% (CI 57.4-85.5) and 3-year-chronicGvHD/rejection-free survival of 58.0% (CI 40.7-71.9). Most causes of death were infections, with higher frequency of viral etiology.

Higher cumulative survival was observed in patients with a diagnosis of PIRD respect to PIDD, with a Karnovsky/Lansky score >50 at the time of haplo-HSCT and when Treosulfan-based CR and TCR-ab$^+$/CD19$^+$-depletion were performed.

Conclusions: Ex vivo T-depleted haplo-HSCT is a feasible and effective alternative in patients lacking a full matched donor that allows to not delay the transplant in presence of a diagnosis of PIDD or PIRD. This is further supported by the negative effect on the outcome of the lower patient's Karnovsky/Lansky score before HSCT, which is more likely in PIDD/PIRDs patients who reach haplo-HSCT with delay. Moreover, Treosulfan-based CR and TCR-ab$^+$/CD19$^+$-depletion seem to lead to the best outcome confirming the importance of the evolution in graft selection methods. Viral infection remained the main issue after T-deplete haplo-HSCT,

therefore careful monitoring for pre-emptive treatment is needed and the access to antiviral adoptive cell therapy should be available.

Disclosure: Nothing to declare.

25 - Immunodeficiency Diseases and Macrophages

P351

OUTCOMES OF UMBILICAL CORD BLOOD TRANSPLANTATION IN CHILDREN WITH CHRONIC GRANULOMATOUS DISEASE

Elizabeth Hicks[1], Taymour Hammoudi[1], Andre Stokhuyzen[1], Timothy Driscoll[1], Paul Martin[1], Joanne Kurtzberg[1], Andrea Bauchat[1], Vinod Prasad[1]

[1]Duke University, Durham, United States

Background: Chronic granulomatous disease (CGD) is a primary immune deficiency caused by a mutation in NADPH-oxidase resulting in neutrophils with defective phagocytosis. This leads to early death from life-threatening bacterial and fungal infections and autoinflammatory disorders. Hematopoietic stem cell transplantation (HSCT) is curative in CGD but may not be available for patients lacking a suitably matched donor. Banked umbilical cord blood (UCB) can provide a viable alternative donor source in the absence of a matched related donor. We present the outcomes of umbilical cord blood transplants performed at our center for CGD.

Methods: A retrospective analysis of all pediatric patients undergoing UCB transplantation (UCBT) for CGD at Duke between 2005 and 2022 identified 19 patients, all males. Prior to transplant, 18 patients had infectious complications including aspergillus pneumonia, cellulitis, lymphadenitis, perianal abscess, and BCGosis, and 11 had autoinflammatory manifestations including enterocolitis, granulomas, lymphadenopathy, and hepatosplenomegaly. Median age at transplant was 2.4 years (range, 0.9 – 11.6 years). All received myeloablative conditioning with targeted busulfan, fludarabine (except one), cyclophosphamide, and ATG. UCB units were sourced from unrelated ($n = 16$) or related ($n = 3$) donors and were HLA mismatched (4/6 in 5; 5/6 in 12) in all but 2 patients. Cyclosporine and mycophenolate were used for prophylaxis against graft versus host disease (GVHD) in 16 patients; cyclosporine and steroids were used in 3.

Results: With a median follow-up of 6.1 years (range, 0.2 – 13.9), 16 of 19 patients are surviving disease free (13 unrelated UCBT, 3 related UCBT). Four patients experienced graft failure of whom 3 were successfully retransplanted with a second UCBT. Median time to neutrophil engraftment was 21 days (range, 12 – 43). At last follow-up, all patients had stable, full ($n = 14$) or near full ($> 85\%$ in whole blood, $n = 4$) donor chimerism. Grade II acute GVHD occurred in 7 patients, and grade III-IV acute GVHD in 2 patients. Chronic GVHD occurred in 6 patients (4 limited and 2 extensive). No patients developed new CGD-related infections after transplant. All 5 patients with CGD-related enterocolitis had resolution of bowel disease. Three patients died: 1 from infections following graft rejection, 1 from unknown causes 1.7 years post-transplant, and 1 from Duchenne muscular dystrophy 12 years post-UCBT, undiagnosed at the time of transplant.

Conclusions: Our experience shows favorable outcomes including survival, sustained high donor chimerism and low rates of significant acute or chronic GVHD. Cord blood transplant expands donor options and should be considered as a graft source for patients with CGD lacking fully matched donors.

Disclosure: Nothing to declare.

25 - Immunodeficiency Diseases and Macrophages

P352

OUTCOME OF PATIENTS WITH SIGNAL-TRANSDUCER AND ACTIVATOR OF OF TRANSCRIPTION 1 (STAT1) GAIN-OF-FUNCTION VARIANTS AFTER HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Emilie Pauline Buddingh[1], Mary A. Slatter[2], Ayca Kiykim[3], Laura Alonso Garcia[4], T. R. Leahy[5], Deepak Chellapandian[6], Renata Formankova[7], Joern-Sven Kühl[8], Safa Baris[9], Emma Morris[10], Petr Sedlacek[7], Alexandra Laberko[11], Jacques Rivière[4], Steven Keogh[12], Troy Torgerson[13], Michael Albert[14], Bénédicte Neven[15], Jennifer Leiding[6], Catharina Schuetz[16]

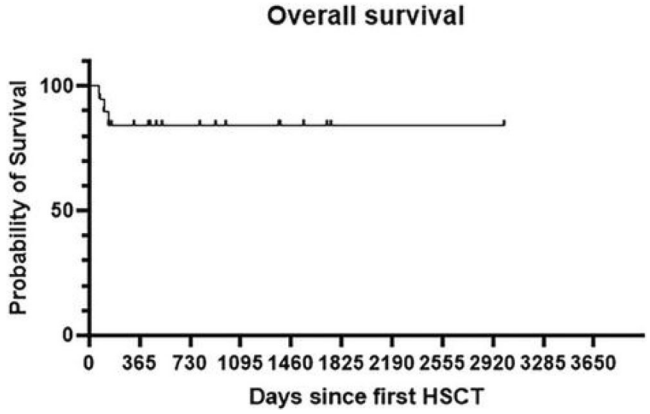
[1]Leiden University Medical Centre, Leiden, Netherlands, [2]Great North Children's Hospital, Newcastle University, Newcastle upon Tyne, United Kingdom, [3]Istanbul University Cerrahpasa, Istanbul, Turkey, [4]University Hospital Vall d'Hebron, Barcelona, Spain, [5]University of Dublin, Trinity College, Dublin, Ireland, [6]Division of Allergy and Immunology, Johns Hopkins University, Baltimore, United States, [7]University Hospital Motol, Prague, Czech Republic, [8]Hospital for Children and Adolescents, Universität Leipzig, Leipzig, Germany, [9]Marmara University, Istanbul, Turkey, [10]University College London Hospitals NHS Foundation Trust, London, United Kingdom, [11]Dmitry Rogachev Federal Research And Clinical Centre Of Paediatric Haematology, Oncology And Immunology, Moscow, Russian Federation, [12]Cancer Centre for Children, Children's Hospital at Westmead, Syndey, Australia, [13]Allen Institute for Immunology, Seattle, United States, [14]Dr. von Hauner University Children's Hospital, Ludwig-Maximilians-Universität, München, Germany, [15]Hôpital Necker Enfants Malades, APHP, Université Paris Cité, Paris, France, [16]Universitätsklinikum Carl Gustav Carus, TU Dresden, Dresden, Germany

Background: The inborn error of immunity caused by STAT1 gain-of-function (GOF) variants has a spectrum of symptoms with early-onset chronic mucocutaneous candidiasis, systemic autoimmunity and a range of infections. Curative therapy with allogeneic hematopoietic stem cell transplantation (HSCT) has been reported in 15 patients (Leiding et al. JACI 2017), but outcome was poor, mainly due to graft failure.

Methods: We here present compiled data of 19 patients with STAT1GOF deficiency transplanted after 2015. Data was collected via a shared eCRF from EBMT and PIDTC centers.

Results: 21 HSCTs were performed in 19 STAT1GOF patients between 2015 and 2022, in Turkey, Australia, Germany, the Netherlands, Russia, Spain, Ireland, United Kingdom; Czech Republic and United States. The median age at first transplant was 11 years (range 2 years – 22 years). Some of these patients were previously reported. Most patients were transplanted because of severe or refractory infections (13/19), with or without auto-immunity (8/13). One patient was transplanted because of auto-immunity and HLH. Five patients were transplanted because of combined immunodeficiency. Indications for second transplant were graft loss (1) and graft failure (1). Donors were HLA-identical siblings (4 transplants), other related donors (3 transplants), 10/10 matched related donors (11 transplants) and 9/10 mismatched unrelated donors (3 transplants). Acute GVHD occured in 10/21 transplant procedures, but only two patients (11%) suffered °III or °IV acute GVHD. Out of 19 patients, three patients died, at 75, 106 and 139 days post-transplant, respectively. Causes of death were GVHD °IV with multi-organ failure (1 patient), invasive fungal infection (1 patient) and treatment refractory CMV-infection with

graft failure (1 patient). 10/16 surviving patients had full donor chimerism at last follow-up, and 6 had mixed chimerism.



Conclusions: Compared to historical data, outcome of HSCT in STAT1GOF patients has improved with 85% overall survival as compared to 40% reported in 2017. HSCT should be discussed as curative option in all STAT1GOF patients who have a severe phenotype or lack of response to conservative management.

Clinical Trial Registry: NA

Disclosure: Nothing to declare.

25 - Immunodeficiency Diseases and Macrophages

P353

EMAPALUMAB AS A BRIDGE TO TRANSPLANT IN A PATIENT WITH STAT1 GOF MUTATION

Alan Bidgoli[1], Binni Kunvarjee[1], Esther Vidal[1], Kinga Hosszu[1], Jaap Jan Boelens[1], Joseph Oved[1]

[1]Memorial Sloan Ketttering Cancer Center, New York, United States

Background: Patients with a gain-of-function (GOF) mutation in signal transducer and activator of transcription 1 (STAT1) have immune dysregulation, predisposing them to infections, autoimmune disorders, and combined immunodeficiency. Clinical phenotypes of STAT1 GOF mutations vary; patients with severe manifestations have been successfully treated with hematopoietic cell transplant (HCT). However, high rates of graft failure (GF) remain a major barrier to success. Emerging data suggests active inflammation inhibits stem cell engraftment and function. Research has focused on the IFNγ pathway, utilizing the downstream chemokine CXCL9 as a marker for IFNγ activity. The increased interferon signaling seen in STAT1 GOF patients is hypothesized to drive the increased rates of GF. Emapalumab is an anti-IFNγ antibody FDA-approved for treatment of primary hemophagocytic lymphohisticytosis. It exhibits target-mediated clearance, for which dose-adaption strategies from 1 mg/kg, with escalations up to 10 mg/kg, have been utilized. Here we report a first-in-patient use of emapalumab to bridge a patient with STAT1 GOF to bone marrow transplant.

Methods: 6-year-old female with a T-cell functional defect due to STAT1 GOF mutation with history of chronic mucocutaneous candidiasis, multi-drug resistant mycobacterium abscesses, and failure to thrive, received an unmodified bone marrow haploidentical BMT from her mother with myeloablative conditioning (Thymoglobulin®, fludarabine and busulfan) and post-transplant cyclophosphamide, tacrolimus and mycophenolate mofetil for GVHD prophylaxis. Four doses of emapalumab 3 mg/kg IV were administered on days -22, -15, -8, and -1 to neutralize IFNγ activity (pre-transplant CXCL9: 3331 pg/mL).

Results: Neutrophils engrafted on day +21 and the patient did not require platelet transfusions. CD4+ immune reconstitution (> 200/μL) occurred by 7 months post-BMT. Complications of transplant included *Clostridium difficile* infection and CMV reactivation treated with antivirals. There is no evidence of acute or chronic GVHD. CXCL9 levels were monitored through the peri- and post-transplant period, with noted reduction in levels beginning with administration of emapalumab and through the post-BMT period. PK analysis demonstrated that plasma unbound emapalumab levels remained present through day +75. Importantly, activated $CD8^+$ T cells were able to expand and contract in response to CMV reactivation despite present emapalumab levels. Targeted proteomics demonstrated dampening of immune pathways during emapalumab administration and through 100 days post-BMT. Patient is currently 9 months post-transplant and remains infection and autoimmune disease-free and maintains 100% donor chimerism across all lineages.

Conclusions: The largest study of STAT1 GOF mutation patients undergoing HCT had dismal outcomes. Primary engraftment rate was 74%, with 50% of patients having secondary graft failure with no association found with disease phenotype, genotype, conditioning regimen, or donor source, resulting in 100-day event free and overall survival of 10% and 40%, respectively. Those surviving HCT with full immune reconstitution had resolution of infections/autoimmunity and had compensatory growth. Thus, strategies to improve graft failure rates in STAT1 GOF and other primary immune regulatory disorders (PIRDs) remain a significantly unmet need. These data have led to the opening of an investigator-initiated phase 2 trial examining the role of a prophase of emapalumab or fludarabine/dexamethasone as bridge to transplant for patients with PIRDs.

Disclosure: J. Oved serves as a member of the Scientific Advisory Board for Emendo Bio, received honorarium for an Advisory Board session from Sobi, and received research support (i.e. drug) from Sobi.

J.J. Boelens receives consulting fees from Sobi, Bluebird Bio, Avrobio, BlueRock, Omeros, SmartImmune, Sanofi, and Advanced Clinical.

A. Bidgoli, B. Kunvarjee, E. Vidal, and K. Hosszu have nothing to declare.

25 - Immunodeficiency Diseases and Macrophages

P354

HAPLOIDENTICAL STEM CELL TRANSPLANTATION FOR CHILDREN WITH PRIMARY IMMUNODEFICIENCIES: EXPERIENCE IN A CENTER FROM NORTHEAST OF MEXICO

María Guadalupe González[1], Myrna Pequeño-Luévano[1], Guillermo Sotomayor[1], Severiano Baltazar[1], Tamara Staines[1], Adriana Sandoval[1], Madia Corolla[1], Edna Venegas[1]

[1]Instituto Mexicano del Seguro Social UMAE 25, Monterrey, Mexico

Background: Primary immunodeficiencies disorders (PID) are a group of heterogenous conditions of the immune system abnormalities that can be expressed by recurrent infectious, autoimmunity, lymphoproliferation granulomatous process, atopy and/or malignancy. An increased susceptibility to severe infections is the hallmark of primary immunodeficiency disease, which leads an increased risk of mortality. The delay of diagnosis is still a problem that result in increased morbidity and mortality. Allogeneic hematopoietic stem cell transplantation (HSCT) is the gold standard curative therapy for this disorders. The prompt diagnosis and treatment can lead to a great prognosis in these

patients. This work describes the outcome of 13 children with PID that underwent haploidentical stem cell transplantation in a single center from the northeast of Mexico.

Methods: Eight patients were male and five female. The mean age of PID diagnosis was 15 months old (from 11 to 72 months old), and the mean age of HSCT was 2 years old (from 14 months to 10 years old). All living patients have an extended follow up (more 180 days). The selected stem cell donor was the father in 10 patients, the mother in 2 patients, and a sibling in one patient. The conditioning regimen used was BuCy16. Graft versus host disease prevention was carried out with post- transplant cyclophosphamide (Cy PT), tacrolimus, and mycophenolic acid.

Results: Median neutrophil engraftment was 13.5 days (from 11 to 50 days), and median platelet engraftment was 14.5 days (from 12 to 60 days). Only one patient had primary failure engraftment, and needed a second CD34+ infusion from the same donor. Every patient developed fever during the neutropenic period, but all of them responded with carbapenemic drugs without complications lead by sepsis. One patient had veno-oclusive hepatic disease, successfully solved with fluids restrictions and symptomatic therapy. Three patients developed cutaneous grade I, and one grade I gastrointestinal graft versus host disease (GVHD), solved with steroids and immunosuppressive drugs without complications; one patient (the one who required a second CD34 infusion) died because of gastrointestinal, hepatic and cutaneous severe GVHD on day +142. Eleven patients had quimerism more than 95%, and one 63% on day +30, and the remaining patient could not be evaluated. All patients had more than 95% quimerism on day +100. Up to date, 12 patients live without co-morbidities, and without clinical evidence of immunodeficiency.

Conclusions: Haploidentical stem cell transplantation is a feasible and excellent treatment modality for PID. Despite the risks of the HSCT, still this seems the best option and, up to date, the only curative option for these patients. The haploidentical variety is a very good choice, when there is no an allogeneic related or unrelated donor. The prompt diagnosis and treatment are essential to have optimal outcomes.

Disclosure: We have no conflict of interest.

25 - Immunodeficiency Diseases and Macrophages

P355

A CASE OF LRBA DEFICIENCY WITH PERSISTENT IMMUNE DYSREGULATION POSTTRANSPLANT

Delfien J. A. Bogaert[1], Tiene Bauters[1], Koen Vanden Driessche[2], Nicolette Moes[2], Koen Norga[2], Filomeen Haerynck[1], Catharina Dhooge[1], Victoria Bordon Cueto De Braem[1]

[1]Ghent University Hospital, Gent, Belgium, [2]Antwerp University Hospital, Antwerp, Belgium

Background: Lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency, first reported in 2012, is an inborn error of immunity/primary immunodeficiency caused by biallelic mutations in *LRBA*. It is characterized by a broad clinical and immunological spectrum. Most patients suffer from immune dysregulation and autoimmunity, which can be very severe and already present at a young age. Additional manifestations include hypogammaglobulinemia, recurrent infections and lymphoproliferative disease with increased risk of lymphoma.

Methods: We report a patient with LRBA deficiency who underwent hematopoietic stem cell transplantation (HSCT).

Results: The patient is a girl born to consanguineous parents of North-African origin. She presented at the age of 9 years with refractory immune thrombocytopenia (ITP) for which she received multiple lines of treatment. In the next years, she also developed severe interstitial lung disease, recurrent pulmonary infections, diffuse lymphadenopathies and multiple T2-FLAIR-hyperintense lesions on brain MRI. Genetic testing confirmed LRBA deficiency (homozygous mutation). She was treated with steroids, sirolimus and abatacept. Despite initial improvement, she continued to suffer from chronic ITP and also developed severe progressive interstitial lung disease. In 2021, at 14 years of age, she underwent a HSCT with a matched sibling donor who was a heterozygous carrier of the *LRBA* mutation. Myeloablative conditioning with Busulfan (AUC 85-95), Fludarabine (140 mg/m^2) and ATG (7.5 mg/kg) was given. The immediate posttransplant period was uncomplicated. Engraftment was seen at D + 25. A stable donor chimerism of 89-91% was reached. There were no signs of graft versus host disease (prophylaxis with cyclosporine and methotrexate). Lung and brain imaging showed regression of the lesions. However, 3 months posttransplant, she developed dyspnea with a recurrence of lung lesions. Because a fungal infection was suspected, cyclosporine was stopped and voriconazole started. Fungal cultures remained negative. One month later, she presented with an immune-mediated hemolytic crisis, splenomegaly, and a further increase of granulomatous lung lesions under voriconazole. Treatment with high-dose steroids and sirolimus was initiated after exclusion of infection (negative cultures/PCRs). Because of insufficient effect of sirolimus, mycophenolate mofetil and eltrombopag were associated leading to gradual resolution of the disease manifestations. Currently, 20 months posttransplant, she is clinically stable under sirolimus and mycophenolate mofetil, but has extensive avascular necrosis of lower limbs and had an episode of pulmonary aspergillosis.

Conclusions: In the here-reported patient, the same manifestations of immune dysregulation that were present pretransplant, recurred a few months after successful HSCT requiring extensive immunosuppressive treatment. This has also been described in other cases reported in literature. We conclude that posttransplant recurrence of severe immune dysregulation in LRBA-deficient patients remains a significant complication.

Disclosure: Nothing to declare.

25 - Immunodeficiency Diseases and Macrophages

P356

MINIMAL DOSE OF HEMATOPOIETIC STEM CELL TRANSPLANTATION WITHOUT MYELOSUPPRESSIVE CONDITIONING FOR T-B + NK- SEVERE COMBINED IMMUNODEFICIENCY

Eunsang Yi[1], Hee Young Ju[2], Hee Won Cho[2], Ji Won Lee[2], Ki Woong Sung[2], Hong Hoe Koo[2], Eun-Suk Kang[2], Kang Mo Ahn[2], Yae-Jean Kim[2], Young Bae Choi[3], Na Hee Lee[4], Keon Hee Yoo[2]

[1]Korea University Guro Hospital, Seoul, Korea, Republic of, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of, [3]Ajou University Hospital, Ajou University School of Medicine, Suwon, Korea, Republic of, [4]Cha Bundang Medical Centre, Cha University, Seongnam, Korea, Republic of

Background: Allogeneic hematopoietic cell transplantation (HCT) is the standard method for reconstituting the immune function in severe combined immunodeficiency (SCID). Graft rejection is rare owing to the absence of functional immune cell development; however, there is no consensus regarding optimal cell doses in patients with SCID.

Methods: We retrospectively reviewed the medical records of five patients with T cell-negative (T-), B cell-positive (B +), and natural killer cell-negative (NK-) SCID who received minimal dose HCT (total nucleated cell count (TNC) lower than 1.0×10^8/kg) between 2002 and 2021. Post-transplant outcomes and immune reconstitution were also assessed.

Results: Patients were administered a median of 5.0 mL (range, 2.5–8.0) of bone marrow or G-CSF-mobilized peripheral blood without conditioning or with anti-thymocyte globulin alone. Three patients received HCT from a matched sibling donor, one from matched unrelated donor, and one from familial mismatched donor. The median TNC, $CD34^+$ cells, and $CD3^+$ cell doses were 0.54 (0.29–0.84) $\times$ 10^8/kg, 0.61 (0.35–0.84) $\times$ 10^6/kg, and 0.44 (0.19–1.14) $\times$ 10^7/kg, respectively. Successful engraftment was achieved in all, and one received a boost infusion for uncontrolled Bacille Calmette-Guérin infection. Except for one patient who showed prolonged immunosuppressive treatments for extensive chronic graft-versus-host disease, total T cell (> 800 cells/mm^3), $CD4^+$ cell (> 400 cells/mm^3), and $CD8^+$ cell (200 cells/mm^3) recovery was obtained within a year, and immunoglobulin replacement was discontinued in all patients at a median of 4 months (range, 1–37 months) after HCT. All patients survived without disease recurrence at a median of 94 months (15–242 months) after transplantation, exhibiting stable donor chimerism in the range of 24.0–100%.

Conclusions: We obtained sufficient therapeutic effects with minimal doses of hematopoietic stem cells without intensive conditioning in patients with T-B + NK- SCID.

Disclosure: None of the authors have any conflicts of interest to report.

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

P357

ALLOGENEIC HSCT IMPROVES QUALITY OF LIFE IN PATIENTS WITH STAT3 DOMINANT-NEGATIVE HYPER-IGE SYNDROME

Christo Tsilifis[1,2], Peter Ciznar[3], Mary Slatter[1,2], Austen Worth[4], Alexandra Freeman[5], Andrew Gennery[1,2]

[1]Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, [2]Newcastle University, Newcastle upon Tyne, United Kingdom, [3]National Institute of Children's Diseases, Bratislava, Slovakia, [4]Great Ormond Street Hospital for Children, London, United Kingdom, [5]National Institutes of Health, Bethesda, United States

Background: Hyper IgE syndrome caused by dominant negative mutations in *signal transduction and activator of transcription 3* (STAT3-DN-HIES) manifests with recurrent skin and pulmonary infections leading to parenchymal lung disease. Allogeneic HSCT reduces the frequency of infections and halts progression of lung disease, but there are no published data on quality of life in STAT3-DN-HIES.

Methods: As part of an international survey of STAT3-DN-HIES patients undergoing allogeneic HSCT, retrospective clinical data and transplant characteristics were collected. Patients were invited to complete quality of life (QOL) questionnaires relating to health-related QOL (adults: SF-36; children: PedsQL4.0 SF15; both scored 0-100, with higher scores indicating better QOL), respiratory health (St George's Respiratory Questionnaire, SGRQ; scored 0-100, with high scores indicating poorer QOL), and dermatological symptoms (adults: dermatology life quality index, DLQI; children: CDLQI; both scored 0-30, with higher scores indicating poorer QOL). Mean scores for the STAT3-DN-HIES QOL cohort who have not undergone HSCT were used as a control.

Results: Twenty-six STAT3-DN-HIES patients in our cohort underwent HSCT; QOL data was available for 7 patients. HSCT was indicated for severe and recurrent infection. Median age at HSCT was 12 years (range: 7–20) and median follow-up was 3.5 years (0.75–26.5).

Patients received grafts from matched sibling (n = 5), matched unrelated (n = 1), or haploidentical (n = 1) donors following conditioning with busulfan- (n = 5) or treosulfan- (n = 2) based regimens. Median T-lymphocyte donor chimerism at latest follow-up is 96%. Summary measures of health-related QOL (SF-36 General Health and PedsQL4.0 SF15 Total Score) ranged 40-60 for adults and 58.3-90.0 for paediatric patients and were higher than control in 5/6 subjects.

All patients had a history of recurrent bacterial pulmonary infection, and five patients had parenchymal damage in the form of bronchiectasis or pneumatocoele formation (**Table 1**). Two patients had suspected or confirmed Aspergillosis. Post-HSCT, all patients are free from further infection; one patient had CMV pneumonitis in the immediate post-transplant period, which resolved. SGRQ subdomain scores ranged: Symptoms, 0-56.7; Activities, 0-53.6; Impact, 0-28.3. Total scores were lower than control, indicating better QOL, in 5/7 subjects including one patient who scored zero in all subdomains.

Six patients had significant dermatological disease with recurrently infected eczema, including two patients who subsequently developed invasive bacterial infection (staphylococcal bacteraemia, and osteomyelitis). Post-transplant, all patients are free from recurrent infection and eczema, with lower DLQI scores than the comparator cohort.

Conclusions: Allogeneic HSCT resolves the immune defect, reduces infection, and improves the impaired quality of life caused by STAT3-DN mutations in this small cohort.

Disclosure: Nothing to declare.

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

P358

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH CHRONIC GRANULOMATOUS DISEASE. THE SPANISH EXPERIENCE

Laura Alonso[1], David Bueno Sanchez[2], Jose María Fernández Navarro[3], Alexandra Regueiro Garcia[4], Miguel Blanquer[5], Maria Isabel Benitez Carabante[1], Yasmina Mozo[2], Jose Luis Fuster[5], Maria Luz Uria Oficialdegui[1], Luisa Sisinni[2], Antonio Perez-Martinez[2], Cristina Diaz de Heredia[1]

[1]Hospital Maternoinfantil Vall d'Hebron, Barcelona, Spain, [2]Hospital Universitario La Paz, Madrid, Spain, [3]Hospital Universitario La Fe, Valencia, Spain, [4]Hospital Clinico Universitario Santiago, Santiago de Compostela, Spain, [5]Hospital Clinico Universitario Virgen de la Arrixaca, Murcia, Spain

Background: Chronic granulomatous disease (CGD) is a primary immunodeficiency secondary to genetic defects in different subunits of the NADPH oxidase complex. As a consequence of these defects, the patients develop recurrent bacterial and fungal infections, immune disregulation and inflammation, which lead to high morbidity with organ disfunction and growth failure, and increased mortality.

Hematopoietic stem cell transplantation (HSCT) is currently the only available curative therapy for CGD. In the last few years, following improvement in transplant procedure and outcomes, interest has increased regarding the role of HSCT in CGD, indications to proceed to transplant have broadened and have

Table 1 - Patient and transplant characteristics, latest donor chimerism, and pre- and post-HSCT respiratory and dermatological morbidity and QOL indices. MUD: matched unrelated donor; MSD: matched sibling donor; BM: bone marrow; PBSC: peripheral blood stem cell; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; SGRQ: St George's Respiratory Questionnaire; DLQI: Dermatology Life Quality Index. Higher SGRQ and DLQI scores reflect poorer QOL.

	Age at HSCT (years)	Follow up (years)	Donor Graft source	Conditioning	Latest donor chimerism (%)	Respiratory Morbidity		SGRQ Total Score	Dermatological Morbidity		DLQI Score
						Pre-HSCT	Post-HSCT		Pre-HSCT	Post-HSCT	
P1	7	26.5	MUD-BM	Busulfan Cyclophosphamide Alemtuzumab	CD3 96 CD15 100 CD19 99	*Staphylococcus aureus* lung abscess, lingula bronchiectasis, previous pneumothorax	-	27.3/100	Newborn rash, recurrently infected eczema with sepsis, *Staphylococcus aureus* bacteraemia, previous MRSA colonisation, mucocutaneous candidiasis	Necrotising fasciitis 26 years post-HSCT	4/30
P2	7	3.5	MSD-BM	Fludarabine Treosulfan Thiotepa Alemtuzumab	CD3 100 CD15 100 CD19 99	Recurrent pneumonia, including pseudomonas and Aspergillus colonisation; bronchiectasis with allergic bronchopulmonary aspergillosis FEV1 84% FVC 92%	-	10.9/100	Newborn rash, recurrently infected eczema	-	0/30
P3	7	6	Haplo-BM	Busulfan Cyclophosphamide Pentostatin	WB 100	Severe recurrent pneumonia with pneumatocoele FEV1 84% FVC 89%	-	6.9/100	Minimal	-	0/30
P4	12	5	MSD-BM	Busulfan Cyclophosphamide Pentostatin	CD3 89 CD15 100	Recurrent sinoopulmonary infection FEV1 81% FVC 104%	-	0/100	Disfiguring eczema with superinfection leading to one episode of osteomyelitis	-	-
P5	20	1.5	MSD-PBSC	Busulfan Fludarabine	CD3 83 CD15 100	Recurrent pneumonia, no bronchiectasis FEV1 90% FVC 84%	-	15.1/100	Recurrent cutaneous abscess	-	4/30
P6	15	1.5	MSD-BM	Busulfan Cyclophosphamide Pentostatin	CD3 100 CD15 100	Recurrent sinopulmonary infection with extension to orbit and cranium causing meningitis; pulmonary nodules FEV1 97% FVC 107%	-	4.5/100	Recurrent skin infection, eczema	-	0/30
P7	17	0.75	MSD-BM	Fludarabine Treosulfan Thiotepa Alemtuzumab	WB 44	Recurrent bacterial pneumonia with bronchiectasis and pneumatocoele formation; previous pneumothorax FEV1 60% FVC 65%	CMV pneumonitis, resolved	28.3/100	Recurrent furunculosis	-	4/30

included unrelated and mismatched donors. And the number of CGD patients in our HSCT units has increased.

We report the outcome of the Spanish series of 30 pediatric patients who have undergone an HSCT for CGD.

Methods: Retrospective review of pediatric patients who underwent an HSCT in any of the centers of the Pediatric Spanish group for bone marrow tranplantation (GETMON).

Results: Data from 30 patients with CGD who underwent an HSCTbetween 2007 and 2020 in 5 transplant centers was analyzed.

The characteristics of the patients are listed on table 1.

Median age	6.9y (0.6-12.7)
Sex	
Female	23
Male	7
Inheritance	
X linked	14
Mc Leod S	1
AR	12
Missing data	4

All the patients had experienced pre-HSCT repeated bacterial or fungal infections and in 18 of them, significant inflammatory episodes were described.

Transplant procedure

Eight patients received grafts from MSD and 22 from unrelated donors. The unrelated donors were 10/10 HLA matched in 13 cases and 9/10 HLA matched in 9.

The most common conditioning regimen was based on busulfan (22): 21 patients received busulfan fludarabine and 1 received busulfan cyclophosphamide. The remaining 8 patients received treosulfan-based conditioning, either treosulfan fludarabine (3) or treosulfan thiotepa fludarabine (5).

Ex vivo graft manipulation was performed in 5 patients, 4 of whom received grafts from 9/10 HLA matched donors. The manipulation consisted of 2 CD19/TCR alfa/beta depletion; 2 partial depletions of the total CD3 dose and 1 CD45Ra depletion.

Outcome

Engraftment

Eight patients experienced graft failure. Two, a primary graft failure and 6 a secondary rejection. All of them had received transplants from unrelated donors: 4 patients from 10/10 HLA matched donors and 4 from 9/10 HLA matched donors. Six of the

patients who rejected had received busulfan-based conditioning and 2 treosulfan-based.

These 8patients received a second transplant; 6 engrafted and 2 required a third transplant. Five of the eight patients are alive and 3 died of TRM.

GVHD

Acute GVHD >/= grade II was diagnosed in 11 patients and grade III-IV was described in 3. Chronic GVHD in 4: mild 2, moderate 1, severe 1. Cummulative incidence of chronic GVHD was 20.5% at 2 years. There were no differences in the incidence of GVHD depending on the donor.

Survival

Twenty four patients are alive. Six died of TRM. Five year OS was 78%.

The causes of death were GVHD, neumonitis, pulmonary hypertension, VOD, necrotizing hepatitis and aspergilosis.

Conclusions: HSCT in patients with CGD is a complex procedure. Graft failure, GVHD and infectious complications account for the associated morbidity. These factors need to be incorporated in the decission making process.

Disclosure: None.

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

P359

COMPOUND HETEROZYGOUS HLH IN A YOUNG ADULT: MULTIMODAL AND MULTIPROFESSIONAL TREATMENT

Katharina Wustrau[1], Charlotte Rebholz[1], Eva Maria Jacobsen[1], Stephan Ehl[2], Kai Lehmberg[3], Elisa Sala[1], Manfred Hönig[1], Ansgar Schulz[1]

[1]Universitiy Medical Center Ulm, Ulm, Germany, [2]Universitiy Freiburg, Freiburg, Germany, [3]Universitiy Medical Center Hamburg, Hamburg, Germany

Background: Hemophagocytic Lymphohistiocytosis can be caused by genetic variants in *PRF1* gene. It represents a subgroup of familiar HLH. Here we report an adult patient with late onset of disease activity and genetic variants of incompletely understood significance.

Methods: Flow-Cytometry (FACS), Sanger-Sequencing, *Insililco* testing, Therapy protocols according to Ehl at al., J Allergy Clin Immunol Pract. 2018 and Moshous et al. Blood 2019.

Results: A female patient (body weight 97 kg), 20 years of age, presented initially with tricytopenia and fatigue, in the later course with 6/8 HLH criteria. Malignancy and other causes of secondary HLH were excluded. At the age of 4 the patient suffered from an episode of thrombocytopenia of unknown origin.

Genetic testing revealed two variants in the *PRF1* gene in exon 2: c.272C>T p.Ala91Val and c.310C>T p.Arg104Cys. The first is a polymorphism with an allele frequency of 9%, which is assigned as not disease causing (zur Stadt, Blood 2004). The latter variant was in insilico analyses rated as probably disease causing. Protein expression of perforin was detectable in flow-cytometry, but mean fluorescence intensity was reduced compared to normal control (MSFI Perforin staining of NK-cells: 65 patient vs 214 healthy control).

Treatment with steroids and iv immunoglobulins resulted in temporary remission. Disease activity reoccurred after partial withdrawal of steroids, so ciclosporin A was started. Relapse of disease activity happened 4, 9,10 and 11 months after diagnosis. Therapy was extended by Il1-blockage anakinra (up to 6 mg/kg BW/d) and ruxolitinib (60 mg/d). Due to ongoing disease activity alemtuzumab (3 mg/kg BW) was given, which resulted in partial response, but still high numbers of activated CD3 + DR+ cells (95%). To achieve complete remission etoposidphosphate was given. There were no viral infections after treatment with alemtuzumab until HSCT. MUD HSCT was performed after conditioning with treosulfan, fludarabine, thiotepa. Hematological and immunological reconstitution are ongoing (day 16 posttransplant).

Initially the patient presented at an adult hematology/oncology department. After pediatric counselling the primary genetic diagnosis was established and the patient was transferred to pediatric immunology. For HSCT the patient was transferred to an adult HSCT department.

Conclusions: The quantification of perforin expression may help to classify clinical severity of the A91V polymorphism in combination with previously unknown other variants. Early HSCT can be considered, if clinical criteria are present and perforin expression is low. Diagnosis and treatment of inborn errors in young adults require close cooperation of adult and pediatric departments.

Disclosure: Nothing to declare.

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

P360

INFLAMMATION IN WOLMAN DISEASE IS GENERATED BY SUBSTRATE ACCUMULATION IN THE MACROPHAGE

Anthea Guha[1], Gloria Lopez-Castejon[2], Robert Wynn[1], Rodrigo Diaz[2], Simon Jones[1]

[1]Royal Manchester Childrens Hospital, Manchester, United Kingdom, [2]University of Manchester, Manchester, United Kingdom

Background: Wolman Disease is an infantile onset disease characterized by Lysosomal Acid Lipase deficiency. Lysosomal acid lipase (LAL) breaks down Low Density Lipoprotein (LDL) derived Cholesterol Esters (CE) and Triglycerides (TG). The symptoms and signs develop due to accumulation of CEs and TGs in macrophages of the liver, gut and spleen.

Although cell based and transplant therapies are curative, many Wolman Disease patients are poor candidates for Haematopoietic Stem Cell Transplant (HSCT) as they are severely malnourished, have significant rapidly progressive liver disease and frequently present with symptoms and signs of Haemophaocytic Lymphohistiocytosis (HLH), a syndrome characterized by severe inflammation, unremitting fevers, cytopenias, raised ferritin and multiorgan dysfunction. Patients with WD have poor outcomes once they develop HLH.

We hypothesized that HLH in WD is caused by overactivated inflammasome activity of macrophages due to substrate accumulation.

Inflammasomes are multimeric proteins found in the cytosol of innate immune cells which assembly is triggered by danger signals of either pathogenic (i.e. Lipopolysaccharide), or non-pathogenic (i.e. crystals) origin. They are key in the initiation of inflammation as inflammasomes leads to the activation and release of pro-inflammatory cytokines IL-1β and IL-18.

Methods: To understand the relationship between substrate accumulation in macrophages in WD and inflammation, healthy and LAL deficient monocytes were isolated from blood and differentiated into macrophages (MDMs). MDMs were primed with LPS to induce a proinflammatory state, and activated with different inflammasome activators extracellular ATP, LDL and Cholesterol Crystals. Functional output of the inflammasome was determined by measuring LDH release (cell death), Caspase 1 activity, and release of cytokines IL-1β and IL-18.

Results: Our preliminary data has shown that macrophages derived from WD patients have an exacerbated response to inflammasome activators ATP and to treatment with LDL or cholesterol crystals compared to healthy donors. We also found that healthy donor cells treated with a LAL inhibitor potentiates inflammasome responses.

Conclusions: In conclusion, we found that LALdeficient macrophages have an exacerbated response to all inflammasome activators tested showing increased levels of caspase 1, LDH, IL1B and IL-18 compared to healthy donors. We also found that treatment with the LAL inhibitor Lalistat in healthy MDMs potentiated inflammasome responses.

These results could be relevant to the mechanism of HLH in patients with WD. Patients with WD have poor outcomes once they develop HLH. Understanding the mechanism of inflammation in these patients will give the opportunity for targeted treatments to be given so that more patients can come to affinitive treatments with cell-based therapies.

Disclosure: Nothing to declare.

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

P361

UNDERGOING TRANSPLANT FOR MALIGNANT OSTEOPETROSIS: DON'T GIVE UP

Giulia Pisano[1], Mar Part López[1], Carolina Fuentes Socorro[1], José María Fernández Navarro[1]

[1]Hospital Universitari i Politècnic La Fe, Valencia, Spain

Background: Autosomal Recessive Osteopetrosis is a rare genetic disease characterized by a defect in the formation and function of osteoclasts, with an increase in bone mass. It has a very low incidence (1:250.000 live births), and it presents soon after birth, being often severe and deadly if untreated. Since the origin of the defect is hematopoietic, stem cell transplantation is considered the main curative treatment. We present the management of a difficult case.

Methods: Retrospective review of the patient records and laboratory investigations.

Results: A 4-months boy, first child of young and healthy parents, presented with bulging of anterior fontanelle and macrocephaly. In addition, on physical examination, he presented frontal bossing and mild splenomegaly. Complete blood count showed hemoglobin of 8.0 g/dL, white blood cell count of 9.200 cells/μL, and 132.000 platelets/μL. Biochemical tests found hypocalcemia, hypophosphatemia, and secondary hyperparathyroidism. Skeletal survey showed features of osteopetrosis (increased bone mineral density, absence of bone marrow cavity). A compound heterozygous mutation in TCIRG1 was detected in the genetic analysis. In the extension study, visual evoked potentials were altered in both eyes, while otoacoustic emissions, cardiac ultrasound, and renal function were normal. He required a ventriculoperitoneal shunt due to increased intracranial hypertension, opisthotonos, and nystagmus. Autologous hematopoietic progenitors were collected on peripheral blood. At that moment, he lacked both identical related and unrelated bone marrow donors, due to COVID-19 pandemic. An unrelated umbilical cord blood allogeneic transplantation (7/8, difference in A) was performed (Negative anti-HLA-antibodies. Total nucleated cellularity (TNC): 22.5x10^7/Kg, CD34 8.55x10^5/Kg). Thiotepa-busulfan-fludarabine conditioning regimen was used. Moreover, antithymocyte-globulin (10 mg/Kg), cyclosporine, and corticosteroids, as GVHD prophylaxis, and defibrotide, as sinusoidal obstruction syndrome (SOS) prophylaxis, were prescribed. He presented primary implant failure, with mixed chimera on day +21 (7% donor). Furthermore, he developed sepsis due to *Staphylococcus aureus*, hypocalcemia, hypophosphatemia, malnutrition, and suspected macrophage activation syndrome that improved with corticosteroids. Reinfusion of autologous hematopoietic progenitors was performed on day +55. He required readmission due to severe cutaneous hemorrhagic syndrome and laminar subdural hemorrhage. A second collection of autologous hematopoietic progenitors on peripheral blood was taken, with combined mobilization (2.7x10^6 CD34/Kg). He developed hyperferritinemia with high hepatic iron overload that required intravenous chelation. Given the numerous complications, a haploidentical transplant from his father (TNC: 12.66x10^8/Kg, CD34 12.34x10^6/Kg, CD3 3.7x10^8/Kg. Negative anti-HLA-antibodies) was performed. This time treosulfan–fludarabine–thiotepa-based conditioning regimen was used. Additionally, he received GVHD prophylaxis with antithymocyte-globulin (8 mg/Kg), cyclosporine, mycophenolate-mofetil and tacrolimus, and prophylactic defibrotide. Engraftment occurred on day +18. He presented grade II cutaneous GVHD with good clinical evolution. On follow-up, he received neurocognitive rehabilitation and his nutritional status improved. He discontinued immunosuppressive drugs, and he started revaccination. He presented bone remodeling, with resolution of bone alterations of osteopetrosis, and later developed FGF23-related hypophosphatemic rickets.

Conclusions: Comments: Our patient presented graft failure after unrelated umbilical cord blood transplantation despite the high cellularity. He was rescued with a haploidentical transplant. In the frame of defibrotide prophylaxis, he didn't develop SOS. Currently, he has a Lansky score of 100 and can attend classes at school.

Disclosure: Nothing to declare.

13 - Infectious Complications

P362

RETROSPECTIVE CHART REVIEW OF TRANSPLANT RECIPIENTS WITH CYTOMEGALOVIRUS INFECTION WHO RECEIVED MARIBAVIR IN THE PHASE 3 SOLSTICE TRIAL: DATA AT 52 WEEKS POST-MARIBAVIR TREATMENT INITIATION

Ishan Hirji[1], Dorothy Romanus[1], Tien Bo[1], Veronique Page[2], Aimee Sundberg[1], Sandra Okala[3], Marielle Bassel[2]

[1]Takeda Development Center Americas, Inc., Lexington, United States, [2]Evidera PPD, St-Laurent, Canada, [3]Evidera PPD, London, United Kingdom

Background: Cytomegalovirus (CMV) infection is a frequent complication in hematopoietic cell/solid organ transplant (HCT/SOT) recipients. Previous literature reports a 1-year mortality rate of 31%–50% in HCT/SOT recipients post-treatment initiation with conventional anti-CMV therapies (Avery RK, et al. 2016; Mehta Steinke SA, et al. 2020). In the open-label Phase 3 SOLSTICE trial (NCT02931539) with a duration of 20 weeks (8 weeks of treatment and 12 weeks follow-up) the primary endpoint was met, with 55.7% of patients in the maribavir group achieving CMV clearance at the end of Week 8 versus 23.9% of patients in the investigator-assigned therapy (IAT) group; fewer patients discontinued treatment due to treatment-emergent adverse events with maribavir than IAT (Avery RK, et al. 2021). The primary objective of this observational, retrospective chart review study was to evaluate mortality and graft status at 52 weeks post-maribavir treatment initiation in the HCT and SOT cohorts from SOLSTICE.

Methods: This was a multi-country, non-interventional, retrospective, medical chart review study of HCT and SOT recipients with refractory CMV infection with or without resistance (R/R) who were randomized to the maribavir treatment arm in SOLSTICE. Patients were selected from 21 SOLSTICE sites across 6 countries that randomized ≥3 patients to the maribavir arm. Patients were followed for 52 weeks; this retrospective study included the SOLSTICE trial period (20 weeks; from start of maribavir treatment [index date]) and the follow-up chart review period (32 weeks; starting 1 day after the SOLSTICE trial period until 52 weeks post-index date or patient death/loss to follow-up, whichever occurred first).

Results: Of the 234 patients who were randomized and received maribavir in SOLSTICE, chart abstraction was completed for all 109 patients enrolled in this retrospective study (68/142 SOT; 41/92 HCT). Median age at index date was 56.0 years (SOT = 55.0; HCT = 59.0). At 52 weeks, the overall mortality rate was 15.6% (17/109) and survival probability was 0.84 (**Table**). Among SOT recipients, 3 (4.4%) deaths were observed during the chart review period. The causes of death for SOT recipients were CMV-related factors, anemia, and renal failure (n = 1 each). Among HCT recipients, 14 (34.1%) deaths were observed; 8 occurred during SOLSTICE and 6 additional deaths were observed during the chart review period. The causes of death for HCT recipients were underlying disease relapse (n = 4), infection other than CMV (n = 6), CMV-related factors, transplant-related factors, acute lymphoblastic leukemia, and septic shock (n = 1 each). Survival probability for SOT and HCT recipients is summarized in the **Table**. No patients had new graft loss or re-transplantation during the chart review period.

Table. All-cause mortality and overall survival at 12 months

	Overall population n = 109	SOT n = 68	HCT n = 41
Death events, % (n)	15.6 (17)	4.4 (3)	34.1 (14)
Survival probability (95% CI)	0.84 (0.76–0.90)	0.96 (0.87–0.99)	0.65 (0.48–0.77)

Conclusions: Overall mortality at 52 weeks post-maribavir treatment initiation in these sub-cohort of patients from the SOLSTICE trial was lower than that reported for similar populations treated with conventional therapies for R/R CMV infection. These results, in addition to the superior efficacy in CMV clearance observed for maribavir in SOLSTICE provide supportive evidence of the potential for the long-term benefit of maribavir treatment for post-transplant CMV infection.

Funding: Takeda Development Center Americas, Inc.

Clinical Trial Registry: N/A

Disclosure: Ishan Hirji, Tien Bo, Aimee Sundberg: employee and stock ownership: Takeda.

Dorothy Romanus: employee: Takeda.

Veronique Page: nothing to disclose.

Sandra Okala, Marielle Bassel: employee: Evidera PPD (designed/conducted the study funded by Takeda).

13 - Infectious Complications

P363

POST-TRANSPLANTATION CYCLOPHOSPHAMIDE FACILITATES LONG-TERM IMMUNOLOGICAL RECONSTITUTION AFTER ALLOHCT COMPARED TO ATG AND NON-ATG BASED GVHD PROPHYLAXIS

Thomas Meyer[1], Melanie Sieder[1], Miguel Waterhouse[1], Kristina Maas-Bauer[1], Ralph Wäsch[1], Robert Zeiser[1], Jürgen Finke[1], Claudia Wehr[1]

[1]University Medical Center Freiburg, Freiburg, Germany

Background: Reconstitution of a functional lymphocyte compartment after allogeneic hematopoietic cell transplantation (alloHCT) is crucial for long-term survival and might differ between graft-versus host disease (GvHD) prophylaxis with post-transplantation cyclophosphamide (PT-CY) versus anti-thymocyte globulin (ATG) and non-ATG based regimens.

Methods: Patient data and lymphocyte subsets on d + 30, d + 100 and at one year were retrospectively collected between 2015 - 2022 from the following groups: (1) haplo-identical (haplo) or mismatch donor (MM) + PT-CY; (2) matched related donor (MRD); (3) matched unrelated donor (MUD) + ATG Grafalon ® 30mg/kg (4) MM + ATG Grafalon ® 30mg/kg. All patients received cyclosporine and mycophenolate acid.

Results: We identified 68 patients in group (1) (PT-CY), 103 patients in group (2) (MRD), 287 patients in group (3) (MRD + ATG) and 58 patients in group (4) (MM + ATG).

CD8+ lymphocyte counts were low early after alloHCT in PT-CY and ATG groups (d + 30 PT-CY 97, MRD 156, MUD + ATG 99, MM + ATG 84 cells/µl, $p < 0.05$) but reconstitution at one year after alloHCT did not differ (PT-CY 421, MRD 437, MUD 505, MM 884 cells /µl, $p > 0.05$).

CD4+ lymphocyte counts at d + 30 were also low in PT-CY and ATG groups (PT-CY 53, MUD + ATG 31, MM + ATG 26, MRD 249 cells /µl, $p < 0.05$). However, at one year CD4+ lymphocyte counts were significantly higher in PT-CY and MRD compared to ATG groups (PT-CY 329.5, MRD 344, MUD + ATG 210.75, MM + ATG 219 cells /µl; $p < 0.05$). This pronounced long-term CD4 + T-cell recovery was reflected in a significantly higher count of CD45RA +, naive CD4+ cells in PT-CY and MRD on both d + 100 (PT-CY 13, MRD 60, MUD + ATG 4, MM + ATG 2 cells /µl; $p < 0.05$) and one year post alloHCT (PT-CY 57.5, MRD 74, MUD + ATG 20.5, MM + ATG 10 cells /µl; $p < 0.05$).

B lymphocyte counts were low on day 30 after alloHCT in all groups (PT-CY 1, MRD 4, MUD + ATG 3, MM + ATG 4 cells /µl, $p < 0.05$). At one year B lymphocyte counts were highest in patients receiving PT-CY and lowest in the MRD group (PT-CY 320, MRD 118, MUD + ATG 237, MM + ATG 213 cells /µl, $p < 0.05$).

The risk of EBV reactivation (> 3000 IU/ml) was lower for both PT-CY and MRD compared to ATG groups (PT-CY 5.88%, MRD 3.88%, MUD + ATG 11.50% and MM + ATG 18.97%, $p < 0.05$). CMV reactivation (> 1000 IU/ml) was comparable in PT-CY, MRD and MUD + ATG but more prevalent in the MM + ATG population (PT-CY 26.47%, MRD 25.24%, MUD + ATG 28.22%, MM + ATG 48.28%, $p < 0.05$).

Conclusions: Thymic function with recovery of naive CD4 cells is facilitated by PT-CY and the lack of ATG treatment after alloHCT. PT-CY also facilitated B lymphocyte reconstitution in our cohort. The superior lymphocyte recovery also translated into better virus control indicating that PT-CY might favour long-term immunological reconstitution.

Disclosure: CW received a honorarium from Takeda, outside of the current work.

RZ received honoraria from Novartis, Incyte, MNK and Sanofi

13 - Infectious Complications

P364

EVALUATION OF COVID-19 VACCINE ANTIBODY RESPONSES IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT

400

RECIPIENTS: USING RUXOLUTINIB OR IBRUTINIB NEGATIVELY EFFECTS VACCINE ANTIBODY RESPONSES

Emine Merve Savaş[1], Şeyma Yıldız[1], Zubeyde Nur Özkurt[1], Zehra Baltacı[1], Özlem Güzel Tunçcan[1], Zeynep Arzu Yeğin[1], Kayhan Çağlar[1], Nurdan Köktürk[1], Gonca Erbaş[1], Gülendam Bozdayı[1], Munci Yağcı[1]

[1]*Gazi University, Ankara, Turkey*

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination is recommended for the prevention of infection in allogeneic stem cell transplant recipients. However, there are many factors that affect the vaccine antibody response and it is not yet known which factors affect it.. We aimed to investigate the antibody responses after Covid-19 vaccination and describe the factors that may affect the responses in patients who underwent allogeneic stem cell transplantation.

Methods: A total of 95 patients [median age 48 (35-56), male/female (61/34)] alloHCT recipients who had at least 2 doses of vaccination (BNT162b2 or CoronoVac), and were at least one month past the last dose of vaccine. Antibodies against the spike protein (S1) receptor region of the virus (SARS-CoV-2 Ig G antibody) were studied in the virology laboratory using the CMIA method.

Results: Vaccinated with at least one dose of BNT162b2 produced significantly higher antibody levels than vaccinated with 2 doses of CoronoVac [23555 (5457-40000) vs 827 (448-7516) $p < 0.0001$]. The antibody response increased significantly as the number of vaccines increased [2 dose vaccination 6693 (318-40000), 3 dose vaccination 12628 (812-40000), >4 dose vaccination 31742 (12875-40000), ($p = 0.025$)]. Due to the significantly lower antibody titer with CoronoVac, subgroup analyzes were performed in the group vaccinated with at least one dose of BNT162b2. Significantly lower antibody response was obtained in individuals with low Ig A levels when compared normal sIgA levels[1895 (147-31696) vs 37604 (10232-40000), $p = 0.006$] and similarly, lower antibody titers were observed in individuals with low Ig G levels and the difference was significant [682(192.5-12202) vs 20519(2260-40000) $p < 0.0001$]. Vaccine antibody responses were similar between groups with low and normal vitamin D levels [17012 (1262-40000) vs 33279 (7100-40000) $p = 0.36$]. Patients receiving immunosuppressive therapy for acute or chronic GVHD were examined. It was observed that antibody titers were significantly lower in patients who received ruxolutinib treatment compared to patients who did not [126 (108-21479) vs 40000 (12875-40000) $p = 0.046$]. Similarly, patients who received ibrutinib [229(163-296), $p = 0.009$] had a lower antibody titer than those who did not receive any immunosuppressive treatment. When comparing patients who did not receive maintenance treatment and those who used tyrosine kinase inhibitor (TKI) and FLT-3 inhibitor as maintenance treatment there were no significant difference between vaccine antibody responses [31220 (8583-40000), 1895 (589-12875), 28300 (11855-37604) respectively, $p = 0.23$]. Patients who received DLI in the last 2 years were examined, and no difference was found between vaccine antibody responses between those who received and those who did not [6410 (982-25463) vs 27488 (16356-40000) $p = 0.14$]. The use of ATG [31089 (11818-40000) vs 23484 (4161-40000 $p = 0.62$] or PT-Cy [29300 (687-40000) vs 23555 (7631-40000) $p = 0.76$] at transplant time also did not affect the vaccine antibody response.

Conclusions: Although adequate vaccine antibody responses seen in many patients after allogeneic stem cell transplantation, agents used for GVHD as ruxolutinib and ibrutinib adversely affect this responses. At the same time, low serum IgA and IgG levels are associated with low antibody responses. Further studies are needed to reveal vaccine antibody response mechanisms.

Table 1: Patient and Transplant Characteristics

Age (years) [median (range)]	48 (35-56)
Gender (male/female) [n(%)]	61 (64.8)/ 34(35.2)
Diagnosis [n(%)]	
Acute myeloid leukemia	49 (51.6)
Acute lymphoblastic leukemia	20(21.1)
Myelodysplastic syndrome	7 (7.4)
Myeloproliferative disorders	7 (7.4)
Others	12 (12.4)
Pretransplant Disease Status [n(%)]	
Complete remission	74(77.9)
Partial remission	2(2.1)
Stable disease	7(7.4)
Progressive disease	12(12.6)
Donor Type [n(%)]	
MRD	66(69.5)
MMRD	1 (1.1)
MUD	8 (8.4)
MMUD	12 (12.6)
Haploidentical	8 (8.4)
Conditioning Regimen [n(%)]	
Myeloablative	48(50.5)
Reduced intensity	47(49.5)
GvHD Prophylaxis I [n(%)]	
CSA-MTX	57(60)
CSA-MMF	38(40)
GvHD Prophylaxis II [n(%)]	
ATG Based	11(11.6)
PTCy Based	13(13.7)
Acute GVHD	8 (8.4)
Chronic GVHD	15(15.8)
Vaccination Type	
CoronoVac	27 (28.4)
BNT162b2	40 (42.1)
CoronoVac+BNT162b2	28 (29.5)
Vaccination Number	
2 dose	37 (38.9)
3 dose	34 (35.8)
4 or 5 dose	24 (25.3)
Transplant to first vaccination time (days) [median (range)]	1269 (650-2487)
First-last vaccination time (days) [median (range)	
2 vaccination	28 (28-32)
3 vaccination	133 (121-150)
4-5 vaccination	265 (251-296)
Antibody screening-last vaccination time (days) [median (range)	128 (72-211)
Follow-up (days) [median (range)]	1786 (1100-2676)

Disclosure: No conflict of interest.

13 - Infectious Complications

P365

RISK FACTORS AND PROGNOSIS OF NOCARDIA INFECTION AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: AN INFECTIOUS DISEASES WORKING PARTY AND FRANCO-BELGIAN NOCARDIA STUDY GROUP CASE-CONTROL STUDY

Julien De Greef[1], Dina Averbuch[2], Laura Tondeur[3], Amélie Duréault[4], Tsila Zuckerman[5], Xavier Roussel[6], Christine Robin[7], Alienor Xhaard[8], Simona Pagliuca[8], Yves Beguin[9], Carmen Botella-Garcia[10], Nina Khanna[11], Amandine Le Bourgeois[12], Jens Van Praet[13], Aloysius Ho[14], Nicolaus Kröger[15], Sophie Ducastelle Leprêtre[16], Damien Roos-Weil[17], Mahmoud Aljurf[18], Nicole Blijlevens[19], Igor Wolfgang Blau[20], Kristina Carlson[21], Matthew Collin[22], Arnold Ganser[23], Alban Villate[24], Christian Junghanss[25], Sonja Martin[26], Arnon Nagler[27], Ron Ram[28], Anna Torrent[29], Maria Stamouli[30], Malgorzata Mikulska[31], Lidia Gil[32], Lotus Wendel[32], Gloria Tridello[32], Nina Knelange[32], Rafael de la Camara[33], Olivier Lortholary[34,35], Arnaud Fontanet[3], Julien Coussement[36], Jan Styczynski[37], David Lebeaux[38,39], Johan Maertens[40]

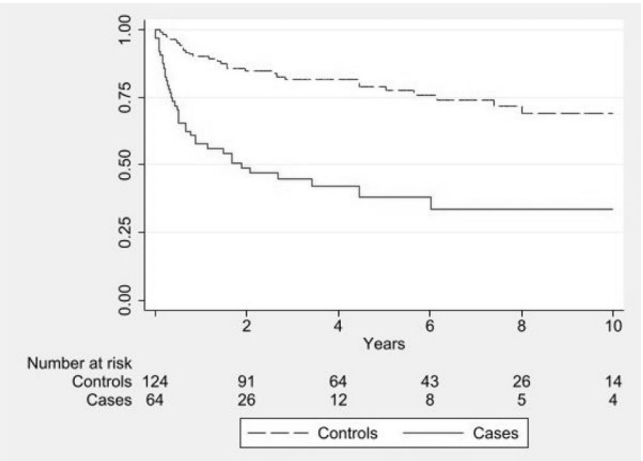
[1]Saint-Luc University Hospital, Université catholique de Louvain (UCLouvain), Brussels, Belgium, [2]Hebrew University of Jerusalem; Hadassah Medical Center, Jerusalem, Israel, [3]Institut Pasteur, Emerging Diseases Epidemiology Unit, Paris, France, [4]Centre d'Infectiologie Necker Pasteur, Hôpital Necker-Enfants Malades, Assistance Publique - Hôpitaux de Paris, Université Paris Descartes, Paris, France, [5]Rambam Medical Center, Haifa, Israel, [6]University Hospital of Besançon, Besançon, France, [7]Henri Mondor University Hospital, Creteil, France, [8]Hospital St-Louis, Paris Diderot University, Paris, France, [9]Centre Hospitalier Universitaire of Liège, University of Liège, Liège, Belgium, [10]Centre Hospitalier Universitaire Bordeaux, Bordeaux, France, [11]University and University Hospital of Basel, Basel, Switzerland, [12]Centre Hospitalier Universitaire Nantes, Nantes, France, [13]Algemeen Ziekenhuis Sint-Jan Brugge-Oostende, Brugge, Belgium, [14]Singapore General Hospital, Singapore, Singapore, [15]University Medical Center, Hamburg, Germany, [16]Hôpital Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France, [17]Sorbonne Université, Hôpital Pitié-Salpêtrière, Paris, France, [18]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [19]Radboud University Medical Center, Nijmegen, Netherlands, [20]Charité, Campus Virchow Klinikum, University Medicine Berlin, Berlin, Germany, [21]Uppsala University Hospital, Uppsala, Sweden, [22]Nordern Centre for Bone Marrow Transplantation Freeman Hospital, Newcastle, United Kingdom, [23]Hannover Medical School, Hannover, Germany, [24]Centre Hospitalier Universitaire de Tours, Université de Tours, Tours, France, [25]Universitaet Rostock, Rostock, Germany, [26]Robert-Bosch-Krankenhaus, Stuttgart, Germany, [27]Chaim Sheba Medical Center, Tel Hashomer, Israel, [28]Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel, [29]ICO-Hospital Germans Trias i Pujol, Josep Carreras Research Institute, Badalona, Spain, [30]Attikon University General Hospital, Athens, Greece, [31]University of Genoa and Ospedale Policlinico San Martino, Genoa, Italy, [32]EBMT Leiden Study Unit, Leiden, Netherlands, [33]Hospital de la Princesa, Madrid, Spain, [34]Paris University, Necker Pasteur Center for Infectious Diseases and Tropical Medicine IHU Imagine, Necker Enfants Malades University Hospital, Paris, France, [35]National Reference Center for Invasive Mycoses and Antifungals, Molecular Mycology Unit, CNRS UMR 2000, Institut Pasteur, Paris, France, [36]Sir Peter MacCallum Cancer Centre, The University of Melbourne, Victoria, Australia, [37]Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland, [38]Université Paris Cité, Paris, France, [39]Assistance Publique - Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France, [40]Universitaire Ziekenhuizen Leuven, Leuven, Belgium

Background: *Nocardia* is a rare but life-threatening infection in allogeneic hematopoietic stem cell transplant (HSCT) recipients. The objectives of this study were to identify risk factors for occurrence of nocardiosis after allogeneic HSCT, and to describe its prognosis.

Methods: We performed a retrospective case-control study of adult and children HSCT recipients diagnosed with nocardiosis between January 2000 and December 2018. To identify cases, European Society for Blood and Marrow Transplantation-affiliated HSCT centers were requested to systematically review their local Microbiology and HSCT databases. Two control subjects per case were matched by center, transplant date, and age group. The date of diagnosis of nocardiosis was defined as the day on which the first clinical sample (e.g., sputum) yielding *Nocardia spp*. was collected. For control patients, a corresponding date was chosen on the basis of their matched case's date of diagnosis, in order to obtain a similar period of time from transplantation. Data considered as possible nocardiosis risk factors were collected in cases and controls, including data on active comorbidities, underlying hematological malignancies and their management, HSCT characteristics, occurrence and management of HSCT complications, ongoing treatment and biological data at the time of nocardiosis. To identify risk factors for nocardiosis, we performed univariate analysis, and included all variables with a P value < 0.25 in a subsequent multivariable analysis using conditional logistic regression. To compare survival between cases and controls, we compared Kaplan-Meier survival curves using the log-rank test.

Results: Sixty-four HSCT recipients with nocardiosis were included, and matched to 128 control HSCT recipients. Nocardiosis occurred at a median of 9.3 months (interquartile range: 4.8-18.1) after HSCT. On multivariable analysis, we found CMV reactivation in the previous 6 months (adjusted odds ratio [aOR] 4.62, 95% confidence interval [95% CI]: 1.13 to 18.97, $p = 0.03$), treatment by corticosteroids within 12 months (aOR 7.78, 95% CI 2.22 to 27.18, $p = 0.001$), tacrolimus use (aOR 9.37, 95% CI 1.47 to 59.89, $p = 0.02$), and lymphocyte count <500/µL (aOR 7.61, 95% CI 2.00 to 28.97, $p = 0.003$) to be significantly and independently associated with the occurrence of nocardiosis after HSCT. Conversely, female gender (aOR 0.13, 95% CI: 0.03 to 0.49, $p = 0.003$) and use of trimethoprim-sulfamethoxazole prophylaxis (aOR 0.24, 95% CI 0.07 to 0.84, $p = 0.03$) were found to be significantly and independently protective for the occurrence of nocardiosis after HSCT. *Nocardia* cases had a significant decreased overall survival, as compared to controls (log-rank test, $p < 0.0001$), with a survival rate of 57.6% (95% CI: 44.6% to 68.7%) for cases and 90.1% (95% CI: 83.2% to 94.2%) for controls at 12 months (Figure 1).

Figure 1. Overall Survival of Nocardia Cases and Matched Controls.



Survival curbs start: Nocardiosis (cases) or corresponding time since graft (controls). Log-rank: $p < 0.0001$.

Conclusions: Using a case-control study design, we identified six factors independently associated with the occurrence of nocardiosis in HSCT recipients; in particular, the use of trimethoprim-sulfamethoxazole *Pneumocystis* prophylaxis was found to be protective against nocardiosis. We also found HSCT recipients with nocardiosis to have a significantly decreased survival, as compared with matched patients who did not develop nocardiosis after HSCT.

Disclosure: Nothing to declare.

13 - Infectious Complications

P366

PREDICTORS OF LENGTH OF SARS-COV-2 POSITIVITY IN HOSPITAL-ADMITTED HSCT RECIPIENTS WITH COVID-19: AN INFECTIOUS DISEASE WORKING PARTY STUDY

Malgorzata Mikulska[1], Gloria Tridello[2], Per Ljungman[3], Jan Styczynski[4], Diana Averbuch[5], Simone Cesaro[6], Nina Knelange[7], Lotus Wendel[7], José Luis Piñana[8], Rafael de la Camara[9]

[1]University of Genova and IRCCS Ospedale Policlinico San Martino, Genova, Italy, [2]EBMT Data Office, Leiden, Netherlands, [3]Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, [4]Nicolaus Copernicus University Torun, Bydgoszcz, Poland, [5]Hadassah Medical Center, Jerusalem, Israel, [6]Azienda Ospedaliera Universitaria Integrata, Verona, Italy, [7]EBMT Data Office, Leuven, Netherlands, [8]Hospital Clínico Universitario de Valencia, Valencia, Spain, [9]Hospital Universitario de la Princesa, Madrid, Spain

Background: Prolonged SARS-CoV-2 positivity in respiratory samples, similarly to what observed in case of other respiratory viruses, might be frequent in HSCT recipients and have significant negative impact on patients' management and outcome.

The aim of this study was to evaluate the length of SARS-CoV-2 positivity and its predictors in hospital-admitted HSCT recipients.

Methods: Data from a prospective EBMT-IDWP-GETH multicentre cohort study were analysed, evaluating patients with data on the length of SARS-COV-2 positivity available (defined as date of the last follow up without SARS-CoV-2 negativity or date of the first negative result and tested with PCR or antigen) from Feb 2020 to July 2022.

In order to reduce bias associated with testing frequency dependent on numerous factors and provide data clinically meaningful data, only patients hospitalised at COVID-19 episode (whatever the reason for hospital admission) were included.

A cause-specific Cox regression model was performed to investigate factors associated with shorter time to first negativity, considering the death without resolution as a competing event. Factors with p-value < 0.1 in univariate analysis was included in the multivariate model.

Results: Among 873 patients (45% of the whole cohort, $n = 1945$) for whom data on virological follow up testing were available, 462 were inpatients (306 after alloHSCT and 156 after autoHSCT). The median time to the first negative result was similar in hospitalised alloHSCT and autoHSCT recipients.

In 306 hospital-admitted alloHSCT recipients, the median length of positivity was 23 days (1-245) in 200 who obtained a negative result, while 89 patients died being SARS-CoV-2 positive (in median 17 days after diagnosis, min-max 1-193) and 17 were still positive at the last follow up (median 44 days, min-max 11-96). Multivariate analysis identified the following independent predictors of shorter time to negativity: donors other than MUD, no need for oxygen/ICU admission, no ongoing steroid therapy and infection in years 2021-2022 (Table 1).

Among 156 hospital-admitted autologous HSCT recipients, the median length of positivity was 24 (min-max, 4-210) in 86 who obtained a negative result, while 63 patients died being SARS-CoV-2 positive (in median 17 days after diagnosis, min-max 1-104) and 7 were still positive at the last follow up (median 44, min-max 10-279). The following variables were associated with shorter time to negativity in univariate analysis: lower age (for 10 years increase HR 0.78 (95%CI 0.66-0.92), $p = 0.004$), underlying disease (multiple myeloma HR 1.00, NHL HR 0.53 (95%CI 0.30-0.96), other HR 1.57 (95%CI 0.94-2.60), $p + 0.006$) and no need for oxygen/ICU admission (HR 3.15 (95%CI 1.96-5.08), $p < 0.0001$). The multivariate analysis confirmed the role of younger age (HR 0.82 (95%CI 0.70-0.97), $p = 0.02$) and no need for oxygen/ICU admission (HR 3.22 (1.94-5.35), $p < 0.0001$).

Conclusions: The time to first negative results in hospital-admitted HSCT recipients was 23-24 days. Factors associated with longer positivity were immunosuppression, MUD donor and COVID-19 severity in alloHSCT, and age and COVID-19 severity in autoHSCT. These results provide timeframe for expected length of SARS-COV-2 positivity.

Disclosure: Nothing to declare.

13 - Infectious Complications

P367

MRNA-1273 SARS-COV-2 VACCINE IN RECENTLY TRANSPLANTED ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS: CELLULAR AND HUMORAL IMMUNE RESPONSES AND BOOSTER EFFECT

Variable (reference categoty)		Univariate analysis HR (95% C.I.)	p	Multivariate analysis HR (95% C.I.)	p
Age at covid (Adult)	Pediatric vs. adult	1.53 (1.08-2.16)	0.016		
Donor type (Unrelated)	Matched family Mismatched family	1.64 (1.18-2.27) 1.73 (1.17-2.57)	0.002	1.81 (1.27-2.59) 1.69 (1.11-2.57)	0.002
Stem cell source (PB, 7 CB excluded)	BM	1.43 (1.02-2.01)	0.04		
In vivo T-Cell depletion (Yes)	No	1.50 (1.13-2.00)	0.005		
Performance status Karnofsky/Lansky (< 90)	≥90	1.38 (1.02-1.85)	0.03		
Ongoing IS therapy (Yes)	No	1.52 (1.08-2.14)	0.015		
Ongoing steroids (Yes)	No	1.60 (1.19-2.14)	0.002	1.57 (1.12-2.18)	0.008
Year of COVID-19 (2020)	2021-2022	1.40 (1.04-1.89)	0.03	1.47 (1.04-2.07)	0.03
Need for oxygen/ICU admission (Yes)	No	1.82 (1.35-2.44)	<0.0001	1.64 (1.18-2.27)	0.004

Not significant: Sex, Age, Diagnosis, Time from most recent transplant, CMV, Immunosuppression other than steroids, GvHD, country, Vaccination, Relapse or progression of underlying disease.

Nil Albiol[1,2,3,4], Elionor Lynton-Pons[5,3,4], Olga Aso[5], Esther Moga[5,3,4,2], Silvia Vidal[5,3,4], Lucía Gómez-Pérez[6], Jose Alejandre Santiago[5,3], Mercè Triquell[5], Nerea Roch[5], Elisabeth Lázaro[5], Iria González[5,4], Joaquín López-Contreras[5,3,4], Albert Esquirol[5,3,4,2], Jorge Sierra[5,3,4,2], Rodrigo Martino[5,3,4,2], Irene García-Cadenas[5,3,4,2]

[1]Institut Català d'Oncologia (ICO)-Girona, Girona, Spain, [2]Josep Carreras Leukaemia Research Institute, Barcelona, Spain, [3]Institut d'Investigació Biomèdica (IIB) Sant Pau, Barcelona, Spain, [4]Autonomous University of Barcelona, Barcelona, Spain, [5]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [6]Hospital del Mar-Parc de Salut Mar, Barcelona, Spain

Background: Allogeneic hematopoietic stem cell transplant (HCT) recipients are at high risk of severe COVID-19 despite vaccination. Few studies have analyzed cellular responses and booster dose results, especially in the early period after HCT.

Methods: This single-center, prospective, and observational study recruited all consecutive adult allo-HCT recipients who were between 3 and 24 months from the infusion date in March-April 2021 (cohort 1, recently transplanted patients –RTP-, n = 49). Another cohort of relapse-free-GvHD and immunosuppression-free long-term (i.e., >2 years away from HCT) transplanted patients was included (cohort 2, LTTP, n = 19). All patients received the Moderna® mRNA-1273 vaccine (two doses 28 days apart and a third dose after 6 months). In addition, a control group of 20 healthy volunteers who received the first 2 doses was recruited.

The humoral response was assessed through in-house ELISAs for IgG antibodies against the SARS-CoV-2 S1 protein. The cellular response was evaluated using a commercial interferon-gamma release assay method (QuantiFERON SARS-CoV-2). Determinations were made one and three months after the second dose (T1 and T2, respectively), and one month after the third dose (T3).

Results: Patient characteristics are available in Table 1. At T1, RTPs showed lower IgG antibody titers than both LTTP (mean 0.50 vs 0.66 arbitrary units -AU-, $p = 0.01$) and healthy controls (0.94 AU, $p < 0.0001$). At T2 no differences were seen between both transplant groups (0.37 vs 0.40 AU, $p = 0.55$), while controls presented higher titers (0.79 AU, $p < 0.0001$). Responses at T3 were similar between RTPs and LTTPs (0.54 vs 0.56 AU, $p = 0.82$). The rate of positive T-cell responses was lower in RTPs than in controls at both T1 and T2 (61.2% vs 95%, $p = 0.007$; 59.2% vs 100%, $p = 0.001$, respectively). On the contrary, differences in cellular responses were not statistically significant at any timepoint either between RTPs and LTTPs [61.2% vs 78.9%, $p = 0.25$ (T1); 59.2% vs 84.2%, $p = 0.08$ (T2); 76.6% vs 94.4%, $p = 0.15$ (T3)] or between LTTPs and healthy controls [78.9% vs 95%, $p = 0.18$ (T1); and 84.2% vs 100%, $p = 0.23$ (T2)]. There were no declines in the T-cell immune response between T1 and T2 in any group ($p = 1.00$), in contrast to humoral responses. A significant number of patients exhibited dissociated responses, especially amongst RTPs. The booster dose was crucial in increasing the rates of positive responses for transplanted patients. Nineteen out of the 33 (58%) RTPs with a negative humoral response at T2 turned positive after the booster. This meant an increase in the proportion of positive responses by 35.4% in RTP ($p < 0.001$) and 30.4% in LTTP ($p < 0.001$). As for the cellular response, nine out of 20 (47%) negative RTPs at T2 turned positive at T3. Active immunosuppressive treatment was the main variable associated with an impaired response to the booster dose.

Table 1

	RTPs (n = 49)	LTTPs (n = 19)
Age (years): median (range)	56 (26-73)	60 (25-70)
Time from HCT: months median (range)	14 (3-24)	43 (30-90)
Sex: n (%)		
Male	25 (51)	12 (63.2)
Conditioning regimen: n (%)		
RIC	30 (61.2)	15 (78.9)
GVHD prophylaxis: n (%)		
PTCy-tacrolimus	34 (69.4)	11 (57.9)
Sirolimus-tacrolimus	11 (22.4)	4 (21.1)
Other	4 (8.2)	4 (21.1)
Acute GVHD at any point: n (%)	18 (36.7)	NA
Grade 2-4	*10 (20.3)*	NA
Chronic GVHD at any point: n (%)	11 (22.4)	NA
Moderate-severe	*2 (4)*	NA
Immunosuppression (2nd dose / BD): n (%)	36 (73.5) / 20 (40.8)	NA
Corticosteroids	*5 (10.2) / 7 (14.3)*	NA
Ongoing prophylaxis	*25 (51) / 11 (22.4)*	NA
Other	*6 (12.2) / 2 (4.1)*	NA

Conclusions: Recently transplanted allo-HCT patients show an impaired vaccine response compared to healthy controls, but also compared to long-term transplanted patients. A booster dose increases the likeliness of achieving a positive response, both for humoral and cellular immunity, despite being less efficacious in those with active immunosuppressive treatment.

Disclosure: Nothing to declare.

13 - Infectious Complications

P368

LONG-TERM IMMUNITY AGAINST TETANUS AND DIPHTHERIA AFTER VACCINATION OF STEM CELL TRANSPLANT RECIPIENTS

Sigrun Einarsdottir[1], Ingigerdur Sverrisdottir[1], Krista Vaht[1], Tomas Bergström[2], Mats Brune[1], Per-Ola Andersson[1], Christine Wennerås[2], Per Ljungman[3]

[1]Institute of Medicine, University of Gothenburg, Gothenburg, Sweden, [2]Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden, [3]Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

Background: Revaccination against tetanus and diphtheria after allogeneic hematopoietic stem cell transplant (HCT) is usually effective, but the duration of the immunity is unknown. Due to the lack of data, no general recommendations are provided in guidelines on how to manage long-term survivors, either regarding the need for additional boosters or regular check-ups of serology status. Therefore, humoral immunity against tetanus and diphtheria was investigated in 143 patients having survived at least eight years after transplantation.

Methods: Anti-Diphtheria toxoid Enzyme linked immunosorbent assay (ELISA) IgG (EI 2040-9601G) and Anti-Tetanus Toxoid ELISA IgG (EI 2060-9601G) both from Euroimmun, Lubeck, Germany, were used to determine IgG antibody levels against diphtheria and tetanus toxoid, respectively. Optical Density (OD) values were converted to International Units per mL (IU/mL) based on international WHO standard control sera. Antibody levels below <0.1 IU/mL for diphtheria and <0.01 IU/mL for tetanus were considered "low" or "seronegative". Values between 0.01-0.5 IU/mL for tetanus and 0.1-1.0 IU/mL for diphtheria were considered to represent "partial protection" and levels above 0.5 and 1.0 IU/

mL, respectively were considered "high" and protective. The cut-offs applied were per the ELISA-kits manufacturer's instructions and in accordance with WHO-recommendations.

Results: All patients were in complete remission following the initial transplant or after subsequent donor lymphocyte infusions (DLI). All patients had received at least 3 doses of vaccines, against both tetanus and diphtheria, either monovalent or combination vaccines containing a full dose of the diphtheria toxoid component (D). In addition, one or more booster doses were administered to 21/146 (14 %) of the patients. In all, 39% were seronegative against diphtheria, 52% had "some protection" and 9% had a high titer. In contrast, no patient had become seronegative to tetanus, 32% had "partial protection" against tetanus and 68% had a high titer. In multivariate analysis active Graft-versus-host-disease (GvHD), gender or time from sampling did not affect the probability of becoming seronegative or seropositive. Younger age was associated with lower antibody levels to tetanus toxoid, but age was not correlated with antibody levels against diphtheria toxoid.

TABLE 1. Patient characteristics (n = 143)

Age at transplantation (tx) in years (median, min-max)	38 (0-71)
Age at blood sampling in years (median, min-max)	53 (20-79)
Time from tx-blood sampling (years, min-max)	14 (8-40)
Sex	
Female	75 (52%)
Male	69 (48%)
Conditioning	
Reduced intensity conditioning (RIC)	36 (25%)
Myeloablative conditioning (MAC)	102 (71%)
Missing data on intensity	5 (4%)
Chronic Graft-versus-Host disease (GvHD) at sampling	
YES	22 (23%)
NO	110 (77%)
Ongoing immunosuppressive treatment (IST) at sampling	18 (13%)
YES	18 (13%)
NO	125 (87%)
Secondary malignancy	
YES	17 (12%)
NO	125 (87%)

Conclusions: Tetanus immunity was maintained after vaccination in most long-term survivors, but immunity against diphtheria was poor and boosters should be considered.

Disclosure: Nothing to declare.

13 - Infectious Complications

P369

TIME SERIES CLUSTERING OF CMV KINETICS AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION DISTINGUISHES PHENOTYPES WITHIN CMV-PEAK-TITER-DEFINED RISK GROUPS

Hayder Alhassani[1], Theresa Graf[1], Saskia Leserer[1], Tobias Liebregts[1], Dietrich Beelen[1], Amin Turki[1]

[1]University Hospital Essen, Essen, Germany

Background: Cytomegalovirus (CMV) viremia threatens patients after allogenic hematopoietic cell transplantation (HCT) via increased non-relapse mortality (NRM). Based on previous results underpinning the importance of CMV kinetics for its impact on NRM (Leserer et al., Am J. Hem 2021), we asked if CMV peak-titer-defined cohorts could be further refined using data-science methods on individual, longitudinal CMV data in patients after HCT.

Methods: We modelled CMV kinetics in 8014 whole blood qPCR samples of 505 patients with HCT between 2013 and 2018, which were stratified into risk groups based on peak CMV titers. Patients' individual longitudinal CMV qPCR results were plotted between days 0-200 after HCT and missing data was filled using data interpolation. We then leveraged for the first time the data-science method of time series clustering for assembling viremia kinetics clusters based on their similarity. Subsequent hierarchical and also partitional clustering was performed using dynamic time warping as distance measure. Clustering performance was evaluated by the silhouette coefficient (*Sil*), indicating a separation of clusters between -1 and +1. Model robustness was tested via 10-fold resampling. Clusters were then analysed for clinical outcome associations.

Results: Cumulative incidence of NRM in HCT patients with CMV reactivation at intermediate levels (peak-titers between 12.828 and 64.140IU/ml) comparing time-series clusters 1 and 2 from the 2_1 configuration. B: Individual longitudinal CMV qPCR results of patients in the intermediate risk group divided into clusters 1 and 2. The time series-clustering revealed new phenotypes with distinct clinical outcome, e.g. within the established intermediate CMV peak titer risk group, which previously associated with reduced relapse. Here, it associated patients with multiple CMV reactivations and reduced overall survival ($p = 0.0023$) due to significantly increased NRM ($p = 0.026$) compared to patients with maximal one CMV reactivation. Importantly, patients with only a single CMV reactivation had reduced relapse rates compared to patients without reactivation ($p = 0.054$) and comparable OS, while patients with repeated CMV viremia at intermediate levels had a significantly higher NRM compared to patients without reactivation ($p = 0.001$). Also, within the low-peak-titer group, clustering identified subsets with distinct overall survival (0.036) via shape differences of CMV viremia curves after HCT.

Conclusions: Time series clustering is a new tool for studying CMV kinetics allowing to dissect individual longitudinal patient kinetics. It reproducibly identifies patterns that associate with higher NRM and underscores the importance of CMV viral load kinetics as surrogate for clinical endpoints.

Disclosure: ATT: Consultancy for CSL Behring, Maat Pharma, Onkowissen.tv.

13 - Infectious Complications

P370

TREATMENT DELAY DURING THE COVID-19 PANDEMIC DID NOT SIGNIFICANTLY IMPACT THE OUTCOME OF STEM CELL TRANSPLANT AND CELLULAR THERAPY: A SINGLE INSTITUTION EXPERIENCE

Eden Biltibo[1], Amy Brehm[1], Nancy Long[1], Reena Jayani[1], Katie Gatwood[1], Lindsay Orton[1], Bhagirathbhai Dholaria[1], Bipin Savani[1], Salyka Sengsayadeth[1], Brittney Baer[1], Olalekan Oluwole[1], Adetola Kassim[1]

[1]Vanderbilt University Medical Center, Nashville, United States

Background: The COVID-19 pandemic significantly impacted adult patients with hematologic malignancies. These patients have high risk of contracting and dying from COVID-19 infection. COVID-19 also causes delay in their treatment due to the impact of the pandemic on

Table: Characteristics of patients and disease type in each intervention group

ASCT Recipients					CAR T-Cell Recipients					Allogeneic-SCT Recipients				
	Not Delayed (N = 212)	**Delayed (N = 7)**	**Overall (N = 229)**	**p-value**		**Not Delayed(N = 41)**	**Delayed (N = 1)**	**Overall (N = 42)**	**p-value**		**Delayed (N = 4)**	**Not Delayed (N = 128)**	**Overall (N = 132)**	**p-value**
Gender				0.537					1.000					1.000
M	114 (53.8%)	11 (64.7%)	125 (54.6%)			25 (61.0%)	1 (100%)	26 (61.9%)			2 (50.0%)	60 (46.9%)	62 (47.0%)	
Age				0.648					0.186					0.581
Median [Min, Max]	61.0 [22.0, 79.0]	62.0 [45.0, 78.0]	61.0 [22.0, 79.0]			67.0 [35.0, 82.0]	55.0 [55.0, 55.0]	66.5 [35.0, 82.0]			57.5 [36.0, 62.0]	59.0 [23.0, 74.0]	59.0 [23.0, 74.0]	
Diagnosis				0.970					0.056					0.135
ALCL	1 (0.5%)	0 (0%)	1 (0.4%)		ALL	1 (2.4%)	0 (0%)	1 (2.4%)		ALL	2 (50.0%)	13 (10.2%)	15 (11.4%)	
Amyloidosis	24 (11.3%)	2 (11.8%)	26 (11.4%)		DLBCL	22 (53.7%)	0 (0%)	22 (52.4%)		AML	1 (25.0%)	53 (41.4%)	54 (40.9%)	
APL	1 (0.5%)	0 (0%)	1 (0.4%)		MCL	4 (9.8%)	1 (100%)	5 (11.9%)		ALCL	0 (0%)	1 (0.8%)	1 (0.8%)	
DLBCL	9 (4.2%)	0 (0%)	9 (3.9%)		MM	14 (34.1%)	0 (0%)	14 (33.3%)		CLL	0 (0%)	1 (0.8%)	1 (0.8%)	
FL	1 (0.5%)	0 (0%)	1 (0.4%)							CML	0 (0%)	11 (8.6%)	11 (8.3%)	
HL	17 (8.0%)	0 (0%)	17 (7.4%)							CMML	1 (25.0%)	4 (3.1%)	5 (3.8%)	
LCDD	1 (0.5%)	0 (0%)	1 (0.4%)							MDS	0 (0%)	26 (20.3%)	26 (19.7%)	
MCL	6 (2.8%)	1 (5.9%)	7 (3.1%)							MF	0 (0%)	14 (10.9%)	14 (10.6%)	
MEITL	1 (0.5%)	0 (0%)	1 (0.4%)							T-cell lymphoma	0 (0%)	5 (3.9%)	5 (3.8%)	
MM	144 (67.9%)	14 (82.4%)	158 (69.0%)											
PCNSL	6 (2.8%)	0 (0%)	6 (2.6%)											
T-cell lymphoma	1 (0.5%)	0 (0%)	1 (0.4%)											
Readiness to Intervention in Days				0.047*					0.65					0.637
Median [Min, Max]	63.0 [24.0, 257]	86.0 [21.0, 339]	63.0 [21.0, 339]			51.0 [13.0, 185]	46.0 [46.0, 46.0]	50.0 [13.0, 185]			63.0 [44.0, 160]	70.0 [36.0, 421]	70.0 [36.0, 421]	

the patients, hospital resources, stem cell donor pool, transportation of stem cells, and other essential services. In this study, we sought to understand the impact of delay in allogeneic stem cell transplant (allo-SCT), ASCT and chimeric antigen receptor (CAR) T-cell therapy in the overall survival (OS) of our patients.

Methods: We conducted a retrospective chart review of all adult patients with hematologic malignancies who had autologous SCT, allo-SCT and/or CAR T-cell therapy at Vanderbilt University Stem Cell Transplant (VUSCT) program between March 1st, 2020, and September 1st, 2022. Descriptive statistics was used to summarize patient and disease characteristics. Fisher's exact test and Wilcoxon rank sum test was used to compare variables. Kaplan-Meir curves and log rank tests were used to compare OS. Binary logistic regression was used to evaluate patient and disease variables associated with delayed intervention. Cox regression analysis was performed to determine the hazard of death based on timing of intervention. R version-4.2.2 was used.

Results: Our study included 403 heterogenous hematologic malignancy patients who underwent ASCT (n = 229, 56.8%), allo-SCT (n = 132, 32.8%) and CAR T-cell therapy (n = 42,10.4%). Twenty-two (17 ASCT, 4 allo-SCT and 1 CAR-T) patients were identified to have COVID-specific delay. Amongst the 22, 7 patients had COVID infection prior to transplant and it took 2-8 weeks to seroconvert to a SARS-CoV-2 negative status. The rest of the 22 patients were delayed due to donor COVID infection, patients' preference to postpone intervention or because of the impact of the pandemic in the logistics of SCT and CAR T-cell therapy. Average time from when patients were deemed ready for therapy to actual treatment was 70 days amongst patients who were not delayed versus 96.3 days in those delayed. Patients in both groups had similar characteristics (Table). There was no statistically significant difference in overall survival analysis based on whether intervention was delayed. Median OS was not reached at the time of data censorship (9/1/2022) amongst all the ASCT and CAR T-cell recipients. Allo-SCT recipients had median OS of 365 days in the delayed intervention group (p-value 0.66). The age, gender, disease type, and category of intervention (ASCT, allo-SCT vs CAR T-cell therapy) was not associated with delay in SCT and/or CAR T-cell therapy. When adjusted for age, gender and disease type, delay in intervention did not increase the hazard of death.

Conclusions: Delay in ASCT, allo-SCT and CAR-T cell therapy did not result in statistically significant difference in the OS of our heterogenous patient cohort during the COVID-19 pandemic. Our strategy of transplant prioritization, cryopreservation of stem cells, use of bridging/maintenance therapy and conservative transfusion strategy likely mitigated against adverse outcomes. This approach can be implemented and validated during other pandemics or natural disasters.

Clinical Trial Registry: Not Applicable

Disclosure: Authors do not have disclosures pertaining to this study. This work is made possible by support from:

- Vanderbilt Integrated Molecular Oncology Research Training Program, grant number: 1T32CA217834-01A1
- American Society of Hematology Minority Hematology Fellow Award
- The Carol and Jim O'Hare Fund

13 - Infectious Complications

P371

EVALUATION OF URINE BKV BY DAY 40 POST-HEMATOPOIETIC CELL TRANSPLANT AS PREDICTOR OF BKV-ASSOCIATED HEMORRHAGIC CYSTITIS

Yeon Joo Lee[1,2], Michael Scordo[1,2], Ilya Glezerman[1,2], Gyuri Han[1], Miguel-Angel Perales[1,2], Sergio Giralt[1,2], Ann Jakubowski[1,2], Genovefa Papanicolaou[1,2]

[1]Memorial Sloan Kettering Cancer Center, New York, United States, [2]Weill Cornell Medical College, New York, United States

Background: BK polyomavirus (BKV)-associated with hemorrhagic cystitis (HC) occurs in 7-54% of adult allogeneic hematopoietic cell transplantation (allo-HCT) recipients. Factors contributing to the pathogenesis of early HC (occurring ≤day 40 post-HCT [D + 40]) include toxicity from conditioning, thrombocytopenia, and viral infections. In contrast, viral infections, GVHD, and poor immune reconstitution are the main risk factors for late HC (occurring >D + 40). Approximately 50% of HCT recipients have BKV viruria with the cumulative incidence reached by D + 30 and persisting >D + 100. We conducted a prospective observational study to evaluate the utility of asymptomatic, early BKV viruria (BKV viruria ≤D + 40) as a predictor for late BKV-HC in the first year post-HCT.

Methods: Adult consecutive allo-HCT recipients at Memorial Sloan Kettering Cancer Center from August 2019 through April 2021 were screened for BKV in the urine by quantitative PCR (Viracor Eurofins, Lee's Summit, MO) on Day 0 (range D-14 to D0). The linear range of quantification is 500 to $1.0x10^{10}$ copies/mL. Patients with negative BKV by D0 had repeat screening by D + 40 post-HCT (range D + 20 – D + 40). Early BKV viruria was defined as any value above the lower limit of detection by D + 40. Patients were followed up to 1-year post-HCT for the development of BKV-HC. Urine BKV PCR was ordered as part of routine care for patients with symptoms of cystitis. BKV-HC was defined as: positive BKV with hematuria and symptoms of cystitis (dysuria, frequency, pain, etc.). BKV-HC was defined as early BKV-HC (HC ≤ D + 40) and late BKV-HC (HC > D + 40) post-HCT. The severity of HC was scored using the Bedi criteria (grade 1 [microscopic hematuria], grade 2 [macroscopic hematuria], grade 3 [macroscopic hematuria with clots], grade 4 [macroscopic hematuria with impaired renal function]).

Results: Of 152 patients analyzed (Table 1), 73 (48%) had BKV viruria by D + 40 (33 pre-HCT and 40 post-HCT). Second allo-HCT and recipient or donor CMV seropositivity were associated with BKV viruria by D + 40. Seventeen (11.2%) patients developed BKV-HC (9 patients ≤D + 40 and 8 patients >D + 40). Of 9 patients with early BKV-HC, 8 had BKV-HC grade 2, and 1 had BKV-HC grade 4. Of 8 patients with late BKV-HC, 1 had BKV-HC grade 1, 5 had BKV-HC grade 2, 1 had BKV-HC grade 3, and 1 had BKV-HC grade 4. When we looked at BKV-HC > 40 days, 0/79 (0%) urine BKV negative by D + 40 and 8/73 (11%) urine BKV positive by D + 40 developed late BKV-HC, respectively.

Table 1. Baseline characteristics

Characteristic		Positive urine BKV by D + 40, N = 73 (%)	Negative urine BKV by D + 40, N = 79 (%)	P value
Median age, years (range)		58.6 (20.5-76.3)	62.9 (24.6-77.4)	0.104
Sex	Male	44 (60.3%)	45 (57%)	0.679
	Female	29 (39.7%)	34 (43%)	
Underlying diseases	Acute leukemia	41 (56.2%)	42 (54.4%)	0.882
	Myelodysplastic syndrome	11 (15.1%)	16 (20.3%)	
	Lymphoma	8 (11.0%)	6 (7.6%)	
	CLL/CML/MPD	9 (12.2%)	12 (15.2%)	
	Multiple myeloma	2 (2.7%)	2 (2.5%)	
	Aplastic anemia	2 (2.7%)	1 (1.3%)	

Characteristic		Positive urine BKV by D + 40, N = 73 (%)	Negative urine BKV by D + 40, N = 79 (%)	P value
Indication	Initial HCT	63 (86.4%)	76 (96.3%)	0.029
	Second HCT	10 (13.8%)	3 (3.7%)	
	T-cell depleted	16 (21.9%)	24 (30.4%)	0.315
Graft type	Unmodified	52 (71.2%)	47 (59.5%)	
	Umbilical cord blood	5 (6.8%)	8 (10.1%)	
HLA match	Matched related	13 (17.8%)	16 (20.3%)	0.595
	Matched unrelated	32 (43.8%)	31 (39.2%)	
	Mismatched related	1 (1.4%)	5 (6.3%)	
	Mismatched unrelated	12 (16.4%)	10 (12.7%)	
	Umbilical cord blood	5 (6.8%)	8 (10.1%)	
	Haplo identical	10 (13.7%)	9 (11.4%)	
Conditioning intensity	Myeloablative	28 (38.4%)	33 (41.8%)	0.871
	Reduced intensity	33 (45.2%)	35 (44.3%)	
	Non-myeloablative	12 (16.4%)	11 (13.9%)	
GVHD prophylaxis	T-cell depletion	16 (21.9%)	24 (30.4%)	0.352
	PTCy-based group	27 (37.0%)	29 (36.7%)	
	Cyclosporin/ MMF/ +/−	5 (6.8%)	8 (10.1%)	
	Toclizumab +/− Methotrexate			
	Tacrolimus/ Methotrexate +/− Sirolimus	25 (34.2%)	18 (22.8%)	
Recipient CMV serology	Recipient positive	50 (68.5%)	41 (51.9%)	0.037
	Recipient negative	23 (31.5%)	38 (48.1%)	
Donor CMV serology	Donor positive	39 (53.4%)	29 (36.7%)	0.038
	Donor negative	34 (46.6%)	50 (63.3%)	
Neutrophil engraftment, days (range)		13 (9-31)	14 (8-37)	0.925

Conclusions: Nearly half of allo-HCT patients had BVK viruria by D + 40 post-HCT. Late BKV-HC did not occur in patients without BKV viruria by D + 40, and the presence of BKV viruria by D + 40 was a poor predictor for late BKV-HC in the 11% of patients who developed BKV-HC post-HCT. In contrast, the absence of BKV viruria by D + 40 was a strong negative predictor for late BKV-HC.

Disclosure: Dr. Lee has served as an investigator for Astellas, Karius, AiCuris, and Scynexis and has received research grant support from Merck & Co Inc.

Dr. Scordo:Clinical trial research support to my institution: Angiocrine Bioscience, Inc.; Omeros Corporation; Amgen, Inc. Consultancy: Omeros Corporation; Angiocrine Bioscience, Inc. (past); McKinsey & Company (past). Ad-hoc advisory board: Kite – A Gilead Company (past). CME activity honorarium: i3Health; Medscape, LLC. (past)

Dr. Perales reports honoraria from Adicet, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Syncopation, VectivBio AG, and Vor Biopharma. He serves on DSMBs for Cidara Therapeutics, Medigene, and Sellas Life Sciences, and the scientific advisory board of NexImmune. He has ownership interests in NexImmune and Omeros. He has received institutional research support for clinical trials from Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis.

Dr. Giralt: Advisory board: Amgen, Actinuum, Celgene, Johnson & Johnson, Janssen, JAZZ Pharmaceutical, Takeda, Novartis, KITE, Spectrum Pharma. Research funding: Amgen, Actinuum, Celgene, Johnson & Johnson, Miltenyi, Takeda, Omeros

Dr. Papanicolaou has served as an investigator for Merck & Co Inc, and Shire/Takeda and has received research grant support from Merck & Co Inc, and consulting and other fees from Astellas, Merck & Co Inc, Takeda, Cidara, Amplyx, AlloVir, Octapharma Vera, and Symbio.

13 - Infectious Complications

P372

CMV REACTIVATION – A TWO-EDGED SWORD AGAINST RELAPSE

Vered Stavi[1], Mats Remberger[2], Carol Chen[3], Jonas Mattsson[3], Jeffrey Lipton[3]

[1]Soroka Medical Center, Beer Sheva, Israel, Uppsala University and KFUE, Uppsala University Hospital, Uppsala, Sweden, [3]Princess Margaret Cancer Centre, toronto, Canada

Background: Cytomegalovirus (CMV) is the most common opportunistic infection in allogeneic hematopoietic cell transplantation (HSCT) recipients. Pre-emptive strategies have dramatically decreased the incidence of early CMV disease. Prophylaxis treatment with Letermovir reduce significantly the incidence of CMV reactivation, at least during the treatment time.

Refractory or resistant CMV infection remains challenging.

Methods: We performed a retrospective analysis of 1147 consecutive allogeneic HSCTs performed at the Princess Margaret Cancer Centre, Toronto, Canada between Aug 2010 and March 2020. We collected all the data for each episode of reactivation following HSCT from patients' electronic medical record.

We used the CMV Resistance Working Group definitions for refractory and resistant CMV.

Results: Among 1147 patients 630 (54.9%) had at least one CMV reactivation. The characteristics are summarized in table 1. There were more HAPLO and MMUD among the patients who had CMV reactivation than among those who didn't (11.0% vs 5.0% $p < 0.001$ and 17.0% vs 11.6% $P = 0.01$ respectively).

CMV refractoriness

Overall, out of 630 patients with CMV reactivation 26 (4.1%) patients were defined as refractory and 166 (26.3%) as probable refractory.

In univariate analysis, several variables influenced the risk of probable refractory\ refractory CMV reactivation. HLA MM, PTCy and RIC all increased the risk. Lymphocytes $>0.45\times10^9$/L at the time of reactivation, and more than one week from the reactivation to initiating treatment were found to decrease the risk. In the multivariate model only HLA MM, PTCy, lymphocytes $>0.45\times10^9$/L and more than one week from the reactivation to initiating treatment were shown to have an impact on having probable refractory or refractory CMV reactivation.

The risk for having refractory or probable refractory CMV reactivation decrease after the first reactivation – while it's 30.5% after the first reactivation, it drops to 15.8% after the second one and to 14.1% after the third.

Outcome: The OS of patients who didn't have CMV reactivation was better than in those who had (1, 3 and 5 year survival 67.3% vs 60.8%, 56.7% vs. 46.7% and 50.1% vs 44.0% respectively, $p = 0.02$). The NRM was higher among those who had CMV reactivation (at 1, 3 and 5 years post HSCT 29.5% vs. 20.1%, 37.6% vs. 24.4% and 39.1% vs. 27.3% respectively $p < 0.001$).

The relapse rate was lower among those who had CMV reactivation (19.6% vs. 24.5% $p = 0.03$). This was only apparent among those who had myeloid malignancy ($p = 0.01$).

Patients with refractory CMV infection had higher CMV related mortality compared to those who responded to CMV treatment, 11.5% vs 3.9% at one year, $p = 0.026$. Probable refractory did not affect CMV related mortality (6.0%, $p = 0.40$ vs not refractory). Refractory or probable refractory does not increase the risk of other causes of mortality.

Table 1 – patients characteristics

	All patients (1147)	CMV infection (630)	No CMV infection (517)	p-value
Age	56 (18-76)	56 (18-76)	55 (18-74)	0.009
Gender (M/F)	624/523	321/309	303/214	0.01
Diagnose: Acute Leukemia	673 (58.7)	384 (61.0)	289 (55.9)	0.10
Chronic Leukemia	81 (7.1)	42 (6.7)	39 (7.5)	
MDS/MPN	187 (18.3)	98 (15.6)	89 (17.2)	
Lymphoma	73 (6.4)	37 (5.9)	36 (7.0)	
MF	91 (7.9)	47(7.5)	44 (8.5)	
Non-malignant	36 (3.1)	19 (3.0)	17 (3.3)	
Other	5 (0.4)	2 (0.3)	3 (0.6)	
Donor:MRD	378 (33.0)	194 (30.8)	184 (35.6)	0.10
MUD	507 (44.2)	260 (41.2)	247 (47.8)	0.03
Haplo	95 (8.3)	69 (11.0)	26 (5.0)	<0.001
MMUD	167 (14.6)	107 (17.0)	60 (11.6)	0.01
Conditioning:MAC	439 (38.3)	227 (36.0)	212 (41.0)	0.10
RIC	708 (61.7)	403 (64.0)	305 (59.0)	
GVHD prophylaxis:PTCy	33 (2.9)	20 (3.2)	13 (2.5)	0.68
ATG	298 (26.0)	165 (26.2)	133 (25.7)	
PTCy+ATG	472 (41.2)	264 (41.9)	208 (40.2)	
Other	344 (30.0)	181 (28.7)	163 (31.5)	

Conclusions: The effect of CMV reactivation on relapse risk is controversial. In this relatively large retrospective study CMV reactivation was found to decrease the risk of relapse in patients with myeloid malignancy. It may contribute to a beneficial GVL effect, though it can't explain why it does so only in the myeloid malignancies.

Disclosure: Nothing to declare.

13 - Infectious Complications

P373

CD4$^+$ T CELLS ARE THE MAJOR PREDICTOR OF HCMV CONTROL IN ALLOGENEIC STEM CELL TRANSPLANT RECIPIENTS ON LETERMOVIR PROPHYLAXIS

Chris David Lauruschkat[1], Ihsan Muchsin[2], Alice Rein[1], Florian Erhard[2], Denise Grathwohl[1], Lars Dölken[2,3], Carolin Köchel[1], Christine S. Falk[4,5,6], Hermann Einsele[1], Sebastian Wurster[7], G. Ulrich Grigoleit[8,1], Sabrina Kraus[1]

[1]University Hospital of Wuerzburg, Wuerzburg, Germany, [2]Julius-Maximilians-University Wuerzburg, Wuerzburg, Germany, [3]Helmholtz-Institute for RNA-based Infection Research (HIRI), Wuerzburg, Germany, [4]Institute of Transplant Immunology, Hanover, Germany, [5]German Center for Infection Research, Hannover Braunschweig Site, Germany, [6]German Center for Lung Diseases DZL/BREATH, Hanover Site, Germany, [7]The University of Texas MD Anderson Cancer Center, Houston, United States, [8]Helios Klinikum Duisburg, Duisburg, Germany

Background: Human cytomegalovirus (HCMV) is the most common viral complication in patients after allogeneic stem cell transplantation (alloSCT), resulting in high mortality and morbidity. Recently, antiviral letermovir prophylaxis during the first 100 days after alloSCT replaced PCR-guided preemptive therapy (PT) as primary standard of care for HCMV reactivations. Here, we compared ("memory-like") NK-cell and (HCMV-specific) T-cell reconstitution in alloSCT recipients receiving PT or letermovir prophylaxis in order to identify potential biomarkers for future prolonged and symptomatic HCMV reactivation.

Methods: Peripheral blood mononuclear cells (PBMCs) of 54 alloSCT recipients on either antiviral strategy were cryopreserved at day +30, +60, +90 and +120 post alloSCT. PBMCs were analyzed for NK-cell (CD56$^+$) "memory-like" NK-cell (CD56^{dim}F-cεRIγ$^-$ and CD56^{dim}NKG2C/CD159c$^+$) and T-cell (CD3, CD4$^+$,CD8$^+$, CD25$^+$, CD127$^+$) markers by flow cytometry. Background-corrected HCMV-specific T-helper (CD4$^+$IFNγ$^+$) and cytotoxic (CD8$^+$IFNγ$^+$CD107a$^+$) T cells were quantified after stimulation with a pp65 peptide mix for 16-18h. Mann- Whitney *U* test, Benjamini-Hochberg procedure (if applicable) and receiver operator curve (ROC) analysis were used to test for statistical significance.

Results: Letermovir prophylaxis is effective in preventing HCMV reactivation and decreased HCMV peak loads until day +120 (0 vs. 1550 copies/mL, $p < 0.001$) and +365 (151 vs. 1550 copies/mL, $p = 0.043$) compared to PT. The first median HCMV reactivation was delayed by 138 days (day +33 vs. day +171, $p < 0.001$) in letermovir-treated recipients. Antiviral prophylaxis resulted in decreased T-cell numbers (day +120: 126 vs. 26 CD8$^+$ cells/µL, $p = 0.024$), however, increased NK-cell numbers (day +120: 131 vs. 244 CD3$^-$CD56$^+$cells/µL, $p = 0.006$). Interestingly, despite the inhibition of HCMV replication by letermovir, we quantified high numbers of "memory-like" NK cells (CD56^{dim}F-cεRIγ$^-$ and CD56^{dim}NKG2C/CD159c$^+$) and an expansion of HCMV-specific CD4$^+$ [1.6 (day +30) vs. 7.8 (day +90) CD4$^+$IFNγ$^+$ cells/100µL at day +90, $p = 0.029$] and HCMV-specific CD8$^+$ [0.9 (day +30) vs. 6.9 (day +90) CD8$^+$IFNγ$^+$CD107a$^+$ cells/100µL at day +90, $p = 0.044$] T cells. When comparing patients on letermovir prophylaxis with non/short-term HCMV reactivation to letermovir patients with prolonged and symptomatic HCMV reactivation (long-term reactivating), HCMV-specific CD4$^+$ T-cell frequencies were increased in non/short-term reactivating patients (day +60: 0.00 vs. 0.35% CD4$^+$IFNγ$^+$ cells/CD4$^+$, $p = 0.018$). In addition, regulatory T cells (Tregs) were decreased in non/short-term reactivating patients (day +90: 2.2 vs. 6.2% CD4$^+$CD25$^+$CD127^{dim}/CD4$^+$ cells, $p = 0.019$). Along these lines, ROC analysis revealed HCMV specific CD4$^+$ (day +60: $p = 0.019$) and Tregs (day +90: $p = 0.021$) as promising biomarkers for future prolonged and symptomatic HCMV reactivation. In contrast, "memory-like" NK cells and HCMV-specific CD8$^+$ T cells were less predictive.

Conclusions: Letermovir prophylaxis delays HCMV reactivation and alters NK- and T-cell reconstitution. High numbers of HCMV-specific CD4$^+$ T cells and low numbers of Tregs seem to be pivotal

to suppress HCMV reactivations in letermovir patients. This finding might have clinical relevance. HCMV-specific $CD4^+$ responses can be measured by commercially available IFN-γ release assays (IGRAs). Addition of Treg signature cytokines to IFNγ and the implementation of IGRA testing at the end of letermovir prophylaxis might lead to the identification of patients at high-risk for prolonged and symptomatic HCMV reactivation. These high-risk patients might benefit from prolonged administration of letermovir.

Disclosure: Nothing to declare.

13 - Infectious Complications

P374

NIRMATRELVIR/RITONAVIR AND TIXAGEVIMAB/CILGAVIMAB AS SARS-COV-2 TREATMENT IN PEDIATRIC AND YOUNG ADULT PATIENTS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) OR CD19-DIRECTED CAR T-CELL TREATMENT

Federica Galaverna[1], Pietro Merli[1], Ilaria Pili[1], Cristina Russo[1], Stefania Bernardi[1], Daria Pagliara[1], Roberto Carta[1], Barbarella Lucarelli[1], Maria Antonietta De Ioris[1], Emilia Boccieri[1], Chiara Rosignoli[1], Marco Becilli[1], Mattia Algeri[1], Marialuigia Catanoso[1], Francesco Fabozzi[1], Francesco Quagliarella[1], Stefania Gaspari[1], Francesca del Bufalo[1], Angela Mastronuzzi[1], Carlo Federico Perno[1], Franco Locatelli[1,2]

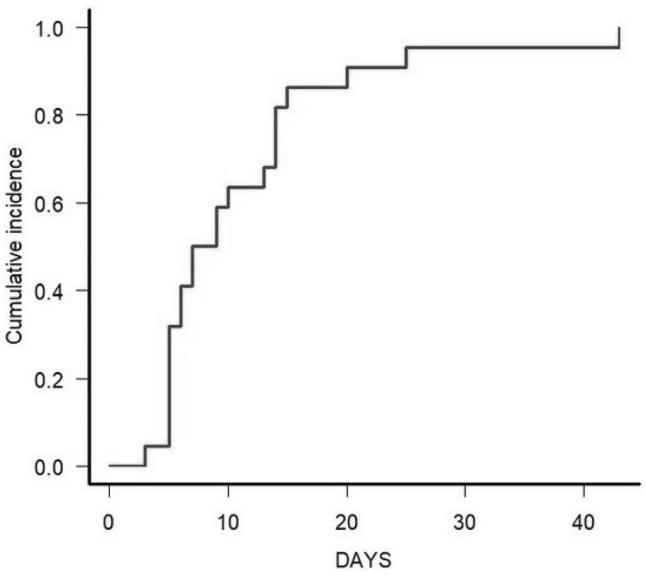
[1]IRCSS Ospedale Pediatrico Bambino Gesu', Roma, Italy, [2]Catholic University of Sacred Heart, Roma, Italy

Background: Patients who undergo HSCT or B-cell depleting therapies (e.g., CD19-directed CAR T-cell treatment) are at higher risk for serious complications during SARS-CoV-2 infection. Nirmatrelvir/ritonavir and tixagevimab/cilgavimab demonstrated activity against SARS-CoV-2 and have been shown to reduce the risk of hospitalization and death among adult patients with COVID-19, but only few data are available in the pediatric population.

Methods: We retrospectively analyzed 29 pediatric and young adult patients who received Nirmatrelvir/ritonavir with or without tixagevimab/cilgavimab for SARS-CoV-2 infection after HSCT or CD19-directed CAR T-cell treatment between April and November 2022. Patients were given antiviral treatment on an off-label basis if SARS-CoV-2 infection occurred within 6 months after HSCT/CART-Cell and/or persistent B-cell aplasia or severe lymphopenia were present.

Results:

Pediatric age groups, n (%)	Infant (1 month to 1 year)	1 (3)
	Toddler and preschool (2-5 years)	5 (17)
	School-age children (6-12 years)	10 (35)
	Adolescents (13-18 years)	10 (35)
	Young adults (19-25 years)	3 (10)
Disease, n (%)		22 (76)
	Hemoglobinopathies	2 (7)
	Bone marrow failure syndromes	3 (10)
	Primary immunodeficiency	2 (7)
Type of treatment, n (%)	HSCT	23 (79)
	CAR-T Cell therapy	6 (21)
Previous SARS-CoV-2 vaccine, n (%)		13 (45)
Concomitant conditions, n (%)	Grade II/III aGvHD	4 (14)
	Autoimmune Hemolytic Anemia	2 (7)
	End-stage renal disease	1 (3)
	Disease relapse	1 (3)
Total Lymphocyte count < 1000/ml, n (%)		23 (79)
B-cell aplasia, n (%)		22 (76)
Total Neutrophil count < 500/ml, n (%)		4 (14)
Sars-CoV-2 genotype	Omicron BA.5	6 (21)
	Omicron BA.4	3 (10)
	Omicron BA.2	4 (14)
	Omicron BE.1	2 (7)
	Missing	14 (48)
COVID Symptoms, n (%)	Fever	24 (83)
	Upper respiratory symptoms	11 (38)
Notable Concomitant drugs	Triazole	14 (48)
	Calcineurin Inhibitors	6 (21)
		Total N = 29



Clinical characteristics of patients are listed in Table1. Median time from treatment to SARS-CoV-2 infection was 190 days (range 1-548), with a median age at infection of 12.7 years (range 1-25). Twenty-three patients received nirmatrelvir/ritonavir after HSCT and 6 after CAR T-cell, while tixagevimab/cilgavimab was administered in 18 cases within 48 hours from SARS-CoV-2 diagnosis. Thirteen patients experienced the infection after receiving SARS-CoV-2 vaccination at a median interval of 80 days after the second dose. Fever was the most common clinical sign (83% of the cases), while 14 (48%) patients experienced upper respiratory syndrome; 7 patients were hospitalized due to persistent/worsening symptoms. Among the 15 patients tested for variants, Omicron BA.5 was the most frequent detected SARS-CoV-2 sublineage (40% of the cases tested). Antiviral treatment and tixagevimab/cilgavimab were well-tolerated without significant toxicity; concomitant CYP3A-metabolised drugs were stopped during Paxlovid administration in all but 2 patients,

who continued cyclosporine at a reduced dosage with close monitoring of plasmatic levels.

All patients reached SARS-Cov2 molecular negativity with a median time of 7 days (range 2-43) after the beginning of nirmatrelvir/ritonavir (Fig.1). Twenty-three patients stopped antiviral treatment after 5 days while 6 patients continued it up to 10 days due to persistent SARS-CoV-2 positivity; 5 patients experienced SARS-CoV-2 viral rebound with a median interval of 6 days (range 5-20) after nirmatrelvir/ritonavir discontinuation and were given additional 5-day treatment. None of the 6 patients treated with nirmatrelvir/ritonavir for 10 consecutive days experienced viral rebound; moreover, molecular negativity rate at the end of more than 5-day treatment was 45%. No patient experienced respiratory failure, nor was admitted to the Intensive Care Unit nor died because of COVID-19; one and 2 patients developed signs of de novo thrombotic thrombocytopenic microangiopathy and autoimmune-hemolytic anemia (one reactivation and one de novo), respectively, which resolved after treatment.

Conclusions: Nirmatrelvir/ritonavir, with or without tixagevimab/cilgavimab, confirms its safety and efficacy in preventing serious SARS-CoV-2 complications also in pediatric and young adult patients after HSCT or CAR T-cell treatment. Longer treatment, up to 10 days, seems safe and more effective in preventing viral rebound.

Disclosure: nothing to disclosure.

13 - Infectious Complications

P375

PRE-EMPTIVE RITUXIMAB FOR EBV REACTIVATION IN TIMES OF COVID-19: IS IT REALLY NECESSARY?

Ana Claudia Ferrari dos Santos[1], Anderson João Simione[1], Anna Beatriz Coelho de Souza[1], Juliana Ribeiro do Prado Moreno[1], Lilian Perílio Zanetti[1], Leila Cibele Serra Oliveira[1], Iago Colturato[1], Fernanda Rodrigues Barbieri[1], Juliana Silva Santos[1], Erika Rodrigues Pontes Delattre[1], Carolina Ferreira Mascarenhas[1], Leticia Galbier Ricetto Pegorari[1], Mair Pedro de Souza[1], Vergílio Antonio Rensi Colturato[1], Clarisse Martins Machado[2,1]

[1]Hospital Amaral Carvalho, Jau, Brazil, [2]Virology Laboratory, Institute of Tropical Medicine (LIM52), School of Medicine, USP, São Paulo, Brazil

Background: The cumulative incidence of Epstein–Barr virus (EBV) reactivation after HCT can be as high as 60%. Although rare (1.2%-13%), post-transplant lymphoproliferative disorders (PTLD) can have a mortality rate greater than 30%. Prospective monitoring of EBV DNAemia and preemptive rituximab have been recommended in HCT recipients at increased risk of developing PTLD. However, recent studies show a poor response to COVID-19 vaccine (19%) in hematological patients (pts) who received rituximab up to 12 months before vaccination. As no specific threshold of EBV DNAemia is established for initiation of preventive therapy, it can be assumed that many pts may possibly being treated with rituximab unnecessarily, which may affect vaccine responses and the course of COVID-19. In this retrospective study, we reviewed the EBV-related outcomes in high risk patients transplanted from 2017 to 2021 at an HCT centre where rituximab is introduced only in pts with increasing EBV DNAemia levels who do not respond to immunosuppression reduction, or those who develop EBV end-organ diseases or PTLD.

Methods: We conducted a retrospective cohort study to estimate the cumulative incidence of EBV reactivation, EBV end-organ disease, PTLD and other outcomes (overall survival, non-relapse mortality and relapses) in allogeneic HCT recipients (MUD, MRD with mismatch and haploidentical). Detection of EBV DNAemia was performed weekly up to d120, by qPCR (Master kit for Epstein-barr virus quantification, Mobius Life Science, Pinhais/Brazil). EBV viral load (VL) was prospectively followed-up by TID doctor and the lab team. Whenever a VL increase of ≥ 1log within one week was detected, a WhatsApp alert was sent to the HCT team that promptly started IS reduction and EBV workup (end-organ disease and images). Rituximab was introduced in the case of EBV encephalitis, PTLD or if no response to IS reduction. EBV reactivation, non-relapse mortality and relapse were estimated by cumulative incidence. Overall survival was estimated by Kaplan Meyer method.

Results: 328 allo-HCT were included. Cumulative incidence of EBV DNAemia was 54.6% (49-59.9%). 178 pts (64 haplo 37.2%; 114 MUD 73.1%, $p < 0.0001$) had EBV reactivation at a median of 53 (3-439) days. Only 12 pts (6.7%) used rituximab, 5 of them due to EBV encephalitis, and one (0.6%) had PTLD. By univariate analysis, the variables significantly associated with EBV reactivation were MUD HCT and source of stem cells (PBSC). The rituximab restrictive policy adopted in our center did not impact significantly the overall survival ($p = 0{,}078$), non-relapse mortality ($p = 0{,}836$) and relapses ($p = 0{,}304$).

Conclusions: In our series, MUD HSCT posed the highest risk for EBV reactivation. EBV encephalitis was the most frequent EBV end-organ disease diagnosed (6.7%). PTLD was rare (0.6%), below the rates described in the literature. Although preemptive rituximab is recommended in high risk pts, IS reduction could control most of the episodes of EBV reactivation, with no impact on OS, relapses and NRM. In times of COVID-19, rituximab should be used with caution, and restricted to symptomatic patients who have not responded to the IS reduction or developed EBV end-organ disease or PTLD.

Disclosure: Nothing to declare.

13 - Infectious Complications

P376

IMPACT OF TIXAGEVIMAB/CILGAVIMAB PROPHYLAXIS IN PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTS AND CAR-T CELLS THERAPY: A PROSPECTIVE SINGLE CENTER EXPERIENCE

Elisabetta Xue[1], Gianluca Scorpio[1], Daniela Clerici[1], Francesca Farina[1], Edoardo Campodonico[1], Andrea Acerbis[1], PAOLO FIORE[1], Alessandro Bruno[1], Matteo Giovanni Carrabba[1], Jacopo Peccatori[1], Raffaella Greco[1], Maria Teresa Lupo Stanghellini[1], Fabio Ciceri[1], Consuelo Corti[1]

[1]San Raffaele Hospital, Milan, Italy

Background: Patients undergoing CAR-T-cell therapy and HSCT are at increased risk for SARS-CoV-2 infection, with older age, poor performance status and high immunodeficiency scoring index being major risk factors for poorer outcomes. This population develops lower protective response rate to SARS-CoV-2-specific vaccination compared to general population. In March 2022, tixagevimab/cilgavimab, a combination of anti-SarsCov2 spike glycoprotein monoclonal antibodies, was approved in Europe for pre-exposure prophylaxis in immunocompromised patients. We aimed to investigate the use of tixagevimab/cilgavimab in CAR-T-cell and allogeneic HSCT recipients in our Institution.

Methods: Starting in April 2022, all patients undergoing CAR-T-cell and allo-HSCT were administered a single intramuscular tixagevimab/cilgavimab 150/150 mg before hospital discharge.

Results: Between April and August 2022, when Covid-19 BA.4 and .5 variants were spreading, seven CAR-T-cell recipients and twenty-six HSCT recipients received prophylactic tixagevimab/cilgavimab a median of 19 days after CAR-T-cell (range 14-45) and 51 days after HSCT (r18-417), respectively. Seven out of twenty-six HSCT patients were beyond day100 and received tixagevimab/cilgavimab due to profound GvHD-related immunosuppressed status. No patients reported adverse events from drug administration.

In the CAR-T-cell group, six had DLBCL, one acute lymphoblastic leukemia; all but one had received ≥3 anti- SARS-CoV-2 vaccination doses a median of 154 days pre-CAR-T-cell (r48-272). Follow-up lasted a median of 199 days post-CAR-T-cell (r119-241). Two patients developed Covid-19 68 and 156 days after CAR-T-cell, and 23 and 140 days after tixagevimab/cilgavimab, respectively. Both had fever and mild respiratory symptoms without criteria for pneumonia. One received nirmatrelvir/ritonavir and had negative swab after 20 days, and one developed Covid-19 while undergoing salvage treatment for disease relapse, received nirmatrelvir/ritonavir but had asymptomatic viral shedding for over two months.

In the HSCT group, diagnoses were acute myeloid (n = 14) and lymphoblastic (n = 2) leukemia, myeloproliferative (n = 4) and lymphoproliferative (n = 4) diseases, myelodysplasia (n = 1), immunodeficiency (n = 1). Thirteen received myeloablative conditioning, twenty-four received post-transplant cyclophosphamide. Five were SarsCov2 unvaccinated, two had received a single anti-SARS-CoV-2 vaccination dose whereas nineteen had received ≥2 doses, most recent vaccination being a median of 175 days pre-HSCT (r29-373). Follow-up lasted a median of 185 days post-HSCT (r120-509). Four developed Covid-19 a median of 107 days after tixagevimab/cilgavimab administration (r58-149); all had CD4 below 200/mcl at time of infection, and only one showed B-cell recovery. One was still receiving immunosuppressants, two were receiving anti-leukemic pre-emptive therapy; none experienced GvHD. All received remdesivir. Three had fever and mild respiratory symptoms and were managed in outpatient setting, two of which are still positive at last follow up and one having a negative swab after 62 days. One required inpatient admission due to pneumonia, and successfully recovered, with a negative swab after 34 days.

Conclusions: Covid-19 in CAR-T and allo-HSCT recipients can have dismal prognosis. In our prospective cohort, tixagevimab/cilgavimab administration was safe and prevented patients from severe forms of infection. Tixagevimab/cilgavimab should be considered as a standard Covid-19 prophylaxis in early phases post-HSCT and CAR-T, carefully monitoring for the dynamics of SARS-CoV-2 variants in the community. Further investigation to evaluate the possibility of multiple tixagevimab/cilgavimab administration should be considered in highly immunocompromised patients.

Disclosure: Nothing to declare.

13 - Infectious Complications

P377

CLINICAL EXPERIENCE WITH LETERMOVIR FOR CMV-PROPHYLAXIS IN HEMATO-ONCOLOGICAL PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION (CELESTIAL): AN OBSERVATIONAL STUDY

Sebastian Wingen-Heimann[1], Annika Classen[1], Torsten Steinbrunn[2], Sabrina Kraus[2], Timo Schmitt[3], Daniel Teschner[2], Vedat Demirkoparan[3], Corinna Hebermehl[3], Olaf Penack[4], Igor-Wolfgang Blau[4], Andrés Rettig[5], Claudia Wehr[5], Sina Hopff[1], Jörg Janne Vehreschild[1]

[1]University Hospital of Cologne, Cologne, Germany, [2]University Hospital of Würzburg, Würzburg, Germany, [3]University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany, [4]Charité Universitätsmedizin Berlin, Berlin, Germany, [5]Medical Center - University of Freiburg, Freiburg, Germany

Background: Infections with cytomegalovirus (CMV) represent a major health challenge in patients undergoing allogeneic stem cell transplantation (aSCT). CMV prophylaxis with letermovir (LET) is a promising option to improve clinical outcome, but real-world clinical and economic evaluation of LET in Germany are lacking.

Methods: An ongoing retrospective, observational, multicenter cohort study of aSCT patients with documented CMV seropositivity in a German tertiary care center between 01/2016 – 12/2020 was implemented by using an epidemiological study platform accessible via www.ClinicalSurveys.net. The study is performed in a matched case/control design of patients who received LET (case group) vs. patients who received no or other antivirals against CMV prior to availability of LET (historical control group) and observed a follow-up period until week 48 following aSCT. Matching criteria were i.a. CMV risk status, age, and underlying disease. The primary study endpoint was prevention of clinically significant CMV infection (csCMVi; defined as onset of CMV end-organ disease or initiation of anti-CMV pre-emptive therapy based on CMV viremia).

Results: To date, 290 (182 case group, 108 historical control group) cases from five participating centers were completely documented into the eCRF and suitable for statistical analysis. In both groups, median age at time of aSCT was 59 years (range: 18-77) and 128 patients (44%) were female. Acute myeloid leukemia was the predominant underlying disease (n = 146; 50%). In the case and the historical control group, csCMVi occurred in 63 patients (35%) and 61 patients (56%; $P < 0.001$) until the end of the observational period, respectively. No adverse or severe adverse events was reported in the case group. The mean initial hospital length of stay with aSCT in the case vs. historical control group was 50 days (95% CI: 47-53 days) vs. 57 days (95% CI: 52-62 days; $P = 0.045$), respectively. At the end of the observational period, 130 patients (71%) in the case group and 69 patients (64%; $P = 0.181$) in the historical control group were alive, whereby two patients in the case group (1%) and eight patients in the historical control group (7%, $P = 0.004$) were rated as CMV related deaths, respectively.

Conclusions: Preliminary study results demonstrate a significantly lower rate of csCMVi and mortality related to csCMVi in the LET patient cohort compared to historical controls not receiving LET. Additionally, CMV-prophylaxis with LET seems to be safe and well tolerated and may prevent significant adverse effects compared to other conventional antivirals.

Disclosure: Sebastian M. Wingen-Heimann, Annika Y. Classen, Sina Hopff, Jörg Janne Vehreschild: Research grant from MSD.

Olaf Penack: Honorarium and travel support, advisory board member of MSD.

All other authors: Nothing to declare.

13 - Infectious Complications

P378

LETERMOVIR FOR CMV INFECTION IN PEDIATRIC PATIENTS UNDERGOING ALLOGENIC HSCT: REAL-LIFE RETROSPECTIVE ANALYSIS BY INFECTIOUS DISEASES WORKING GROUP OF ITALIAN ASSOCIATION OF PEDIATRIC HEMATOLOGY-ONCOLOGY (AIEOP)

Francesco Baccelli[1], Federica Galaverna[2], Daniele Zama[1], Gloria Tridello[3], Alice Giacomazzi[3], Riccardo Masetti[1], Elena Soncini[4], Rossella Mura[5], Federica Barzaghi[6], Antonella Colombini[7], Giulia Prunotto[7], Maria Rosaria D'Amico[8], Elisabetta Calore[9], Maria Grazia Petris[9], Katia Perruccio[10], Pietro Gasperini[11], Francesco Quagliarella[2], Daria Pagliara[2], Franco Locatelli[2,12], Simone Cesaro[3]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [2]IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy, [3]Azienda Ospedaliera Universitaria Integrata, Verona, Italy, [4]ASST Spedali Civili, Brescia, Italy, [5]Azienda Ospedaliera Brotzu, Cagliari, Italy, [6]IRCCS Ospedale San Raffaele, Milano, Italy, [7]Fondazione MBBM - Ospedale San Gerardo, Monza, Italy, [8]AORN Santobono-Pausilipon, Napoli, Italy, [9]Azienda Ospedale-Università di Padova, Padova, Italy, [10]Ospedale Santa Maria della Misericordia, Perugia, Italy, [11]Azienda Unità Sanitaria Locale di Rimini, Rimini, Italy, [12]Catholic University of the Sacred Heart, Roma, Italy

Background: The use of Letermovir prophylaxis has changed the approach to CMV infection in adult HSCT setting, demonstrating to be safe and able to reduce cumulative incidence of CMV reactivation and all-cause mortality. It is the only approved prophylactic strategy with high level of evidence in current ECIL recommendations, while still not conclusive results have been reported regarding CMV treatment. Limited data are available about Letermovir use in pediatric HSCT recipients in which it is used off-label on single-patient basis.

Methods: We retrospectively analyzed data about patients < 18 years who received Letermovir as off-label indication for primary/secondary prophylaxis or therapy from January 2019 to August 2022 among 11 centers of the AIEOP network.

Results: Patients: Letermovir was used as primary or secondary prophylaxis or CMV treatment in 42, 32 and 24 cases, respectively, for a total of 98 courses in 89 transplanted children. Median age at HSCT was 7.2 years (0.2-17.4). Patient, disease and transplant characteristics are listed in Table.

Letermovir administration: Letermovir was given according to patient weight at a median dose of 8 mg/kg/die (120-480 mg/die) with dose reduction in case of concomitant cyclosporine administration.

Safety: No discontinuation due to severe toxicity was reported; 8 grade II and 1 grade III adverse events attributable to the drug were documented, grade II nausea/vomiting being the most frequent (5 cases). Prophylaxis: Median duration was 100 days (15-507) for primary and 90 days (9-325) for secondary prophylaxis (CMV R/D status detailed in Table). None of the patients experienced CMV clinically significant reactivation during Letermovir administration (median maximum CMV-viremia 109 and 517 UI/ml during primary and secondary prophylaxis, respectively). After Letermovir discontinuation, asymptomatic CMV reactivation occurred in 16 cases (9 after primary and 7 after secondary prophylaxis) successfully treated with standard antiviral therapy.

Therapy: Median duration as therapy was 37 days (6-159). Median CMV copies at start of therapy was 2860 UI/ml and 5 cases of CMV disease were treated (4 pneumonia and one gastrointestinal). Among the 24 therapeutic courses, Letermovir showed an overall response rate of 87.5%, reaching CMV negativity in 21 cases. CMV asymptomatic reactivation after treatment suspension occurred in 4 cases, while no cases of CMV disease were reported.

Survival: With a median follow-up of 10.9 months (8.3-12.7), 12 patients (13.5%) died, with 1-year OS of 86%. No CMV-related death was reported in the whole cohort. No GVHD-related deaths were documented in the prophylaxis groups.

	Primary Prophylaxis N = 42 (47.2%)	**Secondary prophylaxis N = 25 (28.1%)**	**Therapy N = 22 (24.7%)**	**Total N = 89 (100.0%)**
	Primary Prophylaxis N = 42 (47.2%)	Secondary prophylaxis N = 25 (28.1%)	Therapy N = 22 (24.7%)	Total N = 89 (100.0%)
Sex F/M, n (%)	13/29	9/16	13/9	35/54 (39.3/60.7)
Diagnosis Malignant/Non malignant, n (%)	28/14	20/5	15/7	63/26 (70.8/29.2)
HSCT number 1/2, n (%)	38/4	20/5	19/3	77/12 (86.5/13.5)
SCT source, BM/CB/PB, n (%)	20/1/21	13/0/12	11/0/11	44/1/44 (49.4/1.1/49.4)
SCT donor, unrelated/sibling/haplo, n (%)	26/2/14	12/1/12	9/6/7	47/9/33 (52.8/10.1/37.1)
Graft manipulation, no/yes, n (%)	23/19	18/7	12/10	53/36 (59.6/40.4)
ATG, no/ yes, n (%)	4/38	6/19	7/15	17/72 (19.1/80.9)
Conditioning regimen, MAC/RIC, n (%)	37/5	24/1	17/5	78/11 (87.6/12.4)
Conditioning, TBI based/BU based/ Other, n (%)	19/9/14	14/3/8	9/4/9	42/16/31 (47.2/18.0/34.8)
CMV R/D, n (%)				
NEG/POS	8	1	0	9 (10.1)
POS/NEG	18	4	8	30 (33.7)
POS/POS	16	21	14	51 (57.2)
CD 34+ infused x 10^6, median (range)	6.6 (0.2 - 23.5)	6.1 (2.1 - 14.8)	6.7 (2.6 - 17.5)	6.6 (0.2 - 23.5) [NA in 6/89]
TNC infused x 10^8, median (range)	4.4 (0.5 - 10.4)	5.3 (0.3 - 17.4)	3.9 (0.2 - 7.8)	4.0 (0.2-17.4) [NA in 15/89]
Acute GVHD, n (%)				
No-I	28	12	16	56 (62.9)
II-IV	14	13	6	33 (37.1)
Chronic GVHD (in 79/89 patients alive at 100 days), n (%)				
No	35	20	16	71
Limited	0	0	4	4
Extensive	2	2	0	4

Conclusions: This is the largest report on Letermovir use in pediatric HSCT recipients. These real-life data confirm an excellent toxicity profile, also in the pediatric population. In the prophylaxis setting, the efficacy data are promising, though limited. No CMV-related deaths were reported. Extensive immune recovery studies are needed to elucidate the impact of Letermovir in restoring CMV-specific immunity. The promising results in CMV-infection treatment should be addressed in larger, prospective trials.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare.

13 - Infectious Complications

P379

DOSAGE, SAFETY AND EFFICACY OF POSACONAZOLE AS PRIMARY ANTIFUNGAL PROPHYLAXIS IN HIGH-RISK RECIPIENTS OF ALLOGENEIC STEM CELL TRANSPLANTATION

Valentin Letailleur[1], Maxime Jullien[1], Pierre Peterlin[1], Alice Garnier[1], Thomas Gastinne[1], Matthieu Grégoire[1], Florent Morio[1], Thierry Guillaume[1], Marie-Christine Béné[1], Patrice Chevallier[1], Amandine Le Bourgeois[1]

[1]Nantes University Hospital Center, Nantes, France

Background: The use of anti-mold prophylaxis with anti-aspergillus activity is recommended for patients (pts) undergoing allogeneic hematopoietic stem cell transplantation (Allo-HSCT) with high risk of fungal infection (Maertens, J Antimicrob Chemother 2018). Yet, few data are available regarding the use of posaconazole.

Methods: This retrospective study included all Allo-HSCT adult recipients having benefited from posaconazole therapy in our center as a primary anti-fungal prophylaxis for high-risk of fungal infection. The latter was defined as use of i)an alternative donor, ii) sequential conditioning regimen, iii)a regimen associated with severe mucositis, iv) post-transplant cyclophosphamide (PT-Cy) or v) previous allo-HSCT. Posaconazole was programmed to be initiated at day (D) 0 or D5/6 (in case of PT-Cy) and administered up to day 100. We report here on the residual concentration of posaconazole during the neutropenic phase then on the tolerance and efficacy of such prophylaxis in this cohort.

Results: Seventy high-risk pts (males 63.3%, median age 54 years old, range 20-73) received Allo-HSCT between April 2020 and December 2021 for a myeloid (n = 51), lymphoid (n = 17) or non-malignant hematological (n = 2) disease and received posaconazole as a primary prophylaxis. The Sorror score at transplant time was ≥ 3 for 24 pts (33.8%). Thirty-two patients had already received posaconazole as a primary prophylaxis before Allo-SCT. Four patients had also received other antifungal agents before Allo-SCT.

All but one pts received posaconazole using the gastroresistant tablet form at a dose of 300mg/day. One patient received the drinkable suspension form at a dose of 200mg 3 times a day. Following prophylaxis initiation, serum posaconazole concentrations were available in 51 and 16 patients at medians of 9 and 39 days, respectively. A protective residual level of posaconazole (> 0.5mg/L) was achieved in 57% of the patients (n = 29) at first assessment and 87.5% (n = 12) at second evaluation.

Posaconazole was stopped early due to related-toxicity in 9 cases (12.6%), including liver toxicity in 7 pts, QT prolongation in 1 and skin hyperesthesia in 1. Treatment was restarted without recurrence of toxicity in 2 cases. Posaconazole was stopped early in 2 patients due to non-related toxicity, including one veno-occlusive disease and one hepatic acute GVHD. Posaconazole was temporary discontinued in 4 patients due to a suspected fungal infection before being restarted.

Most patients (n = 59/70, 84.2%) did not present fungal infections while being under posaconazole therapy. Only 11 cases were documented with this complication, including 8 invasive pulmonary aspergillosis (IPA; possible n = 3; probable n = 5), one possible invasive fungal infection and 2 mucormycoses (1 with possible IPA). Fungal infections occurred despite documentation of a protective residual level of posaconazole (> 0.5mg/L) in 5 of 6 evaluable patients. Of note, 9/11 patients had received PTCY as GVHD prophylaxis.

Conclusions: Posaconazole is a well-tolerated and efficient primary prophylaxis in recipients of Allo-HSCT at high-risk of fungal infection. As some fungal infections occurred very early after D0 while prophylaxis started only a D5/6 after PTCY, our results suggest to propose posaconazole as early as the beginning of the conditioning together with dose monitoring.

Disclosure: Nothing to declare.

13 - Infectious Complications

P380

INDUCED SPUTUM IS AN ACCEPTABLE METHOD OF OBTAINING DEEP RESPIRATORY SAMPLES IN UNWELL HAEMATOLOGY PATIENTS; THE RESULTS OF THE SPITFIRE FEASIBILITY TRIAL

Jonathan Ayling-Smith[1,2], Bronagh McGoldrick[2], Carwyn Bridges[3], Rishi Dhillon[4], Matthijs Backx[4], Esh Mahenthiralingham[1], Philip Lewis White[4], Wendy Ingram[2], Kerenza Hood[1], Jamie Duckers[3]

[1]Cardiff University, Cardiff, United Kingdom, [2]University Hospital of Wales, Cardiff, United Kingdom, [3]University Hospital Llandough, Cardiff, United Kingdom, [4]Public Health Wales, Cardiff, United Kingdom

Background: Broncho-alveolar lavage (BAL) at bronchoscopy remains the gold standard for deep respiratory sampling for patients with an atypical infection. However, bronchoscopy access can be limited by clinical risks which are heightened in unwell haematology patients. Induced sputum (IS) is a procedure used in cystic fibrosis care where by hypertonic saline is inhaled and respiratory physiotherapy techniques are applied in order to expectorate a sample. The Sputum Induction Trial for Improved Respiratory Evaluation (SPITFIRE) was a feasibility trial into whether (IS) is an acceptable alternative to bronchoscopy in this cohort.

Methods: All haematology inpatients in a tertiary transplant centre with evidence of pulmonary infection were considered for the trial. Patients underwent an IS procedure within 24 hours of consent and on the day of the scheduled bronchoscopy. The radiology, serology and culture evidence of bacterial or fungal disease in each patient was reviewed alongside the bronchoscopy results to diagnose infection. IS and BAL samples underwent identical microbiological processing and results compared. Patient experience questionnaires were completed after each procedure.

Results: A total of 33 IS procedures were performed in 19 patients. Twenty-seven procedures (81.8%) successfully produced a useable sputum sample in 15/19 patients (78.9%). All 12 (100%) of the bronchoscopy procedures generated a useable sample.

Eleven patients provided a questionnaire response for both IS and bronchoscopy for comparison. Patient-reported anxiety was higher before bronchoscopy than IS and this reached statistical significance (p = 0.020). There was no statistical difference in patient-perceived tolerance for each procedure, operator-perceived tolerance or patient-reported comfort. However, patients were less prepared to have a bronchoscopy again (p = 0.025).

There were five adverse events reported during IS, all were grade 1. During bronchoscopy, four patients required platelet transfusion, there was one CTAE grade 1 adverse event and three hypoxia events which were grade 3.

Nine patients had paired samples from both IS and bronchoscopy. Four met the diagnostic criteria for probable invasive pulmonary aspergillosis. Two patients had *Pneumocystis* pneumonia (PcP). One patient had radiological and biochemical features of pneumonia but no organism was identified. In two patients, the bronchoscopy was negative but microbiology and radiology indicated different diagnoses (line infection and tonsillar abscess). In each case, the IS results support the clinical diagnosis made with BAL evidence. There were no false positive PcP results from IS. Aspergillus PCR positivity was seen at IS in 100% of those diagnosed with probable invasive pulmonary aspergillosis. Bacteriological culture was positive in 7/9 (77.8%) BAL samples and 8/16 (50%) IS, supporting the clinical diagnosis on one occasion.

Conclusions: SPITFIRE indicates that IS is a safe and well-tolerated procedure in haematology patients with respiratory illness, generating a lower rate of adverse events than bronchoscopy. IS is well tolerated with good sampling success and less patient-reported anxiety than bronchoscopy. The sample size limits statistical analysis of the microbiology but IS supported diagnoses made at bronchoscopy and could be performed earlier. There is likely a role for IS in testing unwell patients early in their infection and SPITFIRE demonstrates the need for a more comprehensive diagnostic accuracy study.

Clinical Trial Registry: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/spitfire-sputum-induction-trial-for-improved-respiratory-evaluation/

Disclosure: Equipment for the study was gifted by Trudell Medical Limited. Trudell had no oversight or input into the study's design or performance.

Nothing to declare.

13 - Infectious Complications

P381

CMV HYPERIMMUNE GLOBULIN AS SALVAGE THERAPY FOR RECURRENT OR REFRACTORY CMV INFECTION IN CHILDREN UNDERGOING ALLOGENEIC HSCT

Melissa Panesso[1,2], María Isabel Benítez[1,2], Berta Renedo[3,2], María Luz Uría[3,2], Natalia Ana Mendoza[3,2,4], Laura Alonso[3,2], Maria Oliveras[3,2], Cristina Díaz de Heredia[3,2]

[1]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [2]Institut de Recerca Vall d'Hebron, Barcelona, Spain, [3]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [4]Universitat Autònoma de Barcelona, Barcelona, Spain

Background: Cytomegalovirus (CMV) is a major cause of allogeneic hematopoietic stem cell transplant (allo-HSCT)-related morbidity and mortality. Because letermovir is not yet authorized for its use in children, the main management strategy remains the early treatment of CMV infection/reactivation, so called pre-emptive approach. However, current antiviral agents have high toxicity and treatment failure is a major issue due to both intolerance and drug resistance.

Cytomegalovirus immunoglobulin (CMVIG) is a hyperimmune globulin obtained from plasma donors, with high titer of CMV-specific antibodies. In an adult setting, CMVIG was used as salvage therapy in allo-HSCT with a good safety and efficacy profile. To the date, there are few studies that evaluate the safety and efficacy of CMVIG in this setting in children.

Methods: Single-center retrospective analysis of a case series. Datasets from patients ≤18 years old who underwent allo-HSCT and received CMVIG between 2018 and 2021 were analyzed to investigate the safety and efficacy of CMVIG for recurrent or refractory CMV infection.

CMVIG was administered according to the following posology: 400 U/kg on days 1, 4 and 8, then 200 U/kg on days 12 and 16.

Results: From July 2018 to December 2021, 95 pediatric patients underwent allo-HSCT in the Pediatric HSCT Unit of a tertiary center. From those, 15 patients (7 male) presented recurrent or refractory CMV infection and received CMVIG as salvage therapy. Median time from HSCT to CMV reactivation was 24 days (range: 10-50).

At the time of CMVIG prescription, 8 children presented with recurrent CMV infection, 6 with refractory CMV infection, and 1 had CMV pneumonia. Clinical situation of patients was as follows: 11 (73%) had other viral infections, 10 (67%) were receiving steroids (≥ 0.5 mg/kg/day), 8 (53%) suffered acute GvHD grades II-IV, 1 had chronic GvHD (7%), and 2 were on their second HSCT for graft failure (13%). All patients received CMVIG in combination with antiviral drugs (ganciclovir in 6, foscarnet in 4, ganciclovir +foscarnet in 2 and cidofovir in 3). Resistance testing was done in 5 patients, with negative results.

Response, defined as negative CMV DNAemia since the initiation of CMVIG without changing antiviral treatment or adding a new CMV therapy, was observed in 10 patients (67%). The response was higher in patients with recurrent infection compared to patients with refractory infection (7/8 (87%) vs 3/6 (50%)). The median time to achieve a response was 27 days (range: 15-50). Four patients with recurrent CMV reactivation (40%) suffered subsequent reactivation. Three patients received CMV-specific cytotoxic T lymphocytes (CTLs) for refractory (1), recurrent CMV infection (1) and CMV pneumonia (1). Overall survival (OS) at 100 days and at 1 year from CMVIG administration was 87% and 73%, respectively. In total, 4 patients died: 3 deaths unrelated to CMV infection, and 1 from CMV pneumonia. CMVIG administration was well tolerated, and no infusion-related adverse events were observed.

Conclusions: CMVIG seems to be effective and safe in children with recurrent or refractory CMV infection after allo-HSCT. A large prospective study is needed to confirm these results.

Disclosure: Disclosure - Melissa Panesso: travel expenses from Biotest.

13 - Infectious Complications

P382

IN VITRO PROFILING OF POST-TRANSPLANT IMMUNOSUPPRESSANTS FOR THEIR IMPACT ON ANTIVIRAL MEMORY EFFECTOR T CELLS

M. Benedikt Krueger[1], Agnes Bonifacius[1], Anna Christina Dragon[1], Maria Michela Santamorena[1], Björn Nashan[2], Richard Taubert[1], Jennifer Becker[3], Ulrich Kalinke[3], Britta Maecker-Kolhoff[1], Rainer Blasczyk[1], Britta Eiz-Vesper[1]

[1]Hannover Medical School, Hannover, Germany, [2]University of Science and Technology of China, Hefei, China, [3]TWINCORE, Hannover, Germany

Background: Infectious complications following hematopoietic stem cell and solid organ transplantation (HSCT, SOT) are common due to the required use of immunosuppressants to prevent graft-versus-host disease (GvHD) and allograft rejection. First-line antiviral therapies sometimes fail due to endogenous factors or drug resistances and are associated with toxic side effects. Despite recent success in prevention, infections with e.g. Cytomegalovirus (CMV) still occur in more than 10% of patients, even after discontinuation of letermovir prophylaxis after HSCT. Restoration of the antiviral T-cell immunity is essential for the ultimate control of CMV and the restoration of long-lasting endogenous antiviral immune defenses. Hence, to fine-tune the administration of immunosuppressive drugs in a way that allograft rejection and GvHD are prevented while at the same time viral infections are efficiently controlled, detailed investigations of the influence of immunosuppression on antiviral T-cell functionality are required.

Methods: We analysed the impact of a range of commonly applied immunosuppressive drugs and their combinatory regimens on antiviral T-cell functionality: Sirolimus (SIR/S), Everolimus (EVR/E), Tacrolimus (TAC/T), Mycophenolic Acid (MPA/M), Prednisolone (PRE/P) and triple combinations T + S/E/M + P. CMV-specific memory T-cell responses under immunosuppressive treatment were analysed in healthy donors after antigenic restimulation using CMV_pp65 overlapping peptide pool via cytokine production and their activation state using IFN-γ ELISpot and multicolour flow cytometry. Moreover, CMV-specific T cells were isolated from healthy donors using Cytokine Secretion Assay and expanded in order to investigate their (a) proliferative capacity in presence of immunosuppression and (b) cytotoxic potential towards antigen-loaded autologous PBMCs as well as CMV-infected human fibroblasts using flow cytometry-based and

impedance-based real-time (xCELLigence®) cytotoxicity assays while under immunosuppressive treatment.

Results: While all triple combinations (T + S/E/M + P) homogenously and broadly attenuated the functionality of CMV-specific memory T cells as defined by reduced activation, cytokine secretion, proliferation and cytotoxicity, distinct patterns were observed in presence of single immunosuppressants despite similar modes of action and cellular targets. SIR, EVR and MPA selectively inhibited T-cell proliferation while mostly sparing the other analysed functional properties such as activation and cytotoxic capacity. In contrast, TAC showed an intermediate inhibition profile and PRE had broad inhibitory effects on CMV-specific T cells.

Conclusions: Appropriate T-cell function relies on a broad variety of aspects such as proliferation, cytokine secretion and cytotoxicity in order to efficiently control CMV infection. In this study, we systematically showed that the investigated immunosuppressants firmly differ in their influence on antiviral T-cell functionality. Our data suggest that the immunosuppressive medication of patients suffering from viral infections needs to be carefully re-evaluated and possibly be adjusted towards SIR or EVR in order to allow restoration of the patients' endogenous antiviral T-cell functionality to control viral infection while at the same time maintaining tolerance towards the allograft and avoiding development of GvHD.

Disclosure: Nothing to declare.

13 - Infectious Complications

P383

EVALUATION OF BK POLYOMAVIRUS INFECTION FREQUENCY, RISK FACTORS AND EFFECT ON SURVİVAL FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION: A SINGLE CENTER EXPERIENCE

Barış Gezici[1], Nur Akad Soyer[1], Ajda Ersoy Günes[1], Güray Saydam[1], Mahmut Tobu[1], Fahri Sahin[1], Mehmet Soylu[1], Filiz Vural[1]

[1]Ege University, Izmir, Turkey

Background: Hemorrhagic cystitis (HC) is a clinical entity that mostly occurs after allo-SCT and reduces the quality of life of patients, prolongs hospitalization and increases the financial burden of treatment. While the main reason for early-onset HC is the toxicity of the conditioning regimen, BK polyomavirus (BKV) is the main cause in late-onset HC. BKV-associated hemorrhagic cystitis (BKV-HC) also draws attention due to the lack of a definitive treatment agreed in the literature. In this study, it was aimed to investigate frequency and risk factors of BKV-HC development and its effect on overall survival.

Methods: Overall, 221 adult patients who underwent first allo-SCT between 2012 and 2020 at our institution, were included in this single center, retrospective, observational study. Data on patients' sociodemographic information, characteristics of the allo-SCT procedure and complications, donor characteristics, and parameters related to BKV-HC were collected.

Results: Mean age was 41,5 years and sex ratio (F/M) was 2/3. The mean follow-up period was 1067.4 days. The indications for allo-SCT were malignant in 93%. Matched related donors in 166 (75.1%), matched unrelated donors in 47 (21.3%) and haploidentic donors in 8 (3.6%) transplants were used. Of the conditioning regimens used in transplants, 167 (75.6%) were myeloablative, 36 (16.3%) were reduced-intensity and 18 (8.1%) were nonmyeloablative. The mean engraftment time was 17.9 days. aGVHD, cGVHD, BKV-HC occured in 86 (38.9%), 44 (23%), 17 (7.7%) of the patients included in the study, respectively. Patient and transplant-related characteristics categorized by BKV-HC status are shown in Table-1. Use of myeloablative conditioning regimen (P = 0,047), development of CMV infection (P = 0,02) and history of CMV infection prior to allo-SCT (P = 0,009) were determined as risk factors for the development of BKV-HC (Image-1, Table-1). No correlation was observed between the severity of BKV-HC and peak BKV DNA in urine. It was also found that, the risk of mortality was 3.94 (1.83-8.45) times higher in patients who developed BKV-HC compared to those who did not (P = 0,004).

BKV-HC		**Present (n = 17)**	**Absent (n = 204)**	
Characteristics		**n (%)**	**n (%)**	**P value**
Donor Characteristics	Matched related	10 (58,8)	156 (76,5)	0,09
	Matched unrelated	7 (41,2)	40 (19,6)	
	Haploidentical	-	8 (3,9)	
Conditioning Regimen	Myeloablative	17 (100)	150 (73,5)	**0,047**
	RIC	-	36 (17,6)	
	Nonmyeloablative	-	18 (8,8)	
Conditioning Regimen	With cyclophosphamide	16 (94,1)	174 (85,3)	0,48
	Without cyclophosphamide	1 (5,9)	30 (14,7)	
Conditioning Regimen	With ATG	-	23 (11,3)	0,23
	Without ATG	17 (100)	181 (88,7)	
History of CMV Infection Prior to Allo-SCT	Positive	5 (29,4)	14 (6,9)	**0,009**
	Negative	12 (70,6)	190 (93,1)	
Acute GVHD	Positive	10 (58,8)	76 (37,3)	0,08
	Negative	7 (41,2)	128 (62,7)	
Chronic GVHD	Positive	2 (15,4)	42 (23,6)	0,74
	Negative	11 (84,6)	136 (76,4)	
CMV Infection after Allo-SCT	Positive	14 (82,3)	107 (52,5)	**0,02**
	Negative	3 (17,7)	97 (47,5)	

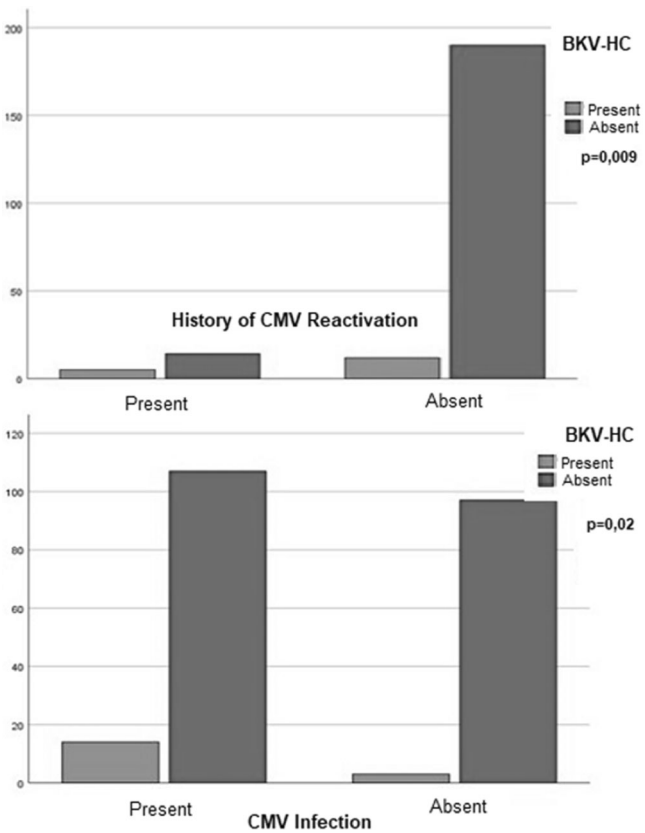


Image-1: Comparison of BKV-HC according to CMV infection and history of CMV infection prior to allo-SCT

Conclusions: In our study, frequency and risk factors of BKV-HC and its effect on overall survival were determined. Reporting of development of CMV infection and a positive history of CMV infection prior to allo-SCT as risk factors for development of BKV-HC was especially significant. The results suggest that in patients with a history of CMV infection prior to allo-SCT, avoidance of other factors that may increase the risk of BKV-HC, such as the use of a myeloablative conditioning regimen, may improve overall survival.

Disclosure: Nothing to declare.

13 - Infectious Complications

P384

EPIDEMIOLOGY OF INFECTIOUS COMPLICATIONS IN PATIENTS WITH GRAFT-VERSUS-HOST DISEASE

Aleksandr Siniaev[1], Anna Grinenko[1], Marina Popova[1], Yulia Rogacheva[1], Yulia Vlasova[1], Anna Smirnova[1], Sergey Bondarenko[1], Ivan Moiseev[1], Alexander Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation

Background: Patients with graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT) are at increased risk of developing infectious complications (IC), however number of published studies covering incidence and spectrum of these complications are limited.

Methods: Single center retrospective study included 131 and 128 adult patients with acute and chronic GVHD respectively after allo-HSCT from 2014 to 2021. The analysis of IC was carried out from the onset of GVHD to the follow-up date. The median follow-up time was 513 days (22 – 2688) and 1160 days (176–2854) in acute and chronic GVHD groups respectively. The analysis was carried according to the EBMT statistical recommendations.

Results: Cumulative incidence (CI) of IC and median time of onset are outlined in table 1.

	Cumulative incidence (CI 95%)	Median day of the 1st episode onset
Acute GVHD (100 days)		
Bacterial infections (BI)	39.6% (31.3 – 47.9)	28 (0 – 91)
Viral infections (VI)	67.9% (59.2 – 75.2)	15,5 (0 – 88)
Invasive fungal disease (IFD)	11.4% (6.7 – 17.6)	38 (0 – 119)
Chronic GVHD (2.5 years)		
Bacterial infections (BI)	22.8% (15.8 – 30.6)	56,5 (9 – 650)
Viral infections (VI)	24.8% (17.5 – 32.8)	75,5 (10 – 579)
Invasive fungal disease (IFD)	9.9% (5.2 – 16.3)	243 (115 – 523)

In aGVHD group, 54 patients developed 70 episodes of bacterial infection (BI) total. The main pathogens of BI were gram-negative bacteria: *Klebsiella pneumoniae* with 36 episodes (51,4%) and *Pseudomonas* spp. with 12 (17,1%). 14 episodes (20%) were caused by gram-positive agents. Most common localization were pneumonia and blood stream infections with 20 episodes (28,5%) each. In cGVHD, 30 patients developed 43 episodes. The key gram-negative pathogens were also *Klebsiella pneumoniae* and *Pseudomonas* spp. – 17 (39,5%) and 6 (14%) episodes respectively. 9 episodes (21%) were caused by gram-positive agents. Most common localization were pneumonia with 25 cases (58,1%) and sinusitis – 9 cases (20,1%). Ninety patients developed 129 episodes of viral infection (VI) in aGVHD group. The key pathogens were CMV with 70 (53,4%) and HHV-6 with 32 (24,4%) episodes. Most common localization – blood/BM – 71 (54,2%). In cGVHD, 41 patients developed 52 episodes. The main pathogens were CMV – 25 cases (48%) and EBV – 7 cases (13,5%). Most frequent localization was blood/BM – 26 (50%). In patients with aGVHD, number of patients with invasive fungal disease (IFD) was equal to number of episodes – 17 (100%). IFD were caused by *Aspergillus* spp. in 14 cases (82,3%) and *Candida* spp. in 3 (17,7%). Localization was represented mostly by pulmonary aspergillosis (PA) in 12 cases (70,5%). Number of patients with IFD in cGVHD group also was equal to number of episodes. PA was diagnosed in 12 cases (92,3%) and in 1 case (7,7%) – pulmonary mucormycosis (*Lichtheimia ramose*). Result of risk factor analysis are presented on picture 1.

In multivariable analysis aGVHD overall grading ($p = 0.017$) and GI tract involving ($p = 0.0038$) correlated with CI of BI and only aGVHD overall grading ($p = 0.009$) correlated with CI of VI. In multivariable analysis of risk factors in cGVHD group, GI tract involving ($p = 0.0035$) correlated with CI of BI. Lungs involving and "salvage" pre-HCT risk group significantly correlated with increase CI of VI ($p = 0.0039$, $p = 0.012$) and IFD ($p = 0.0005$, $p = 0.0068$). Only BI significantly decreases OS in aGVHD group – 64,2% (CI 95% 47,6 – 76,7) ($p = 0.018$). IC did not affect 3-year OS in cGVHD group.

Conclusions: CI of IC varied from 9,9% to 67.9% and depend on the etiology of infection and type of GVHD. The key risk factors were GVHD severity, GI and lungs involving and "salvage" pre-HCT status. Only BI in aGVHD group significantly decreases OS.

Disclosure: Nothing to declare.

13 - Infectious Complications

P385

COMPASSIONATE USE PROGRAMME OF MARIBAVIR FOR ADULT PATIENTS WITH POST-TRANSPLANT CMV INFECTION AND/OR DISEASE REFRACTORY (WITH OR WITHOUT RESISTANCE) TO ONE OR MORE PRIOR THERAPY

Catherine Cordonnier[1], Nassim Kamar[2], Faouzi Saliba[3], Vincent Bunel[4], Fanny Vuotto[5], Lionel Couzi[6], Emmanuel Morelon[7], Cinira Lefèvre[8], Michèle Maric[8], Sophie Alain[9]

Assistance Publique-Hopitaux de Paris (AP-HP), Henri Mondor Hospital and University Paris-Est-Créteil, Créteil, France, Dialysis and Organ Transplantation, CHU Rangueil and INSERM U 1043, IFR –BMT, University Paul Sabatier, Toulouse, France, [3]Centre Hépato-Biliaire, Hôpital Paul Brousse, Villejuif, France, [4]Service de Pneumologie B et Transplantation Pulmonaire, Hôpital Bichat, AP-HP and Inserm U 1152, Université de Paris, Paris, France, [5]Service des Maladies Infectieuses et Tropicales, CHU Lille, Lille, France, [6]Service de Néphrologie, Transplantation, Dialyse – Aphérèses, Hôpital Pellegrin, CHU Bordeaux, Bordeaux, France, [7]Service de Néphrologie, Transplantation et Immunologie Clinique, Hôpital Edouard Herriot, Hospices Civils de Lyon and Université de Lyon 1, Lyon, France, [8]Takeda France SAS, Paris, France, Limoges University Hospital, UMR Inserm 1092, University of Limoges, Limoges, France

Background: Cytomegalovirus (CMV) infection may compromise the benefit of transplantation and even be fatal for some patients due to limited treatment options. Moreover, there are severe treatment-limiting toxicities with existing agents. Thus, there is an unmet medical need for new CMV therapies.

Maribavir is a benzimidazole riboside that inhibits human CMV replication. Its antiviral activity is mediated by competitive inhibition of the HCMV protein kinase UL97. Its European indication is "Treatment of adults with post-transplant CMV infection and/or disease who are refractory (with or without resistance) to one or more prior therapy, including ganciclovir, valganciclovir, cidofovir or foscarnet." The recommended daily dose of maribavir is 400mg BID, administered by oral tablets. The recommended treatment duration is 8 weeks.

Methods: In France, patients were treated with maribavir prior to granting of the European marketing authorization, through the compassionate use program (CUP), according to the new early access reform deployed in 2021. Patients had to fulfill the eligibility criteria (aligned with the pivotal study inclusion criteria (NCT02931539)) according to the protocol approved by the French health authority. An amendment to this protocol broadened the inclusion criteria in February 2022, with less stringent hematological and renal function cut-off values.

To ensure alignment with data already generated in the pivotal study and to meet the French authorities' request for data generation as part of the CUP, the main analytical objectives were to describe patient characteristics, maribavir use, effectiveness (i.e. viral clearance) and safety data. The present analysis describes here the CUP methodology and patients' baseline characteristics at initiation visit, from November 3, 2021 to October 3, 2022.

Results: Out of the 64 requests received, 50 were accepted according to CUP eligibility criteria. The analyses were based on the 47 patients with a completed treatment initiation study form.

At access request, the median age was 58.6 years (range: 23.9 – 78.8), with 72.3% of male patients. The majority had a solid organ transplant (n = 40, 85.1%), with kidney (n = 30, 75.0%), heart (n = 5, 12.5%), lung (n = 4,10.0%) and pancreas (n = 1, 2.5%); and 14.9% (n = 7) of patients had a hematopoietic stem-cell transplantation. The proportion of patients with severe renal impairment at baseline (i.e. creatinine clearance ≤ 30 mL/min/1.73²) was 14.9% (n = 7). Resistance testing was performed for 44 (93.6%) patients, of which 40 samples were tested in the French National Reference Center for Herpesviruses and 30 (68%) of them had an identified mutation. The most frequently identified mutation was UL97, indicating a resistance to ganciclovir/valganciclovir in 23 (76.7%). There were 12 (40%) mutations in the UL54 gene, indicating multidrug resistance to available antivirals.

Conclusions: A considerable effort from 41 French hospitals was undertaken to collect data from patients who enrolled the maribavir CUP in France, resulting in a high data completeness above 95%. In the CUP population compared with the pivotal study maribavir cohort, we observed a higher proportion of patients with SOT and identified antivirals resistance at baseline to conventional agent. Future analysis on effectiveness should provide further data on maribavir use.

Disclosure: References:

[1] Avery RK et al. Maribavir for refractory Cytomegalovirus infections with or without resistance: Results from a phase 3 randomized clinical trial. Clin Infect Dis 202?. doi: 10.1093/cid/ciab988

Disclosure:

- CC has received speakers fees and participated to advisory boards for *Cidara, Equillium, Gilead, MSD, Mundipharma, Takeda*
- NK has received speakers fees and participated to advisory boards for Astellas, AstraZeneca, Biotest, CSL Behring, Chiesi, ExeViR,Hansa, Merck Sharp and Dohme, Glasgow Smith Kline, Novartis Pharma, Sanofi, Sandoz, Takeda
- FS has received speakers fees and participated to advisory boards for Novartis, Chiesi, Biotest, Takeda, Gilead, Mundipharma.
- VB participated to advisory boards: Biotest, Takeda
- SA: Research funding as a scientific expert and site principal investigator: Altona, BioMérieux, Biotest, GlaxoSmithKline, Merck, Merck Sharp & Dohme, Qiagen, Shire/Takeda; honoraria for lectures paid to institution: Biotest, Merck Sharp & Dohme, IQone, Takeda; support for attending meetings: BioMérieux, Biotest, QCMD, Takeda; advisory board (unpaid): QCMD. Primary investigator for this study in France.

13 - Infectious Complications

P386

GRAM NEGATIVE BLOODSTREAM INFECTION IN AUTOLOGOUS STEM CELL TRANSPLANTATION: A COMPARATIVE STUDY BETWEEN AT HOME AND HOSPITAL CARE MODEL

Sara Fernandez-Luis[1], Juan Jose Parra[1], Soledad Barreda[1], Tatiana Fernandez-Barge[1], Rodrigo Cantera[1], Pedro Sanroma[1], Enrique Maria Ocio[1,2], Arancha Bermudez[1,2], Lucrecia Yañez[1,2]

[1]Marqués de Valdecilla University Hospital-IDIVAL, Santander, Spain, [2]University of Cantabria, Santander, Spain

Background: Hospitalization at home (HaH) is a feasible option after autologous stem cell transplantation (ASCT) but bloodstream infections caused by Gram-negative bacilli (GN-BSI) may impact the patient's safety. Additionally, the benefit of fluoroquinolone prophylaxis (FQP) is under continuous debate. The aim of this study is to evaluate the differences in the incidence and characteristics of GN-BSI during the neutropenia period in ASCT followed by HaH or in an inpatient setting (H) as well as the overall survival (OS).

Methods: We performed a retrospective study. Patients were matched 1:1 taking into account the diagnosis and conditioning regimen and at least two of the following variables: age, gender and year of ASCT. Per protocol, no patient received G-CSF except if sepsis or septic shock was diagnosed. Patients followed at home received FQP with levofloxacin except if they have been discharged with a therapeutic antibiotic.

Results: 88 patients (H = 44; HaH= 44) received an ASCT between 2009 and 2019. Both groups included non-Hodgkin's lymphoma (n = 16), Hodgkin's lymphoma (n = 7) and multiple myeloma (n = 21). Median age at transplant was 57.7 years and 67% were male. HCT-CI was ≥3 in 11.4% of HaH and 38.5% in H. We did not find other significant differences between both groups in patients' and transplant characteristics (Table 1) as well as in the use of tunneled central venous catheter (HaH:79.5% vs. H:70.5%), the history of prior BGN-BSI (HaH:11.4% vs. H:11.4%) or ≥0.5x10^9/L neutrophil engraftment (HaH:13 days vs. H:12 days).

FQP was mostly used in HaH (72.7% vs. 2.3%, $p < 0.001$). All patients hospitalized and 38 patients (86.4%) in HaH had ≥1 episode of neutropenic fever ($p = 0.013$). 32 patients had ≥1 BSI episode being less frequent in HaH (20.5 vs. 52.3, $p = 0.002$). GN-BSI was less frequent in HaH (n = 3; 2 *K. pneumoniae*, 1 *O. anthropi*) than in H (n = 9 with a total of 13 isolations; 6 *E. coli*, 3 *K. pneumoniae*, 1 *O. anthropi*, 1. *C. youngae*, 1 *H. parainfluenzae*, 1 *F. nucleatum*), $p = 0.059$. Median time from ASCT to GNB-BSI was 5 days in HaH and H patients. Sepsis was documented in 3 (8%)

patients in each group. All isolates were sensitive to meropenem and aminoglycoside and there were no significant differences between HaH and H in terms of resistance to quinolones (0 vs. 2 isolates), cefepime (0 vs. 1 isolate) and piperacillin-tazobactam (1 vs. 0 isolates). One admitted at hospital patient died due to septic shock caused by no resistant *E. coli* BSI. Mortality at day +30 of ASCT was 2.3% in H and 0% in HaH. With a median follow-up of 68.3 months OS at 5 years was 75.3% in HaH and 77.8% in H.

		Total (n = 88)	HaH (n = 44)	H (n = 44)	p value
Age, yr, median (min-max)		57.7 (23.2-73.4)	57.5 (23.6-73.3)	58.0 (23.2-73.4)	0.953
Female, n (%)		29 (33.0)	15 (34.1)	14 (31.8)	0.500
Disease, n (%)	NHL	32 (36.4)	16 (36.4)	16 (36.4)	0.951
	HD	14 (15.9)	7 (15.9)	7 (15.9)	
	MM	42 (47.7)	21 (47.7)	21 (47.7)	
Disease status pre-ASCT, n (%)	CR	26 (29.5)	11 (25.0)	15 (34.1)	0.597
	VGPR	23 (26.1)	13 (29.5)	10 (22.7)	
	PR	39 (44.3)	20 (45.5)	19 (43.2)	
HCT-CI, median (min-max)		1.5 (0-7)	1 (0-7)	2 (0-5)	0.164
HCT-CI, n (%)	<3	55 (74.3)	31 (88.6)	24 (61.5)	0.007
	≥3	19 (25.7)	4 (11.4)	15 (38.5)	
DRI, n (%)	Low	12 (13.6)	5 (11.4)	7 (15.9)	0.379
	Intermediate	76 (86.4)	39 (88.6)	37 (84.1)	
Conditioning regimen, n (%)	BEAM	45 (51.1)	23 (52.3)	22 (50.0)	0.500
	Melfalan	43 (48.9)	21 (47.7)	22 (50.0)	
Year of ASCT, median (min-max)		2014 (2009-2019)	2014 (2009-2019)	2015 (2010-2019)	0.259

HaH Hospitalization at home; *H* Admitted at hospital; *NHL* Non-Hodgkin Lymphoma; *HD* Hodgkin disease; *MM* Multiple Myeloma. *CR* Complete remission; *VGPR* Very good partial response; *PR* Partial response; *DRI* Disease risk index; *ASCT* Autologous stem cell transplantation.

Conclusions: The use of FQ in patients hospitalized at home reduces the incidence of neutropenic fever and documented BSI compared to admitted at hospital patients. The bacterial strains isolated at blood in both regimens of care after ASCT were full susceptible to the recommended antibiotics for febrile neutropenia. The absence of FQ in admitted patients did not worsen the overall survival.

Clinical Trial Registry: No applicable.

Disclosure: Nothing to declare.

13 - Infectious Complications

P387

MONITORING AND MANAGEMENT OF CMV AND EBV AFTER AUTOLOGOUS HAEMATOPOIETIC CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES: A SURVEY OF THE EBMT AUTOIMMUNE DISEASES WORKING PARTY (ADWP)

Tobias Alexander[1,2], Manuela Badglio[3], Myriam Labopin[3], Thomas Daikeler[4], Dominique Farge[5,6], Majid Kazmi[7], Montserrat Rovira[8], Riccardo Saccardi[9], John Snowden[10], Raffaella Greco[11]

[1]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, [2]Deutsches Rheuma-Forschungszentrum Berlin, ein Institut der Leibniz-Gemeinschaft, Berlin, Germany, [3]EBMT Paris Study Office, Hôpital Saint-Antoine, Paris, France, [4]Klinik für Rheumatologie, Universitätsspital Basel, Basel, Switzerland, [5]Unité de Médecine Interne, Maladies Auto-Immunes et Pathologie Vasculaire (UF 04), Hôpital St-Louis, Paris, France, [6]Centre de Référence des Maladies Auto-Immunes Systémiques Rares d'Ile-de-France, Paris, France, [7]Kings Health Partners, Guys Hospital, London, United Kingdom, [8]BMT Unit, IDIBAPS, Hospital Clinic, Josep Carreras Leukemia Research Institute (IJC), Barcelona, Spain, [9]Cell Therapy and Transfusion Medicine Unit, Careggi Hospital, Florence, Italy, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, [11]Haematology and BMT Unit, San Raffaele Hospital (IRCCS), Milano, Italy

Background: Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) reactivations are common complications after haematopoietic cell transplantation (HSCT), but data focusing on autoimmune diseases (ADs) are limited.

Methods: The policy for monitoring and management of CMV and EBV after autologous HSCT for ADs was assessed with a survey performed by the Autoimmune Diseases Working Party among European Society for Blood and Marrow Transplantation (EBMT) centers in 2022.

Results: Fifty-five of 125 EBMT centres contacted (44%) responded. The centres were from 19 different countries, and the majority JACIE accredited (84%). 56% of the centres used the same protocol for monitoring CMV or EBV in autologous HSCT for autoimmune and haematological indications, with the vast majority of the remaining centres monitoring autologous HSCT recipients only for autoimmune HSCT. In 96% of centres, conditioning intensity had no impact on CMV/EBV monitoring policy.

CMV-specific serology before HSCT was tested by 91% of centres and CMV monitoring with quantitative PCR for CMV-DNAemia was used by 100% of centres (40% of centres on plasma and 60% on whole blood), with 95% of centres monitoring at early follow up ($\leq D+100$), 52% at late follow-up ($D+100$ until $D+180$) and 27% at long-term follow up ($> D+180$ and -≤1 year from HSCT). The most used cut-off for pre-emptive therapy was a threshold of $>10^3$ copies/ml or $>10^3$ IU/ml. Ganciclovir/valganciclovir were the preferred first line both for pre-emptive and CMV disease therapy.

EBV-specific serology before HSCT was assessed by 100% of centres, and EBV monitoring with quantitative PCR for EBV-DNAemia was performed by 100% of centres (41% of centres on plasma, 54% on whole blood and 3% other), with 92% of centres monitoring at early follow up ($\leq D+100$), 46% at late follow-up ($D+100$ until $D+180$) and 23% at long-term follow up ($> D+180$ and -≤1 year from HSCT). The most used value for initiating pre-emptive therapy was a threshold of $>10x10^3$ copies/ml or $>5x10^3$ IU/ml. Rituximab was the first line treatment both for pre-emptive and EBV disease therapy (97%), along with reduction in steroids (51%) and administration of immunoglobulins (21%).

Conclusions: This survey reveals a high degree of consistency across EBMT centres regarding the monitoring and management policies implemented for CMV and EBV infection and/or disease in HSCT recipients for autoimmune diseases. The largest differences between centers were found in the PCR methods for monitoring and cut-off values for initiating pre-emptive therapy, which may benefit from harmonisation in the future.

Disclosure: T. Alexander declares speaking honoraria from Amgen, Roche, and Pfizer, travel grants from Neovii, and study support from Amgen, Janssen-Cilag, and Miltenyi Biotec. J. A. Snowden declares advisory board membership from Medac. R. Greco discloses speaking honoraria from Biotest, Pfizer, Medac, and Magenta.

13 - Infectious Complications

P388

INFECTIONS WITH *PSEUDOMONAS AERUGINOSA* IN CHILDREN UNDERGOING ANTICANCER THERAPY OR HEMATOPOIETIC CELL TRANSPLANTATION: A MULTICENTER NATIONWIDE STUDY

Monika Richert-Przygonska[1], Krzysztof Czyzewski[1], Robert Debski[1], Patrycja Zalas-Wiecek[1], Jowita Fraczkiewicz[2], Olga Zajac- Spychala[3], Agnieszka Zaucha-Prazmo[4], Jolanta Gozdzik[5], Liliana Chelmecka-Wiktorczyk[5], Lukasz Hutnik[6], Olga Gryniewicz-Kwiatkowska[7], Agnieszka Gietka[7], Katarzyna Semczuk[7], Anna Szmydki-Baran[6], Wojciech Czogala[5], Iwona Zak[5], Malgorzata Salamonowicz- Bodzioch[2], Renata Tomaszewska[8], Ninela Irga- Jaworska[9], Ewa Bien[9], Marcin Plonowski[10], Tomasz Ociepa[11], Pawel Wawrykow[11], Filip Pierlejewski[12], Justyna Urbanska-Rakus[13], Tomasz Brzeski[14], Katarzyna Mycko[14], Agnieszka Urbanek-Dadela[15], Weronika Stolpa[8], Jakub Musial[16], Joanna Zawitkowska[4], Jan Styczynski[1]

[1]Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland, [2]Wroclaw Medical University, Wroclaw, Poland, [3]Poznan University of Medical Sciences, Poznan, Poland, [4]Medical University of Lublin, Lublin, Poland, [5]Jagiellonian University Medical College, Krakow, Poland, [6]Medical University of Warsaw, Warszawa, Poland, [7]The Children's Memorial Health Institute, Warszawa, Poland, [8]Medical University of Silesia, Katowice, Poland, [9]Medical University of Gdansk, Gdansk, Poland, [10]Medical University of Bialystok, Bialystok, Poland, [11]Pomeranian Medical University, Szczecin, Poland, [12]Medical University of Lodz, Lodz, Poland, [13]Pediatrics and Oncology Center, Chorzow, Poland, [14]University of Warmia School of Medicine, Olsztyn, Poland, [15]Swietokrzyskie Centrum Pediatrii, Kielce, Poland, [16]University of Rzeszow, Rzeszow, Poland

Background: Infections caused by Pseudomonas aeruginosa (PSA) are associated with high recurrence rate and high mortality in immunocompromised patients. Among hematopoietic cell transplant (HCT) recipients PSA invasive blood stream infections with rising incidence of non-susceptibility are observed. There are limited studies on treatment recommendations of PSA infections after HCT. Moreover, data regarding pediatric HCT recipients are lacking.

Methods: **Aim:** This nationwide multicenter study was performed to analyze the epidemiology of PSA infections in children undergoing hematopoietic cell transplantation (HCT) or anticancer therapy (pediatric hematology and oncology, PHO) over 2014-2021, including incidence and outcome of PSA infections, as well as treatment regimens and multidrug resistance.

Methods: We analyzed retrospectively the clinical and microbiological data of children who underwent anticancer therapy or hematopoietic cell transplantation in 17 Polish PHO centers and 6 pediatric HCT centers. Data were collected in two years intervals.

Results: During the study period of 8 years, a total number of 1389 HCTs and 7365 children newly diagnosed for malignancy were analyzed. The cumulative incidence of PSA infections was significantly higher in PHO group (6.93% vs. 5.25%, $p = 0.024$). There was no significant difference in total number of PSA blood stream infections for both groups of patients (27.4% HCT vs. 29.9% of PHO; $p > 0.05$). In both groups antipseudomonal drugs of choice were: meropenem, tazobactam/piperaciline or ceftazidime in combination with other antibiotics. In HCT group high rate of ceftazidime (9.5%) and meropenem (17.8%) non-susceptibility was observed. That led to collistin therapy in 12.3% cases and use of ceftazidime/avibactam in 5.4% cases. Although median antibiotic therapy time was significantly longer in HCT group than in PHO group (29.9 days vs. 20.3 days), survival rates from PSA infections were significantly lower in HCT group (73.9% vs. 86.7%, $p = 0.0043$; OR = 0.4; 95% CI = 0.2-0.8).

Conclusions: The risk of PSA infections in allo-HCT patients was lower than in PHO patients. Although occurrence of resistant bacterial strains and invasive blood stream infections in allo-HCT patients were comparable with PHO patients, the target therapy outcome of PSA infections was better in the PHO setting.

Disclosure: Nothing to declare.

13 - Infectious Complications

P389

THE IMPACT OF CARBAPENEMIC RESISTANT ENTEROBACTERIACEAE COLONIZATION IN ALLOGENEIC STEM CELL TRANSPLANT: SINGLE CENTRE EXPERIENCE IN THE ERA OF NEW AGENTS AND SARS-COVID19 PANDEMIC

Maria Celentano[1], Maria Esposito[1], Mariangela Pedata[1], Serena Marotta[1], Tiziana Ascione[1], Rossella Iula[1], Lisa Mercante[1], Marta Raimondo[1], Cira Riccardi[1], Aldo Leone[1], Mafalda Caputo[1], Rosa Peluso[1], Mirella Alberti[1], Domenico Buonanno[1], Assunta Viola[2], Felicetto Ferrara[2], Simona Muggianu[1], Alessandra Picardi[1,3]

[1]Stem Cell Transplant Program, AORN A.Cardarelli, Naples, Italy, [2]Hematology Unit, AORN A. Cardarelli, Naples, Italy, [3]Dep. of Biomedicine and Prevention, Tor Vergata University, Rome, Italy

Background: Infections are among the main cause of mortality in allogeneic stem cell transplantation (HSCT). In the last decades, the progressive raise of Carbapenemic Resistant Enterobacteriaceae (CRE) infections was associated with a corrispondent increase in terms of morbidity and mortality rates. Our primary aims were to analyze the impact of SARS-COVID19 pandemic on CRE colonization on our Transplant Program and the efficacy of new antibiotics on the 100 days and 1-yr TRM in both CRE colonized and non-colonized patients. The secondary aims were to compare the colonized versus non colonized cohorts in terms of hospitalization's duration, aGVHD occurrence and PMN and PLTS engraftment.

Methods: From July 2019 to November 2022, 83 patients (median age of 48 years) underwent first allogeneic HSCT at Cardarelli Transplant Program in Naples. Fifty-nine (71%) patients

were affected by high risk Acute Leukemia (AML 52%, ALL 19%) and 34 (41%) received HSCT from a HLA-identical sibling donor. The patients characteristics are detailed in table 1. Conditioning regimen was TBI based or Valencia schedule (TBF) in almost all ALL (75%) and AML (82%), respectively, and MAC or RIC according to the patient's age and comorbidities. GVHD prophylaxis consisted of CSA + MTX, CSA + MTX + ATG or PT-CY + CSA + MMF association according to the stem cell source and type of donor. Patients were divided in 2 groups and 2 subsets according to the CRE colonization (35 vs 48) and the period of SARS-COVID19 associated restrictions (36 vs 47). CRE colonized patients reporting fever received empirical antibiotic treatment based on ceftazidime/avibactam, meropenem/vaborbatcam and cefiderocol.

Table 1: Patients characteristics

	N %
Gender: Male/Female	52/31 63%/37%
Diagnosis	
AML	43 52%
ALL	16 19%
MDS/MPN	11 13%
HL	6 7%
NHL	3 4%
SAA	3 4%
MM	1 1%
Median age years (range)	8 (20-69)
***Conditioning regimen* MAC/RIC**	51/32 61%/39%
***Source of HSC* BM/PBSC**	27/56 33%/67%
Type of donor	
HLA-identical sibling	34 41%
Relatives 5/6	1 1.2%
MUD (8/8 HLA id)	22 26.5%
mMUD (7/8 matched)	4 4.8%
Haploidentical	22 26.5%
GVHD prophilaxis	
CsA + MTX	14 17%
CsA + MTX + ATG	43 51%
CsA + MMF + PT-CY	26 32%

Results: Overall, 35 out of 83 (42%) patients were colonized by CRE. Median follow up was 10 months (range 1-42), significantly longer in non colonized group (512 *Vs*. 274 days, $p < 0.001$). No other significant difference was observed between the 2 groups. CRE colonization rate at our Transplant Program was 61% and 19%, respectively before and after COVID-19 associated restriction were adopted (29/47 *Vs*. 7/36 colonized patients; $p < 0.0001$). However, 100 days and 1 yr-TRM were similar in the 2 groups of CRE colonized and not colonized patients: 0.6% vs 1.5% (p= ns) and 1.3% vs 5.5% (p=ns). Moreover, there were no significant differences in terms of aGVHD occurrence, median hospitalization duration and median time to PMN and PLTS recovery with 4.32 vs 9.5 % (p=ns), 39 (20-75) vs 43 (25-109) (p=ns), 21 (8-97) vs 21(6-53) (p=ns) and 18 (11-25) vs 17 (10-27) days (p=ns) in colonized and non colonized group.

Conclusions: COVID-19 associated restrictions significantly reduced the CRE colonization rate at our Transplant Program. Despite CRE colonized patients are considered at high risk of an unfavourable outcome, in our case-series, an empiric schedule considering novel anti-MDR antibiotics for febrile cases allowed the disappearence of the difference in terms of poor outcome of CRE-colonized patients in respect to non-colonized cases.

Disclosure: Nothing to declare.

13 - Infectious Complications

P390

THIRD PARTY FECAL MICROBIOTA TRANSPLANTATION RESULTS IN DECOLONIZATION OF MDR BACTERIA FROM THE GUT ALLOWING SAFER ALLOGENEIC HSCT

Pietro Merli[1], Federica Galaverna[1], Francesco Quagliarella[1], Federica Del Chierico[1], Mattia Algeri[1], Francesca Rea[1], Erminia Francesca Romeo[1], Luisa Strocchio[1], Stefania Pane[1], Michele Massa[1], Emilia Boccieri[1], Paola Bernaschi[1], Daria Pagliara[1], Lorenza Putignani[1], Franco Locatelli[1,2]

[1]Bambino Gesù Children Hospital, IRCCS, Rome, Italy, [2]Catholic University of the Sacred Heart, Rome, Italy

Background: Colonization from multi-drug resistant (MDR) bacteria is a risk factor for the development of post-HSCT bloodstream infections (BSI) and is thus associated with increased non-relapse mortality (NRM). Fecal microbiota transplantation (FMT) has emerged as an effective therapy for eradication of resistant/relapsing *Clostridium difficile* infection; more recently, it has been successfully used to decolonize hematologic patients with MDR bacteria on stools in order to reduce the risk of subsequent BSIs.

Methods: We retrospectively analyzed all consecutive cases of pediatric patients undergoing FMT (according to hospital standard operative procedure) in order to eradicate MDR bacteria before HSCT at bambino Gesù Children's Hospital. All procedures were performed on a compassionate use/nominal basis after local ethical committee approval; informed consent of patients or parents/legal guardians of patients was obtained. Before FMT patients were given oral colistin to favor eradication of the pathogens. FMT (fresh in 1 case, frozen in all the others) was administered through endoscopy in the jejunum under general anesthesia. A nasogastric tube was left in place to prevent vomiting/aspiration. Patients were then monitored weekly with stool cultures and microbiota profiling (16S sequencing).

Results: Between October 2018 and September 2022, 9 patients (see Table I for details) underwent FMT for this purpose (the outcome of 5 patients was already reported; Merli et al., Haematologica 2020). Median age at FMT was 9 years (range 0.9-18). All patients received 1 procedures from a third party donor. The procedure was well tolerated and the side effects were mild, with nausea and abdominal pain being the most common findings. Short-term (i.e., 1 week after FMT) decolonization was obtained in 8 out of 9 patients. Interestingly, 1 patient with both stool and urine positive cultures, became negative for both (i.e., because of removal of the reservoir). However, only 3 patients were still negative 4 weeks after the FMT (1 of these was the patient who did not have negative stools at 1 week). All patients proceed to HSCT (6 for acute leukemia, 3 for a non-malignant condition) at a median of 14 days after HSCT (range 12-45). Two patients developed a sepsis due to the previous-colonizing bacteria (always identified with T2 Magnetic Resonance Technology but not on blood cultures); in all cases the infection resolved with specific antibiotic therapy without complications. All patients survived HSCT; only 1 developed grade II acute GVHD. Microbiota profiling showed, in decolonized patients, an increase in diversity.

	N	% / range		N	% / range
Age (years) at FMT	9	0.9-18	Stool		
Gender (M/F)	7/2	78%/22%	Frozen	8	88.8%
Hematological disease			Fresh	1	11.1%
Acute leukemia	6	66.6%	Preparation with oral antibiotic		
Non-malignant disorders	3	33.3%	Yes	8	88.8%
MDR pathogen*			No	1	11.1%
Pseudomonas aeruginosa	3	23%	Quantity ml/kg (median)	5.1	2.9-12.5
Klebsiella spp	5	38%	Decolonization		
E Coli	3	23%	at 1 week	8	88.8%
Other	2	16%	at 1 month	3§	33.3%
AMR gene			HSCT post FMT (days)	14	12-45
VIM	6	66.6%	Type of donor (and stem cell source)		
NDM	2	22.2%	haplo (PBSC)	6	66.6%
OXA	1	11.1%	HLA-matched (BM)	3	33.3%
Relevant infections pre FMT			Sepsis after HSCT	2	22.2%
Sepsis	5	55.5%	Acute GvHD	1	
Donor			Follow-up (days after FMT)	180	50-180
Third party	9	100%			

* 3 patients had multiple colonization; § 1 patients had a new positivization at day +60

Conclusions: FMT from a third party donor administered in the upper gastrointestinal tract seems safe and effective in pediatric patients (up to 10 months of age) affected by hemato/oncologic diseases in need of an allograft. In this cohort, an high rate of decolonization was obtained 1 week after the procedure (allowing proceeding to HSCT), although many patients became recolonized from the same pathogens 3 weeks later, this indicating incomplete eradication of the MDR bacteria with this approach. Amelioration of the protocol (e.g., performing multiple FMT) might further improve the transplant outcome in this high-risk population.

Disclosure: None related to this abstract.

13 - Infectious Complications

P391

IDENTIFICATION OF NOVEL T-CELL EPITOPES SPECIFIC FOR THE NON-FREQUENT HAPLOTYPES HLA-A*03 AND HLA-B*15 FOR MONITORING OF ALLOSCT PATIENTS

Alice Rein[1], Chris D. Lauruschkat[1], Ihsan Muchsin[2], Carolin Köchel[1], Maria M. Santamorena[3], Sabine Tischer-Zimmermann[3], Agnes Bonifacius[3], G. Ulrich Grigoleit[4], Britta Eiz-Vesper[3], Lars Dölken[2], Hermann Einsele[1], Florian Erhard[2], Sabrina Kraus[1]

[1]University Hospital of Wuerzburg, Wuerzburg, Germany, [2]Julius-Maximilians-University Wuerzburg, Institute for Virology and Immunobiology, Wuerzburg, Germany, [3]Hannover Medical School, Institute of Transfusion Medicine and Transplant Engineering Molecular Immunotherapy, Hannover, Germany, [4]Helios Hospital Duisburg, Oncology and Immunology, Duisburg, Germany

Background: Reactivation of human cytomegalovirus (HCMV) is a major problem in immunocompromised patients after allogeneic stem cell transplantation (alloSCT).

Early identification of alloSCT recipients that are at high-risk for prolonged and symptomatic HCMV reactivation reduces non-relapse related morbidity and mortality. The ability of a patient to prevent prolonged and symptomatic HCMV reactivation can be predicted by immunomonitoring. For immunomonitoring, peripheral blood mononuclear cells (PBMCs) are stimulated with a HCMV peptide pool consisting of frequently recognized epitopes (FREPs). However, these FREPs cover only a limited percentage of alloSCT patients mostly due to HLA-I haplotype restrictions. While patients with common HLA-I restrictions can be monitored, the detection of HCMV-specific T-cell responses in a significant number of patients with less common HLA haplotypes such as HLA-A*03:01 and HLA-B*15:01 remains challenging. Here, we identified novel HCMV-derived, HLA-A*03:01 and HLA-B*15:01-restricted immunogenic peptides by an innovative combined in vitro and in silico method for HCMV immunomonitoring.

Methods: A combination of mass spectrometry, peptide-PRISM- and PRICE-analyses was used to identify potentially immunogenic peptides, deriving from canonical and cryptic open reading frames. PBMCs of healthy HCMV-seropositive and -seronegative donors were stimulated for 16-18 hours with peptide pools or single peptides. Afterwards, IFNγ expression was quantified by intracellular staining using flow cytometry. A 7x7-pool test strategy, in which a single peptide was included in two peptide pools, was used to narrow down the number of potentially immunogenic peptides. Finally, immunogenicity of the most promising peptides was validated in healthy donors and alloSCT patients on a single peptide level.

Results: By combining mass spectrometry, Peptide-PRISM- and PRICE-analyses, we were able to identify 49 canonical and 49 cryptic potentially immunogenic peptides for each HLA-constellation deriving from more than 50.000 peptide candidates. In total three canonical and eight cryptic peptides restricted to HLA-A*03:01 as well as seven canonical and one cryptic peptide restricted to HLA-B*15:01 were found to be immunogenic (background-corrected $CD8^+/IFN\gamma^+$ T-cell response of ≥0.02%) by using the in vitro 7x7-pool test strategy. In vitro T-cell stimulation with single peptides resulted in the direct identification of three canonical and one cryptic HLA-A*03:01-restricted peptide and four HLA-B*15:01-restricted canonical peptides. Background-corrected, peptide-specific T-cell frequencies ranged from 0.02% to 0.07% ($CD8^+IFN\gamma^+/CD8^+$ T cells) in healthy HCMV-seropositive donors for both HLA haplotypes, while specific T-cell frequencies in HCMV-seronegative donors were negligible (≤ 0.01% $CD8^+IFN\gamma^+/CD8^+$ T cells). In alloSCT recipients, PBMC stimulation with these novel HCMV peptides confirmed two canonical peptides for both HLA haplotypes with background-corrected, peptide-specific T-cell frequencies of 0.02% to 0.08% ($CD8^+IFN\gamma^+/CD8^+$ T cells). Moreover, no peptide-specific T cells were detectable in HCMV-seronegative alloSCT recipients.

Conclusions: We identified and validated two novel canonical HLA-A*03:01- and B*15:01-restricted peptides, which represents potential candidates for the expansion of the FREP-pool. This might broaden the spectrum of immunogenic HCMV-derived peptides, allowing accurate immunomonitoring of significantly more alloSCT patients at high risk for prolonged and symptomatic HCMV reactivation.

Disclosure: Nothing to declare.

13 - Infectious Complications

P392

COMPARISON BETWEEN RIFAXIMIN AND CIPROFLOXACIN IN MICROBIOTA DIVERSITY AS NEUTROPENIA PROPHYLAXIS IN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Eleni Gavriilaki[1], Maria Christoforidou[2], Christos Varelas[1], Despina Mallouri[1], Fani Minti[2], Andriana Lazaridou[1], Eirini Baldoumi[1], Angeliki Giannakopoulou[1], Christos Demosthenous[1], Anna Vardi[1], Zoi Bousiou[1], Alkistis Panteliadou[1], Ioannis Batsis[1], Evangelia Yannaki[1], Achilles Anagnostopoulos[1], Georgia Gkioula[2], Ioanna Sakellari[1]

G Papanikolaou Hospital, Thessaloniki, Greece, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: Patients undergoing allogeneic hematopoietic cell transplantation (alloHCT) have reduced microbiota diversity compared to healthy controls. Rifaximin is an antibiotic that

allows higher microbiota diversity even in the presence of systemic broad-spectrum antibiotics, according to retrospective data. In this prospective, randomized study, we aimed to compare our standard-of-care neutropenia prophylaxis (Ciprofloxacin) with Rifaximin and determine possible differences in microbiota diversity.

Methods: We enrolled consecutive adult patients that underwent alloHCT according to EBMT indications, at our JACIE-accredited Unit and provided written informed consent to participate in this study (June 2019 - December 2020). Patients were randomly assigned to receive standard doses of ciprofloxacin or rifaximin at day -1. Initiation of treatment for neutropenic fever resulted in cessation of ciprofloxacin or rifaximin. Stool samples were collected at days −2 to +2 (T1), +11 to +17 (T2), +25 (T3) to +30 (T4) post alloHCT. Primary stool samples were pretreated according to the procedure protocol of the Project of the Human Microbiome of the National Health Organization; DNA was isolated and then used for PCR to amplify the entire 16S portion of the microbiome. The generated amplicons were sequenced using Torrent next-generation-sequencing technology. The Shannon Diversity Index and Linear discriminant analysis Effect Size (LEfSe) were used for the measurement of a-diversity, while Bray-Curtis dissimilarity was used for the estimation of b-diversity.

Results: We present data of 19 alloHCT recipients; 10 received ciprofloxacin and 9 rifaximin as neutropenia prophylaxis for at least 5 days. Transplant characteristics did not differ between the two groups. Cumulative incidence (CI) of acute graft-versus-host disease (GVHD) grade II-IV and moderate/severe chronic GVHD was similar in both groups. At phylum level we detected Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria and Verrucomicrobia at T4 in both groups. Actinobacteria abundance was significantly higher in the ciprofloxacin group ($p = 0.02$) at T4, with the other phyla presenting no major differences. Examining the effect of Ciprofloxacin and Rifaximin administration in comparison with T1 (baseline) at phylum level, we noticed increase of Firmicutes in both groups, but the difference was statistically significantly different in the Rifaximin group ($p = 0.02$). The a-diversity LEfSe algorithm resulted in the following statistically differentially abundant genera: abundance of Erysipelatoclostridium (phylum: Firmicutes) was higher in the Rifaximin group compared to the Ciprofloxacin group (1.02% in 6 patients vs 0.07% in 2 patients, $p = -0.02$), while abundances of Eubacterium (phylum: Furmicutes) and Parabacteroides (phylum: Bacteroidetes) were higher in the Ciprofloxacin group ($p = 0.04$). The genus of Actinomyces (phylum: Actinobacteria) was found only in 5 patients receiving Ciprofloxacin. Multivariate b-diversity analysis did not conclude with a statistically significant difference of the composition of the microbiome between the Rifaximin and Ciprofloxacin groups.

Conclusions: Our preliminary data of microbiota diversity suggest certain differences at phylum and genus level between Rifaximin and Ciprofloxacin groups at various time points. However, further studies are needed to carefully determine the effect of these differences on the outcome of the patients' clinical course.

Disclosure: Nothing to declare.

13 - Infectious Complications

P393

CLINICAL IMPACT OF ANTIBIOTIC ADEQUACY BASED ON MULTI-DRUG RESISTANT ORGANISM TESTING IN STEM-CELL TRANSPLANTATION

Beatriz Astibia[1], Carlos Jimenez[1], Valentin Garcia-Gutierrez[1], Anabelle Chinea[1], Pilar Herrera[1], Javier Lopez[1]

[1]Hospital Universitario Ramón y Cajal, Madrid, Spain

Background: Hematological patients (pts) are at high risk of multidrug-resistant organisms (MDRO) colonization, mainly because of their immunosuppression status and in-patient treatments. Colonization status is a known risk factor for MDRO infections. An inadequate empiric antibiotic therapy can compromise prognosis in MDRO infections, as their mortality is higher compared to non-resistant.

Methods: We performed a retrospective study in our center aimed to analyze the adequacy of empiric antibiotic treatment during admission and its impact, based on carrier (CR) or non-carrier (non-CR) MDRO status. For that purpose, we included 139 pts who underwent Stem-Cell Transplantation (SCT) from June 2021 to October 2022; 121 pts tested for MDRO colonization (87%, 116/121 at admission and 5/121 during hospitalization). MDRO screening was performed, with rectal swabs in 120 pts (99%), with pharyngeal in 117 pts (96.7%) and with nasal in 39 pts (32.2%). Target bacteria for identification were: multi-drug resistant (MDR) Gram-negative bacteria, MDR *Acinetobacter*, MDR *Enterococci*, MDR *Pseudomona aerogynose* and *Methicillin-resistant Staphylococcus Aureus* (MRSA). None of the pts received antibacterial prophylaxis. Our antibacterial policy for empiric treatment is piperacillin-tazobactam plus amikacin.

Results: 122 pts of 139 SCT pts were tested, 18 pts (14.8%) tested positive for MDRO, with three different isolates; smaller than those reported by the EBMT or German studies (30-50%). No significant differences were found in baseline characteristics between CR and non-CR pts, neither in other categories (Table 1). Median hospital stay was 24 days, 128/134 SCT pts (95.5%) presented fever. In these cases, the empirical antibiotic was modified in 23 cases (18%), 11 (47.8%) because of CR status and 12 (16.5%) based on clinical status. Microbiological cultures tested positive in 45/128 pts (35.2%). Empiric therapy was adequate in 36/45 pts (80%) and changed after bacterial isolation in 9/45 pts (20%). **Of 17/18 (94.4%) CR status pts with fever, empirical antibiotic was modified based on CR status in 12/17 (70.6%) pts. Only three pts in the CR group (17.6%) suffered from bacteremia, being treated with an adequate antibiotic 2/3 (66.7%) pts**. Of interest, our only MDRO-related death happened in a non-tested SCT pts, whose adequate antibiotic was delayed for 3 days till a carbapenem-resistant *Klebsiella pneumoniae* was isolated. Considering Intensive Care Unit (ICU) requirements, 13/134 (9.7%) pts were admitted in ICU, having 2/13 (15.4%) CR status. **Cause for ICU was septic shock in 8/13 (61.5%) pts, empirical antibiotic was appropriate in 4/8 pts (50%), being the only inadequate one in the MRDO sepsis death**, the other 3/8 pts (37.5%) did not have bacterial isolation.

Table 1. Baseline characteristics

		All patients n = 139	Non-carriers n = 104	Carriers n = 18
Median age in years (range)		57 (18-72)	58.5 (19-72)	55 (18-71)
Sex n, %	Male	95, 68.3%	68, 65.4%	11, 61.1%
	Female	44, 31.7%	36, 34.6%	7, 38.9%
Hospital n, %	Own hospital	85, 61.2%	60, 57.7%	13, 72.2%
	Referred hospital	54, 38.8%	44, 42.3%	5, 27.8%

		All patients n = 139	Non-carriers n = 104	Carriers n = 18
SCT n, %	Autologous	93, 66.9%	71, 68.3%	11, 61.1%
	Allogeneic	46, 33.1%	33, 31.7%	7, 38.9%
Diagnosis: n, %		MM: 52, 37.4%	MM: 38, 36.5%	MM: 6, 33.3%
		HL: 9, 6.5%	HL: 6, 5.8%	HL: 3, 16.7%
		FL: 8, 5.8%	FL: 7, 6.7%	FL: 1, 5.6%
		CML: 7, 5%	CML: 6, 5.8%	CML: 1, 5.6%
		PCNSL: 1, 0.7%	PCNSL: 1, 1%	AML: 2, 11.1%
		AML: 19, 13.7%	AML: 16, 15.6%	DMS: 3, 16.7%
		DLBCL: 8, 5.8%	DLBCL: 7, 6.7%	ALL: 1, 5.6%
		DMS: 11, 7.9%	DMS: 6, 5.8%	Others PCN: 1, 5.6%
		MF: 2, 1.4%	MF: 1, 1%	
		ALL: 6, 4.3%	ALL: 4, 3.8%	
		CMML: 2, 1.4%	CMML: 1, 1%	
		CLL: 2, 1.4%	CLL: 2, 1.9%	
		Others PCN[1]: 5, 3.6%	Others PCN: 4, 3.8%	
		Others NHL[2]: 3, 2.2%	Others NHL: 2, 1.9%	
		Others[3]: 4, 2.9%	Others: 3, 2.9%	
Disease risk for colonization n, %[4]	Low risk	82, 59%	58, 55.8%	10, 55.6%
	High risk	57, 41%	46, 44.2%	8, 44.4%

[1]*Others Plasma Cell Neoplasm: POEMS Syndrome, Amyloidosis, Plasma Cell Leukemia*
[2]*Others Non-Hodgkin's Lymphoma: Non-Hodgkin's T Cell Lymphoma, Plasmablastic Lymphoma*
[3]*Others: Ewings Sarcoma, Follicular Dendritic Cell Sarcoma, Prolymphocytic Leukemia*
[4]*Disease risk for colonization was defined based on previous time of in-patient treatment. In high risk group were included: Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Follicular Lymphoma, Diffuse Large B Cell Lymphoma, Cell Mantle Lymphoma, Primary Central Nervous System Lymphoma And Hodgkin Lymphoma.*
MM Multiple Myeloma; *HL* Hodgkin Lymphoma; *FL* Follicular Lymphoma; *CML* Cell Mantle Lymphoma; *PCNSL* Primary Central Nervous System Lymphoma; *AML* Acute Myeloid Leukemia, *DLBCL* Diffuse Large B Cell Lymphoma; *DMS* Myelodysplastic Syndrome; *MF* Myelofibrosis; *ALL* Acute Lymphoblastic Lymphoma; *CMML* Chronic Myelomonocytic Leukemia; *CLL* Chronic Lymphocytic Leukemia; *PCN* Plasma Cell Neoplasm; *NHL* Non-Hodgkin's *Lymphoma*.

Conclusions: Despite a small size, our MDRO rates display better results than other European studies; being our CR rate of 14.8%, compared to 30-50% described in similar SCT centres according to published data. This could be due to a non-antibacterial prophylaxis policy. Also, a higher rate of antibiotic adequacy could be related to lower UCI admissions. This highlights the importance of monitoring MDRO carrier status in SCT in order to ensure adequate empiric therapy.

Disclosure: Nothing to declare.

13 - Infectious Complications

P394

EVALUATION OF THE USEFULNESS OF INTERFERON-GAMMA RELEASE ASSAY FOR THE DETECTION OF LATENT MYCOBACTERIUM TUBERCULOSIS INFECTIONS IN PATIENTS WHO UNDERWENT HEMATOPOIETIC STEM CELL TRANSPLANTATION

Sungnam Lim[1], Beongseok Sohn[2]

[1]Inje University College of Medicine, Haeundae Paik Hospital, Busan, Korea, Republic of, [2]Inje University College of Medicine, Sanggye Paik Hospital, Seoul, Korea, Republic of

Background: Tuberculosis (TB) is still a major global public health problem. The likelihood of developing the active disease is much higher in frail patients, such as those with hematopoietic stem cell transplantation (HSCT). Patients undergoing HSCT have severe and prolonged immunodeficiency due to underlying hematologic malignancies, chemo- and immunosuppressive therapy, and graft-versus-host disease, and are generally considered to be at higher risk for active TB or reactivation of latent TB infections.

The aim of this study was to evaluate the occurrence of active TB in patients who received a **QuantiFERON test** for the detection of latent TB infection.

Methods: This is a retrospective observational cohort study, including all adult patients (> 18 years old) with hematopoietic malignancies who underwent HSCT.

In total, 201 patients who received an interferon-gamma release assay and underwent auto- or allogeneic hematopoietic stem cell transplantation between September 2010 and December 2021 were recruited to determine the usefulness of latent TB infection screening tests.

Results: A total of 201 patients, 96 (47.8%) autologous and 105 (52.5%) allogeneic stem cell transplants, underwent **QuantiFERON test** screening: 148 (51.0%) were negative, 17 (5.9%) indeterminate, and 36 (12.4%) positive. Most of the enrolled patients were male (58.7%) with a median age of 54 years old (range, 19 ~ 69 years old). The most common hematologic malignancy affecting patients before HSCT was acute myeloid leukemia (36.6%), followed by multiple myeloma (14.2%), non-Hodgkin lymphoma (13.9%), and acute lymphoblastic leukemia (12.4%). The **QuantiFERON screening test was performed within one month before HSCT. There was no difference in test positive rates between men and women. However, the positive rate was statistically significantly higher in elderly patients (p = 0.001). Only 20% of the patients whose test was QuantiFERON test positive took isoniazid prophylaxis, and none of them progressed to active TB over a median follow-up period of 40.4 months. Active TB recurrence did not occur even in 80% of QuantiFERON test-positive who did not take isoniazid, also**.

Conclusions: In conclusion, 12.4% of our HSCT population had latent TB infection, only 20% of them received isoniazid prophylaxis. There were no cases of active TB progression in a cohort of 201 patients who underwent HSCT from 2010 to 2021.

Disclosure: There is no disclosure of a conflict of interest.

13 - Infectious Complications

P395

CYTOMEGALOVIRUS-SPECIFIC T CELL EXPANSION KINETICS AND VIRAL CONTROL IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

Sung Han Kang[1], Ho Joon Im[1], Soo Hyun Yoon[1], Young-Kwon Koh[1], Hyery Kim[1], Kyung-Nam Koh[1], Eun Seok Choi[1], Sang Hyun Whang[2]

[1]Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea, Republic of, [2]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of

Background: Cytomegalovirus (CMV) is a leading cause of infectious complications following hematopoietic stem cell transplantation (HSCT). Although various methods of CMV prevention and prophylaxis are widely used, reconstitution of immunity is critical in CMV control and prevention. However, little is known about the post-HSCT kinetics of CMV-specific T cells. In this preliminary report, we investigate the kinetics of CMV-specific T cell reconstitution and its role in virus control.

Methods: We used a rapid cytokine inspector to perform flow cytometric analysis of the CMV-specific T cell response to pp65 and IE-1 at 1, 2, 3, and 6 months after HSCT. In the current study, 58 patients have been enrolled since January 2022. The number and duration of CMV reactivation were used to categorize patients. Group 1 included eleven patients (19%) who did not have CMV reactivation. Group 2 included sixteen patients (28%) with a single reactivation event. Group 3 included twenty patients (34%) with more than two reactivation events, while group 4 (eleven, 19%) included any number of reactivations with more than two consecutive months. In addition, we performed a preliminary analysis of the VST proportion of a cryopreserved, CD45RA-depleted graft.

Results: The median age at HSCT was 10.5 years (range, 0.8-20.5). 25 (43%) of the 58 patients received HSCT from a haploidentical family donor using low-intensity conditioning and an ex vivo T cell-depleted graft. At a median of 10 days after HSCT, all patients had primary engraftment. Twenty-nine patients experienced acute GVHD of grade 2 or higher. Corticosteroids were administered to 29 patients over the course of 31 days. CMV reactivation occurred in 47 patients after HSCT, with a median of 23 days (range 0-36). Six patients were diagnosed with CMV disease (4 retinitis only, one pneumonitis, one retinitis, and pneumonitis). VST proportions and absolute counts among CD4+ and CD8+ lymphocytes differed significantly between the four groups. Group 2 had the best CMV VST response after CMV reactivation (mean absolute CD4 + VST cell counts, first month post-HSCT, Gr1 vs Gr2 vs Gr3 vs Gr4, 2.27 vs 3.81 vs 1.05 vs 0.17, $P = 0.028$; CD8 + VST cell counts, Gr1 vs Gr2 vs Gr3 vs Gr4, 3.81 vs 29.33 vs 5. Group 2's CD4+ and CD8 + CMV VST remained higher than the other groups during the first three months post-transplant. Following the second reactivation, patients in Group 3 had an increase in both CD4+ and CD8 + CMV VST, whereas patients in Group 4 had no significant change. The VST of a cryopreserved CD45RA depleted graft contained 9.55% CD3 + CD8 + CMV VST, according to preliminary analysis.

Conclusions: VST reconstitution in response to primary CMV reactivation was associated with subsequent additional reactivation. Significantly, the early and sustained response of CD4+ and CD8 + VST appears to play an important role in virus control. More research into therapeutic interventions, such as selective CD45RA depleted lymphocyte infusion, that could improve the VST response is required.

Disclosure: Nothing to declare.

13 - Infectious Complications

P396

COADMINISTRATION OF ISAVUCONAZOLE AND SIROLIMUS IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS: A SINGLE-CENTER EXPERIENCE

Andrea Acerbis[1,2], Francesca Farina[1], Chiara Oltolini[1], Matteo Chiurlo[1,2], Elisabetta Xue[1], Sarah Marktel[1], Sara Mastaglio[1], Simona Piemontese[1], Elisa Diral[1], Alessandro Bruno[1,2], Giorgio Orofino[1,2], Edoardo Campodonico[1,2], Daniela Clerici[1], Consuelo Corti[1], Maria Teresa Lupo Stanghellini[1], Antonella Castagna[1,2], Jacopo Peccatori[1], Fabio Ciceri[1,2], Raffaella Greco[1]

[1]IRCCS San Raffaele Scientific Institute, Milan, Italy, [2]University Vita-Salute San Raffaele, Milan, Italy

Background: Invasive fungal infections (IFIs) represent a major cause of morbidity among allogeneic HSCT (allo-HSCT) recipients, although transplant survival rates improved in recent years.

Isavuconazole (ISA) is a second-generation broad-spectrum triazole with yeast and moulds activity, favourable safety profile, few drug–drug interactions and predictable pharmacokinetics.

Methods: This single-center retrospective analysis was conducted to evaluate the real life use of ISA in allo-HSCT between July 2017 and June 2022 in our center. Patient's characteristics are summarized in table 1. Patients were treated according to institutional protocols, upon written informed consent for transplant procedures and use of medical records for research. During the study period, GvHD prophylaxis was based on PTCy, sirolimus and MMF. Letermovir as CMV prophylaxis was administered in all CMV-seropositive transplant recipients after March 2019. ISA serum levels were measured weekly and doses were adjusted according to therapeutic drug monitoring (TDM). MSG EORTC 2020 criteria were used to define breakthrough proven-probable IFIs (b-PP-IFIs).

Results: Overall, 50 transplant recipients received more than 2 weeks of ISA with a median follow up of 372 days. Median treatment duration with ISA was 142 days. The median age at allo-HSCT was 52 years (range 24-75 years).

Sixteen patients were treated with ISA as anti-fungal agent during allo-HSCT as ISA continuous treatment started for a previous IFI.

1/16 patients experienced a b-PP-IFI under ISA continuous treatment with a probable invasive pulmonary aspergillosis. Median ISA TDM in patients that had b-PP-IFIs or not was respectively 2.5 mg/L and 4.5 mg/L. One patient changed empirically ISA for persistent fever and progressive respiratory distress and died few days later.

Thirty-four patients were started on ISA as antifungal therapy.

Sixteen patients were treated for a b-PP-IFI during mould-active prophylaxis (7 posaconazole, 7 voriconazole and 2 amphotericin B). Three IFIs were proven (1 *Candida glabrata* sepsis, 1 disseminated aspergillosis and 1 *Aspergillus flavus*–biopsy proven sinus aspergillosis) and 13 were probable invasive pulmonary aspergillosis. Median ISA TDM was 3.7 mg/L (range 3.1-4.5 mg/L). In this group, 6/16 patients (37.5%) died for IFI at a median time of 51 days (median 14-93 days) after the start of ISA. At 6 weeks after b-PP-IFI diagnosis, 8/16 (50%) patients had resolved the IFI, 2 patients had a persistent IFI, 5 patients were already died for IFI and 1 patient was died for disease progression. All patients that continued ISA after b-PP-IFI had no other IFIs, even during immunosuppressive therapy.

Eighteen patients were treated with ISA as empirical anti-fungal therapy in patients with fever and pulmonary infiltrates. At 6 weeks after the start of ISA, 1 patient was died for disease progression, the others were alive with resolution of infection.

Significantly, no patients had isavuconazole and/or sirolimus-related toxicities (i.e. liver toxicity, sinusoidal obstructive syndrome, thrombotic microangiopathy or neuropathy).

Conclusions: The coadministration of isavuconazole and sirolimus was safe and feasible in 50 patients, also in the context of prophylaxis with letermovir. No adverse events related to ISA were reported.

Table 1. Patient and HSCT characteristics

Characteristics of patients	Overall population, n	%
Age		
20-50 years	24	48
51-65 years	18	36
>65 years	8	16
Sex		
Male	29	58
Female	21	42
Disease		
Acute myeloid leukemia	30	60
Acute lymphoblastic leukemia	6	12
Myelodysplasia and myeloproliferative neoplasms Lymphoma	5	10
Severe aplastic anemia	8	16
	1	2
Disease status		
First complete remission	20	40
Second complete remission	17	34
Active disease	13	26
Allo-HSCT		
I transplant	47	94
II transplant	3	6
Donor type		
Matched-related donor	6	12
Matched-unrelated donor	12	24
Mismatched-related donor	27	54
Cord blood unit	5	10
aGVHD		
Yes		
Grade I-II	14	28
Grade III-IV	8	16
No	28	56
cGVHD		
Yes		
mild	3	6
moderate	1	2
severe	4	8
No	42	84
Letermovir		
yes	23	46
no	27	54

Disclosure: Nothing to declare.

13 - Infectious Complications

P397

EVALUATION OF CYTOMEGALOVIRUS INFECTION FREQUENCY, RISK FACTORS AND EFFECT ON SURVİVAL FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION: A SINGLE CENTER EXPERIENCE

Barış Gezici[1], Ajda Ersoy Günes[1], Nur Akad Soyer[1], Güray Saydam[1], Mahmut Tobu[1], Fahri Sahin[1], Mehmet Soylu[1], Filiz Vural[1]

[1]Ege University, Izmir, Turkey

Background: Cytomegalovirus (CMV) infection is the most common infection after allo-SCT procedure and CMV disease still carries a relatively high risk of mortality despite advances in diagnostic and treatment methods. The aim of our study was to investigate the risk factors and frequency of CMV infection, CMV disease and their effects on overall survival.

Methods: Overall, 221 adult patients who underwent first allo-SCT between 2012 and 2020 at our institution, were included in this single center, retrospective, observational study. Data on patients' sociodemographic information, characteristics of the allo-SCT procedure and complications, donor characteristics, and parameters related to CMV infection/disease were collected.

Results: 60.6% of the patients were male, with a mean age of 41.5 years. The mean follow-up period was 1067.4 days. The indications of allo-SCT were malignant in 93%. Matched related donors in 166 (75.1%), matched unrelated donors in 47 (21.3%) and haploidentic donors in 8 (3.6%) transplants were used. Of the conditioning regimens, 167 (75.6%) were myeloablative, 36 (16.3%) were reduced-intensity, and 18 (8.1%) were nonmyeloablative. The mean engraftment time was 17.9 days. aGVHD, cGVHD, CMV infection, CMV disease occured in 86 (38.9%), 44 (23%), 121 (54.8%), 18 (8,1%) patients, respectively. Of those who developed CMV infection, 111 (91.7%) developed in early period and 10 (8.3%) in late period. The mean day and standart deviation of CMV infection was 48.2 ± 38.9 days and the median value was 39 days. Patient and transplant-related characteristics categorized by CMV infection status are shown in Table-1. As expected, the presence of aGVHD and cGVHD were determined as risk factors for both CMV infection ($P < 0,001$, $P < 0,001$, Table-1) and CMV disease ($P < 0,001$, $P = 0,001$). It was observed that the risk of developing CMV infection in early period of allo-SCT increased in patients using BuCy protocol as conditioning regimen ($P = 0,03$) and also CMV disease involves gastrointestinal system more frequently in the presence of aGVHD ($P = 0,04$) or HLA-matched unrelated donor ($P = 0,03$). It was found that peak CMV DNA measured during CMV infection was associated with risk of progress to CMV disease ($P = 0,008$) and count of leukocytes, neutrophils and lymphocytes at onset of CMV infection was inversely associated with the risk of recurrence of CMV infection ($P = 0,005$, $P = 0,004$, $P = 0,01$, respectively). The risk of death was 1.46 (1.04-2.04) times higher in those with CMV infection and 1.79 (0.91-3.51) times higher in those with CMV disease but this increase in mortality risk for CMV disease was not statistically significant (Image-1).

CMV Infection		Present (n = 121)	Absent (n = 100)	
Characteristics		**n (%)**	**n (%)**	**P value**
Donor Characteristics	Matched related	85 (70,2)	81 (81)	0,16
	Matched unrelated	30 (24,8)	17 (17)	
	Haploidentical	6 (5)	2 (2)	
Conditioning Regimen	Myeloablative	95 (78,5)	72 (72)	0,39
	RIC	16 (13,2)	20 (20)	
	Nonmyeloablative	10 (8,3)	8 (8)	
Conditioning Regimen	With cyclophosphamide	104 (86)	86 (86)	0,99
	Without cyclophosphamide	17 (14)	148 (14)	
Conditioning Regimen	With ATG	14 (11,6)	9 (9)	0,53
	Without ATG	107 (88,4)	91 (91)	
	Positive	12 (9,9)	7 (7)	0,44

CMV Infection		Present (n = 121)	Absent (n = 100)	
Characteristics		**n (%)**	**n (%)**	**P value**
History of CMV Infection Prior to Allo-SCT	Negative	109 (90,1)	93 (93)	
Acute GVHD	Positive	70 (57,9)	16 (16)	**<0,001**
	Negative	51 (42,1)	84 (84)	
Chronic GVHD	Positive	34 (33,7)	10 (11,1)	**<0,001**
	Negative	67 (66,3)	80 (88,9)	

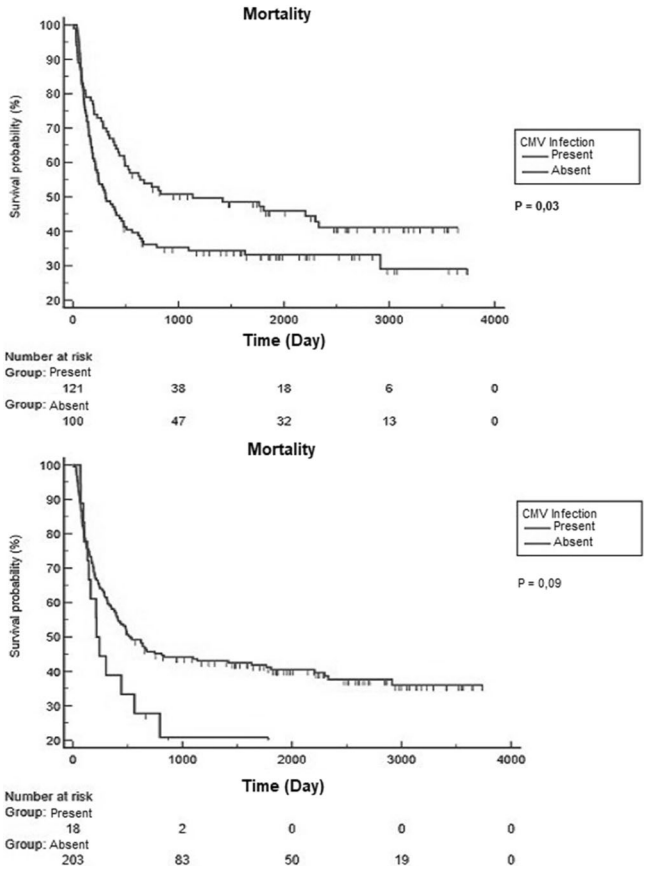


Image-1: Effect of CMV infection and disease on overall survival

Conclusions: In our study, among the parameters mentioned in the results section for CMV infection and CMV disease, risk factors and overall survival were determined seperately for both. In particular, in patients with high peak CMV DNA in blood or cytopenia at the onset of CMV infection, close follow-up may be beneficial for early detection of progression to CMV disease and recurrence of CMV infection, respectively.

Disclosure: Nothing to declare.

13 - Infectious Complications

P398

SUCCESSFUL TREATMENT OF REFRACTORY COVID19 WITH "SARS-COV2 SPECIFIC OFF-THE-SHELF T CELLS (VST)" IN A HEMATOLOGIC MALIGNANCY (HM) AND AN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT (HCT) PATIENT

Sanjeet Dadwal[1], Alfredo Puing[1], Tanya Siddiqi[1], Jana Dickter[1], Ryotaro Nakamura[1], Stephen Forman[1], Deepa Nanayakkara[1], Monzr Al Malki[1], Randy Taplitz[1], Seiung Moon[1], Elizabeth Budde[1], Amandeep Salhotra[1]

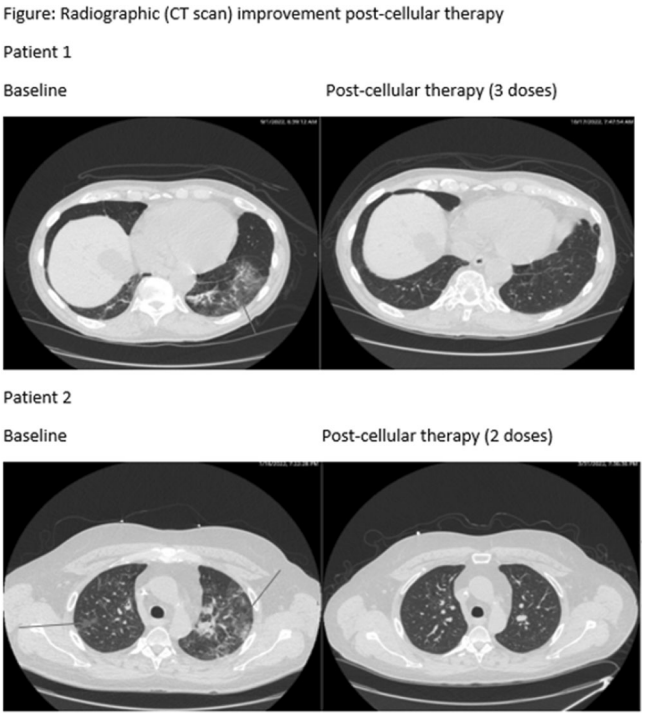
[1]City of Hope National Medical Center, Duarte, United States

Background: T cell immune response is important in the eradication of viral infections, including SARS-CoV2. Prolonged shedding with viable SARS-CoV2 has been reported in HM/HCT patients, which can delay treatment of the underlying disease. In HM/HCT immunosuppressed patients, antivirals alone may not be sufficient to clear the infection. Here we report successful clearance of prolonged viral shedding and resolution of symptoms/ radiographic findings with the use of ALVR109, a SARS-CoV2 VST.

Methods: Two patients with HM and COVID19 were treated with ALVR109 on compassionate grounds (with approval from USFDA and the sponsor, Allovir, Inc. and after IRB approval and informed consent obtained). A maximum of 3 doses were allowed, infused 2 weeks apart. Nasal samples were obtained at baseline and at defined intervals for viral testing. Data collected included demographics, diagnosis, duration of viral shedding before ALVR109 infusion, prior antiviral and immunosuppressive treatment, diagnostic studies, and side effects of ALVR109.

Results: ***Patient 1*** – 74-year-old, male, had Juno CD-19 CAR-T in March 2019 for CLL, complicated by pure red cell aplasia refractory to rituximab, cyclosporine, and antithymocyte globulin. COVID19 was diagnosed in May 2022, treated with nirmatrelvir/ ritonavir for 5 days, followed by remdesivir in June for 10 days. Viral shedding with low cycle time (Ct) which suggested high viral load (VL) persisted, and in September he was hospitalized for lower respiratory tract infection (LRTI) with CT scan showing diffuse pneumonia (see Figure 1). He tested positive for SARS-CoV2 by PCR from bronchoalveolar lavage (BAL) fluid. Work-up for other infections was negative. He was re-treated with remdesivir for 10 days and received 3 doses of ALVR109 with last dose in 10/2022. Duration of viral shedding before ALVR109 given was 120 days. He had rapid clinical improvement; CT scan done 5 weeks post-1st dose showed clearance of pneumonia and he tested negative for SARS-CoV2 by PCR.

Figure: Radiographic (CT scan) improvement post-cellular therapy



Patient 2 – 48-year-old male had allogenic HCT in October 2015 complicated by severe cGVHD treated with ruxolitinib, extracorporeal photopheresis, prednisone 10 mg/ daily, tacrolimus and sirolimus. COVID19 was diagnosed in November 2021, treated with three courses (10 days each) of remdesivir over next 2 months. Viral shedding with low Ct (high VL) persisted and he developed LRTI confirmed by CT scan of chest. He declined BAL and was empirically treated with antimicrobials. Duration of viral shedding before ALVR109 given was 94 days. He received 2 doses of ALVR109 in February 2022 and within 2 weeks felt remarkably better and declined to get 3rd dose of ALVR109. CT scan 8 weeks later showed resolution of pneumonia. He had persistent viral shedding with declining VL and finally tested negative 4 months later. Both patients tolerated ALVR109 with no apparent adverse events.

Conclusions: In our patients, ALVR109 was well tolerated and effective. Adjunctive therapy with ALVR109 is an attractive therapeutic option in treatment of COVID19 infections in severely immunocompromised patients with defective B and T cell immunity and should be explored as an upfront therapeutic option to prevent progression to LRTI and in the setting of refractory illness.

Disclosure: Sanjeet Singh Dadwal, MD: Research funding - Allovir, Ansun Biopharma, Merck, Amplyx/ Pfizer. Consulting/ Advisory board: Merck, Allovir, Aseptiscope. Speakers bureau: Astellas, Merck, and Astellas

Seung Hyun Moon, Employee of Allovir

Monzr M. Al Malki, MD: Consultancy: CareDx, Gilead; NexImmune; Incyte. Research Funding: Streamline, Gilead; NexImmune; Miltenyi Biotec; Incyte

Elizabeth Budde, MD: Advisory board/consultancy: Roche, Genentech, ADC therapeutics. Research funding: Mustang Bio, Merck, Amgen, AstraZeneca

Other authors: Nothing to disclose

13 - Infectious Complications

P399

RISK FACTOR ASSOCIATED WITH HEMORRHAGIC CYSTITIS SECONDARY TO BK VIRUS INFECTION IN CHILDREN AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION: EXPERIENCE OF AN INSTITUTION IN MÉXICO

Alberto Olaya-Vargas[1], Haydee del Pilar Salazar-Rosales[1], Gerado López-Hernández[1], Nideshda Ramírez-Ortiz[1], Alfredo Galindo-Martínez[1], Virginia Diaz-Jiménez[1], Hugo Sánchez-Fuentes[1], Yamil Arias-Delgadillo[1], Basauri-Garrido Luisa Basauri-Garrido[1], Yadira Melchor-Vidal[2], José Lecona-Cruz José[2], Alberto Olaya-Nieto[3]

[1]Instituto Nacional de Pediatria, Ciudad de Mexico, Mexico, [2]Centro Medico ABC, Ciudad de Mexico, Mexico, [3]Saint Lucke, México, Mexico

Background: Hemorrhagic cystitis (HC) associated with BK virus is a common cause of morbidity after hematopoietic stem cell transplantation (HSCT). Exist several risk factors associated with HC such as viruria y/o viremia very high BK viral loads, myeloablative conditioning regimen, graft versus host disease (GvHD), and cytomegalovirus infection, match unrelated donor or haploidentical donor. The presence of a high blood BK viral load and cytopenia have been implicated as important predictors of the prolonged course of the disease. These patients often require hospitalization that can last for several weeks for generally supportive including pain control, intravenous fluids, bladder irrigations y transfusion support.

Methods: Retrospective cohort study to assess risk factors associated with hemorrhagic cystitis secondary to BK virus infection in children after HSCT. The data was collected and digitized in Excel office database version 2019. Absolute and relative frequencies are reported in the qualitative variables, measures of central tendency and dispersion (mean, standard deviation, median, range, and quartiles according to the observed distribution). In the case of quantitative variables, a univariate analysis was performed with Chi-Square Test, the Kolmogorov-Smirnov Test, and logistic regression for the multivariate analysis with SPSS Version 22 program.

Results: A total of 76 patients with diversity pathologies (benign and malignant blood disorders, solid tumors, and innerity error immunity) after transplant were included: 46 patients with haploidentical donor, 27 matched sibiling donor, 2 autologous, and 1 matched unrelated donor. The graft source was peripheral blood in 55.56%, bone marrow in 43.42%, and umbilical cord blood in 1.3%. The intensity of conditioning regimens was 5.9% myeloablative, 43.9% reduced intensity, 1.3% non-myeloablative, and 1.3% without conditioning regimen. The 76.5% presented viruria (30.6% with hemorrhagic cystitis) and 28.9% viremia.

The factors associated with hemorrhagic cystitis were haploidentical transplant ($p = 0.0035$), GvHD prophylaxis with Mycophenolate mofetil (MMF) ($p = 0.002$), and viremia greater than 40467copies/dl ($p = 0.003$). No significant relationship was found between the myeloablative conditioning regimen and total-body irradiation. El treatment with statistical significance for the management of hemorrhagic cystitis was Leflunomide ($p = 0.0001$). Only 1 patient presented related mortality to the BK virus.

Conclusions: BK virus infection is a common complication in HSCT and children with this infection can present various secondary complications such as: secondary graft failure, cytopenia, and hemorrhagic cystitis. In our series, the haploidentical transplant, use of MMF, and blood high BK viral load were the variables associated with an increased risk of presenting hemorrhagic cystitis.

Disclosure: All the authors declare or have conflicts of interest, the present investigation was carried out with economic resources of the National Institute of Pediatrics (Mexico).

13 - Infectious Complications

P400

COMPARISON OF INFECTIOUS COMPLICATIONS BETWEEN SUBJECTS WHO RECEIVED HYPERBARIC OXYGEN THERAPY VERSUS CONTROLS IN AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTS FOR MULTIPLE MYELOMA

Purba Gupta[1], Basil Al-Kaabneh[1], Andrea M. Baran[1], Catherine A. Bunce[1], Prishanya Pillai[2], Omar Aljitawi[1]

[1]University of Rochester Medical Center, Rochester, United States, [2]Medstar Georgetown University Hospital, Washington D.C., United States

Background: Autologous hematopoietic cell transplant (Auto-HCT) is the standard of care procedure for consolidation in transplant-eligible multiple myeloma patients. Based on retrospective data, pre-transplant hyperbaric oxygen therapy (HBO) in patients undergoing high-dose chemotherapy and Auto-HCT improved time to neutrophil and lymphocyte recovery post-transplant and reduced rates of mucositis. Our aim was to evaluate the effect of HBO on the incidence, severity, and

outcome of infections in myeloma patients who enrolled in the completed phase II multi-center randomized clinical trial evaluating HBO versus control in Auto-HCT.

Methods: We conducted an observational cohort study of multiple myeloma patients, who received high-dose Melphalan with or without HBO before Auto-HCT at Wilmot Cancer Center between June 2018 and June 2021. Electronic medical records were reviewed for demographic, clinical, and laboratory data. Primary outcome was to compare incidence of any infection between the two groups occurring within 100 days post-transplant. Secondary outcomes were to assess the types of infection, severity and outcome for each infection episode, time to onset of infection (days), and time to neutrophil and lymphocyte recovery (days). The incidence rates were calculated as the number of infections over the number of person-years at risk. Person-years were defined as the time from a patient's stem cell infusion until death or end of follow-up. Incidence rates within each arm is presented with associated 95% Poisson confidence intervals. Incidence rate ratios are presented with associated 95% confidence intervals.

Results: 72 patients with multiple myeloma who received high-dose Melphalan and underwent Auto-HCT with (N = 37) or without HBO (N = 35) were included. 37.8% (14/37) of HBO patients and 45.7% (16/35) of non-HBO patients experienced at least 1 infection {OR = 0.72, 95% CI = 0.28-1.85, p = 0.50}. The incidence rate of infection in HBO patients is 0.43 infections/100 person-days {95% CI = 0.26, 0.71}, and in non-HBO patients is 0.51 infections/100 person-days {95% CI = 0.32, 0.82}. There is insufficient evidence of a difference in incidence rate between the two groups, with no significant difference in severity or outcome of infections seen between the two groups {IRR = 0.84, 95% CI 0.43-1.65, p = 0.61}. Fewer patients (2.7%) in the HBO group had Clostridium difficile infection than the non-HBO group (14.3%) {OR = 0.17, 95% CI = 0.02-1.51, p = 0.11}. Blood Stream Infections were less common in the HBO group (16.2%) than in the non-HBO group (22.9%) {OR = 0.65, 95% CI = 0.20-2.12, p = 0.48} (table1). Median days to onset of first episode of infection was greater in the HBO arm (10.13 days) than in the non-HBO arm (8.5 days). Fewer patients in the HBO-arm developed a second episode of infection (8.1% vs 14.2%). Median time to lymphocyte engraftment was 13.37 days in the HBO arm compared to 14.9 days in the non-HBO arm; there was no difference in time to neutrophil engraftment between the two groups.

Infection type	HBO (N = 37)	Non-HBO (N = 35)	Fisher's exact p-value
Pneumonia	4 (10.8%)	1 (2.9%)	0.18
Clostridium difficile Infection	1 (2.7%)	5 (14.3%)	0.10
Blood Stream Infections	6 (16.2%)	8 (22.9%)	0.56
Skin and Soft Tissue Infections	1 (2.7%)	1 (2.7%)	1.00
Urinary Tract Infections	1 (2.7%)	3 (8.6%)	0.35
Other infections	2 (5.4%)	0	0.49

Conclusions: Pre-transplant HBO therapy shows a trend towards improving the median time to lymphocyte engraftment, prolonging median days to onset of infections, and decreasing incidence of Clostridium difficile and Blood Stream Infections, although a study on a larger group of patients is needed.

Disclosure: Nothing to declare.

13 - Infectious Complications

P401

IDENTIFICATION OF RISK FACTORS FOR CMV PRE-EMPTY THERAPY IN CHILDREN AFTER ALLOGENEIC HSCT

Giulia Ferrando[1], Francesca Bagnasco[1], Filomena Pierri[1], Gianluca Dell'Orso[1], Stefano Giardino[1], Eddi Di Marco[1], Elio Castagnola[1], Maura Faraci[1]

[1]*IRCCS Istituto G. Gaslini, Genova, Italy*

Background: Reactivation of cytomegalovirus (CMV) represents the most frequent herpesvirus reactivation occurring after allogeneic hematopoietic stem cells transplantation (allo-HSCT). About 70% of seropositive CMV allo-HSCT recipients experienced early CMV reactivation. There is no a consensus about the number of CMV copies to start a pre-emptive antiviral therapy in children. The aim of this retrospective single center study is to evaluate the management of children who developed CMV reactivation after allo- HSCT and to evaluate the adherence to treatment according to first identified groups of risk.

Methods: All patients who developed CMV reactivation after allogeneic HSCT (from matched related, unrelated or haploidentical donor) during the period between 2009 to 2019 are included in this study. CMV DNAemia was monitored regularly twice a week. Two groups of patients were first identified to apply a treatment plan with ganciclovir or foscavir.

Results: 65 children (median age 8.5 years) who received 69 allo HSCTs (36 from matched unrelated donors, 18 from haploidentical donors, 15 from matched related donors) developed CMV reactivation during the study period.

59 patients received pre-emptive therapy and 55 of them (93.2%) fitted with the first established criteria.

49/59 patients (83%) were included in high-risk group for CMV reactivation and they received pre-emptive therapy with a median viremia of 2200/ml copies. The remaining 6 patients (10.1%) who had not risk factors, received therapy with higher median viremia of 7550/ml copies. Four patients (6.7%) not included in predefined risk group, received pre-emptive because presented specific individual risk factors as second haploidentical transplant for previous rejection of the first, pre transplant CMV disease or other clinical fragile conditions. Ten children did not receive pre-emptive therapy and in these cases the adherence to the established criteria was 40%.

The univariate analysis demonstrated that no statistically significant correlations emerged between the characteristics of the HSCT (including gender, age at HSCT, underlying disease, type of conditioning regimen, stem cell source, presence of acute or chronic GVHD, high dose of steroids above 2 mg/Kg) and the indication to pre-emptive therapy. Patients who presented more than one reactivation had higher probability to developed more CMV reactions and these patients received more pre-empty therapies (33 vrs 1; p = 0.013). Identification of these patients was useful in order to prevent CMV disease and mortality related to the infection. Non patients developed CMV disease. In our experience the adherence of established guidelines was high (85.5%; p < 0.001).

Conclusions: Identifications of groups of risk to develop CMV reactivation could help to make decisions about the pre-emptive therapy. Further studies are necessary to validate this approach in order to prevent CMV disease.

Clinical Trial Registry: not applicable

Disclosure: Conflict of interest: nothing to declare.

13 - Infectious Complications

P402

SUCCESSEFUL TREATMENT OF JC-ENCEPHALITIS WITH PEMBROLIZUMAB AFTER ALLOGENIC STEM CELL TRANSPLANTATION

Martina Crysandt[1], Patrick Hess[1], Fabian Beier[1], Robert Brunkhorst[2], Simone Tauber[2], Francis Ayuketang Ayuk[3], Tim Brümmendorf[1], Edgar Jost[1]

Hemostaseology and Stem Cell Transplantation, RWTH Aachen University, Aachen, Aachen, Germany, RWTH Aachen University, Aachen, Aachen, Germany, University Hospital Hamburg-Eppendorf, Hamburg, Hamburg, Germany

Background: Complications involving central nervous system occur in about 10 % of patients after allogeneic stem cell transplantation (allo-HCT). Encephalitis is a rare complication after HCT and is mostly related to toxic influences, viral infections e.g., by HHV6, HSV1 or JC virus or can be induced by an autoimmune disease. Encephalitis by polyoma-JC virus (JCV), presenting as a multifocal progressive leukoencephalopathy (PML) has a dismal prognosis in patients after HCT. Here, we report the course of a patient with JC induced encephalitis successfully treated with the checkpoint-inhibitor pembrolizumab. Pembrolizumab targets the inhibitory programmed cell death protein 1 (PD-1) receptor on lymphocytes and is associated with beneficial expansion of pre-existing virus-specific T cells.

Methods: A 47 year old female patient underwent allo-HCT for relapsing multiple myeloma 8 years before the here described episode. In the posttransplant setting, she received maintenance therapy with pomalidomide and low dose dexamethasone and DLIs for incomplete remission proven by persistence of a monoclonal protein at a low level in immunofixation. At appearance of neurological symptoms the patient was immunocompromised with a CD4 T-cellcount of 137/nl. The patient presented eight years after HCT with right-sided hemiplegia. During workup, she developed a number of further neurological symptoms including headache, confusion and aphasia. Brain MRI demonstrated bilateral, multiple T2-hyperintens lesions in supratentoriel white substance. The cortex was not affected by this inflammatory process. No abnormalities of intracranial vessels were observed. After all she was found to have newly diagnosed JC-Virus encephalitis proven by JCV-DNA in the CFS. Due to the lack of evidence for effective treatment choices for PML, the patient was treated with pembrolizumab, based on recent reports in the literature.

Results: Overall, the patient received twelve doses of pembrolizumab. During treatment, a decrease in JCV-DNA level was measured and finally undetectable. Neuroimaging after treatment showed regression of all lesions without further signs of inflammation or disease activity. Our patient showed stability and later on slow improvement of neurological symptoms. Up to now she is still suffering from residual dysathria and partial palsy of the right arm. During the whole treatment course, no signs of chronic graft versus host disease (GVHD) could be detected.

Conclusions: PML is a demyelinating disease occurring in patients with prolonged immunosuppression, caused by the reactivation of JC-virus. The use of pembrolizumab for treatment is based on the inhibition of programmed cell death protein 1 (PD-1), potentially improving the anti JCV-specific response. In our patient we could show that in this rare but clinically significant disease, pembrolizumab is an effective and well tolerated treatment option. Our observation confirms results of other cases reported in the literature and presents an alternative to other rarely effective and potentially more toxic treatment options like cidofovir or other experimental approaches like JCV-specific T cells. The role of prolonged treatment with the immunomodulatory drug (IMID) pomalidomide cannot be determined. Early detection, and prompt intervention play a crucial role in the prognosis of PML in patients with hematological malignancies especially with prolonged immunosuppression after HCT.

Disclosure: Nothing to declare.

13 - Infectious Complications

P403

CYTOMEGALOVIRUS PROPHYLAXIS WITH LETERMOVIR IN PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANT USING EX VIVO CD34 + SELECTED GRAFTS

Carla Alonso-Martínez[1], Ariadna Gracia-Moya[1], Ana Pérez-González[1], Antonieta Molero[2], Ángela Sánchez[2], Adaia Albasanz-Puig[3], Isabel Ruiz-Camps[3], Anna Farriols-Danés[1], Carolina Valdivia-Vadell[1], Lucas Rivera-Sánchez[1], Maria Guerra-González[1], Patricia Marrero[1], Sara Garrido[2], Maria Sola[2], Pablo Sánchez-Sancho[1], Pere Barba[2], Olga Salamero[2], MariaQueralt Gorgas-Torner[1], Guillermo Orti[2], Laura Fox[2], Francesc Bosch[2], MariaJosep Carreras-Soler[1], David Valcárcel[2]

Vall d'Hebron Hospital University, Barcelona, Spain. Vall d'Hebron Hospital University, Barcelona, Spain, Vall d'Hebron Hospital University, Barcelona, Spain

Background: Allogeneic stem cell transplant (allo-HSCT) using CD34+ selection (allo-CD34s-HSCT) is a platform that mitigates the development of graft versus host disease while maintain antitumoral effect. Its main drawback is the deep and prolonged immunosuppression which is associated with a particularly high risk of viral infections, such as cytomegalovirus (CMV).

Letermovir is the first antiviral drug indicated for CMV prophylaxis in high risk allo-HSCT.

The aim of our study was to evaluate the results of the introduction of letermovir in CMV positive recipients (R^+) who receive an allo-CD34s-HSCT in our institution and compare it with a historical group of allo-CD34s-HSCT patients without LET prophylaxis (LETp).

Methods: This is a single-center retrospective observational study. We included all adult patients who received an allo-CD34s-HSCT from August 2016 to December 2022 with a minimum follow-up of 100 days.

We defined two groups; patients who received LETp (LET group) since September 2021 as standard practice and patients who did not received LETp (Historical group) since August 2016 to September 2021 (before letermovir availability at our center).

Bio-demographic data were assembled from the patient's medical history, and letermovir prescription data from the pharmacy software.

CMV reactivation (CMV-R) was defined as two consecutive whole blood determinations of PCR > 1000 IU/ml.

CMV disease (CMV-D) was defined as a specific organ involvement.

Blips were defined as positive viral load < 1000 IU/ml not amenable for therapy.

Letermovir dose was 480 mg daily and it was started on day 0 and maintained up to day +100.

CMV-R, CMV-D and Blips were monitored for the first 24 weeks (blips were not recorded in the Historical group).

Results: We included 14 patients who received letermovir (LET group) and 52 patients who did not (Historical group), both groups had similar basal characteristics.

In LET group a total f 6 R + /D+ patients developed CMV-R between allo-CD34s-HSCT and week +24 (42,9%): 4 during the

first 14 weeks [day +2 (2336 IU/ml), day +12 (3895 IU/ml), day + 13 (1319 IU/ml) and day +68 (3167 UI/ml)] and prompted treatment with foscarnet or valganclovir as standard dose; 2 patients after letermovir discontinuation (> week 14) in day +135 (13762 UI/ml) and day +143 (28491 UI/ml). Interestingly no R^+/D^- patients had CMV-R in the first 24 weeks.

In comparison, in the Historical group there were 36 CMV-R (69,2%) during the first 24 weeks after allo-CD34s-HSCT.

No patient in the LET group developed CMV-D while it was documented in 4 patients (7,7%) in the Historical group.

Among LET group, two patients developed CMV blips during the first 24 weeks.

No adverse reactions due to treatment with letermovir were reported.

Conclusions: Letermovir is a safe drug in our group of transplanted patients with CD34+ selection and it reduce the incidence of CMV reactivations in our high risk population of patients who underwent allo-CD34s-HSCT.

CMV disease was not diagnosed in LET group patients.

Disclosure: No disclosure.

13 - Infectious Complications

P404

FEASIBILITY OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN A HIGHLY VACCINATED ASIAN POPULATION DURING THE ACUTE CORONAVIRUS DISEASE 2019 PANDEMIC

Christopher Shwei Wen Tham[1], Yeh Ching Linn[1], Lawrence Cheng Kiat Ng[1], Jeffrey Kim Siang Quek[1], Aloysius Yew Leng Ho[1], Francesca Wei Inng Lim[1], Yunxin Chen[1], Chandramouli Nagarajan[1], William Ying Khee Hwang[1], Jing Jing Lee[1], Gina Gan[1], Jasmine Shimin Chung[1], Ban Hock Tan[1], Thuan Tong Tan[1], Hein Than[1]

[1]Singapore General Hospital, Singapore, Singapore

Background: Timely haematopoietic stem cell transplantation (HCT) is indicated in patients with haematological malignancies during acute Coronavirus disease 2019 (COVID-19), despite limited data on its optimal timing and safety.

Methods: We studied real-world transplant-related outcomes of consecutive patients admitted to Singapore General Hospital, a tertiary transplant centre, for planned HCT between September 2021 and April 2022, when COVID-19 community transmission was high. Patients diagnosed with COVID-19 within 120 days prior to stem cell infusion were included in the retrospective analysis, and written informed consent was obtained. The date of diagnosis of COVID-19 was based on the first positive SARS-CoV-2 PCR nasopharyngeal swab.

Results: 11 HCT patients (10 allogeneic and 1 autologous) were included, with acute myeloid leukaemia (n = 3), acute lymphoblastic leukaemia (n = 2), chronic myeloid leukaemia (n = 2), myelofibrosis (n = 1), severe aplastic anaemia (n = 1), Hodgkin lymphoma (n = 1) and multiple myeloma (n = 1). Median interval between diagnosis of COVID-19 to HCT infusion was 53 days (range 1-118). 3 patients were diagnosed with COVID-19 immediately prior to HCT infusion, at days -1, -3 and -5 respectively. Median duration of COVID-19 infection, defined by time to negative PCR, was 20 days.

All allogeneic HCT patients had 2 doses of COVID-19 mRNA vaccines (Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273) prior to infection. The autologous HCT patient was unvaccinated. Median receptor binding domain IgG serology titre (Abbott assay) in vaccinated patients was 1301 AU/ml at the time of COVID-19 diagnosis. COVID-19 severity by WHO guidelines was mild in 9, moderate in 1 and critical in 1 patient. 8 patients received antivirals; 5 had concurrent monoclonal antibody treatment (sotrovimab, n = 4; casirivimab/imdevimab, n = 1).

Median age at HCT was 53 years (range 26-70); 64% of patients had low-risk HCT-comorbidity index, 45% were male, and 55% were of high-risk by the disease risk index. Allogeneic HCT patients received peripheral blood stem cells from matched sibling donors (n = 3), matched unrelated donors (n = 2) or haploidentical donors (n = 5). 50% received myeloablative conditioning. Graft-versus-host disease (GvHD) prophylaxis included calcineurin inhibitors and/or mycophenolate mofetil. Haploidentical transplant patients received post-transplant cyclophosphamide (n = 3) or ex-vivo TCR alpha-beta depleted grafts (n = 2). A relapsed AML patient received haploidentical TCR alpha-beta depleted graft without conditioning regimen. A median of 5.5 x 10^6 $CD34^+$ cells/kg (range 2.9-10.1) were infused.

Median time to neutrophil and platelet engraftment was 10 (range 10-17) and 12 (range 10-20) days, respectively, comparable to that of standard non-COVID-19 cohorts. 2 patients died of non-relapse pulmonary complications on D + 43 and D + 50 post HCT respectively. 2 out of 10 allogeneic HCT patients developed grade II acute GvHD of skin, but none grade III-IV acute GvHD. Median follow up was 103 days (range 43-208), and GvHD-free/relapse-free survival (GRFS) among surviving patients at D + 100 was 78%. There was no evidence of COVID-19 reinfection or late complications, or increase in viral reactivation of CMV, EBV and HHV6.

Conclusions: Our study suggests that timely HCT can be safely performed with favourable outcomes following acute COVID-19 in a highly vaccinated cohort. Immunisation, viral therapeutics, and a careful disease risk-benefit assessment play a crucial role.

Disclosure: Nothing to declare.

13 - Infectious Complications

P405

USE OF CMV HYPERIMMUNOGLOBULINS (CYTOTECT) AS PREEMPTIVE TREATMENT OF CMV INFECTION IN PATIENTS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION - A SINGLE CENTRE EXPERIENCE

Lana Desnica[1], Nadira Durakovic[1], Zinaida Peric[1], Ranka Serventi-Seiwerth[1], Pavle Roncevic[1], Dubravka Sertic[1], Mirta Mikulic[1], Drazen Pulanic[1], Radovan Vrhovac[1]

[1]University Hospital Centre Zagreb, Zagreb, Croatia

Background: Cytomegalovirus (CMV) infection and disease still remain severe life-threatening complications after allogeneic stem cell transplantation (alo-SCT). Available treatments for CMV infection and disease (ganciclovir, valganciclovir, foscarnet) have significant limitations - resistance and serious adverse events such as myelosupression, nephrotoxicity, electrolyte disbalance, etc. making CMV infection treatment very challenging. It has been shown that the use of hyperimmunoglobulins (Cytotect) in alo-transplanted patients is save and may help in CMV infection treatment, but there is no exact guidelines on dose and treatment timing available.

Methods: We retrospectively collected data on 61 patients after all-SCT, transplanted mostly for haematological malignancies in whom Cytotect was used for treatment of CMV infection/disease and EBV infection or both from March 2021- October 2022. All patients received letermovir as CMV reactivation prophylaxis for 90 days after transplant and all patients were

defined as high risk due to presence of at least one risk factor for CMV reactivation.

Results: The median patient age was 49 years; 23/55 (42%) patients reactivated CMV virus before day 100, and 32/55 (58%) after day 100; 45 patients received Cytotect for preemptive treatment of CMV infection (2 had CMV disease) along with one of the antiviral drugs (valganciclovir, ganciclovir or foscarnet). Six patients received Cytotect along with rituximab for EBV reactivation, 3 patients received Cytotect with an antiviral drug for simultaneous CMV and EBV infection. In high viremia cases 4 mL/kg was given on days 1, 4 and 8, followed by 2 mL/kg on days 12 and 16, and continued thereafter at 100 mL once a week for 4 weeks (Alsuliman et al.), or (100-300 mL) once per week for 4 weeks. Ten patients with low CMV viremia (< 1000 IU/mL) received Cytotect as monotherapy (in most cases 100 mL once weekly for 4 weeks) with an intent of avoiding antiviral drug induced myelosuppression in neutropenic patients with total viral clearance. Most patients (44/55; 80%) achieved complete response, 11/55 (20%) did not respond to therapy, and 7 (12.7%) had a breakthrough infection. All patients treated with Cytotect as monotherapy for low CMV viremia achieved a complete response and only patient had a breakthrough infection.

Conclusions: In our patients, Cytotect was safe and well tolerated - no significant adverse events were recorded. With all its limitations, this single-centre retrospective study could indicate that some patients with low CMV viremia might be successfully managed by adding Cytotect in order to spare them of prolonged treatment with myelotoxic and nephrotoxic antivirals. However, prospective studies are needed to define the categories of patients who might benefit most from Cytotect and to determine optimal treatment regimens for each patient population.

Disclosure: nothing to declare.

13 - Infectious Complications

P406

CYTOMEGALOVIRUS INFECTION IN PATIENTS WHO UNDERWENT ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLO-HSCT): A SINGLE-CENTER EXPERIENCE

Laura Pardo Gambarte[1], Javier Cornago Navascués[1], Mónica Sánchez de la Fuente[2], Jose Luis López Lorenzo[1], Laura Solán Blanco[1], Pilar LLamas Sillero[1]

[1]Fundación Jiménez Díaz University Hospital, Madrid, Spain, [2]Autonomous University of Madrid, Madrid, Spain

Background: Cytomegalovirus (CMV) infection develops frequently following allogeneic hematopoietic stem cell transplantation (allo-HSCT), being the most common significant viral infection in allo-HSCT recipients. Although the use of letermovir is changing the current practice in the management of CMV infection, preemptive antiviral therapy (PET) with antivirals might continue to be employed in a subset of patients for prevention of CMV-related end-organ disease.

The aim of the this study was review CMV infection in a cohort of 91 patients with different malignancies undergoing allo-HSCT and their impact, in the absence of end-organ disease, on the risk of overall mortality (OM).

Methods: We performed a retrospective study in a cohort of 91 adult allo-HSCT recipients at a single Spanish transplant center (Fundación Jiménez Díaz University Hospital) between January 2017 and December 2021. The patients did not receive Letermovir prophylaxis.

Demographic information including age, gender donor, underlying disease, stem cell source, response at transplantation, donor type, conditioning regimen, donor/recipient CMV status and graft-versus-host disease (GVHD) prophylaxis were collected.

Statistical analysis was performed with SPSS program 25.0. Categorical variables were compared among groups with the chi-square test, and continuous variables were compared with the Kruskall-Wallis test. The Kaplan-Meier method with long-rank test was used to calculated the association between CMV infection and overall survival (OS). For all univariable analyses, p-values less than 0.05 were considered statistically significant.

Results: Patient characteristics of each group are summarized.

Our case series revealed that 44 patients (48.4%) developed CMV infection, being the majority viral infections rather that primary infections (88.6% versus 11.4%). The statistical analysis revealed the risk of CMV infection was significantly increased in CMV seropositive recipients ($P = .040$), in the donor/recipient CMV status D+ /R+ ($P = .024$) and in patients that were receiving corticoids ($P = .001$).

Median follow-up for all surviving patients was 35 months. There was no difference in 2-year OS between patients who developed CMV infections (66.2%, (95% confidence interval [CI]: 55.8–73.7)) and those who did not developed CMV infections (65.3%, (95% CI: 58.2–72-4)).

Conclusions: Our study revealed that CMV infection was a frequent event, especially in CMV-seropositive recipients and patients that were receiving treatment with corticoids. We did not find differences in the OS between the patients that developed CMV infections and those who did not developd CMV infection.

Disclosure: The authors declare no conflicts of interest regarding the publication of this paper.

13 - Infectious Complications

P407

HHV-6 VIRUS REACTIVATION AFTER ALLO-HSCT: A SINGLE CENTRE CASE SERIES

João Gaião Santos[1], Rosa Branca[1], Luís Leite[1], Carlos Pinho Vaz[1], Inês Baldaque[1], António Campos Júnior[1]

[1]Instituto Português de Oncologia do Porto, Porto, Portugal

Background: HHV-6 reactivation is common after allo-HSCT, with HHV-6 DNA detectable in blood in up to 40% of patients. HHV-6 is the most frequent infectious cause of encephalitis after allo-HSCT and has been linked to myelosuppression, allograft failure, CMV reactivation, acute GVHD and pneumonia. Both ganciclovir or foscarnet can be used to treat HHV-6 encephalitis, although there is no established therapy for other HHV-6-associated complications.

Methods: Retrospective analysis of all allo-HSCT cases with detectable HHV-6 DNA in blood by quantitative PCR (qPCR) assays from January 1st 2017 to November 15th 2022 in a single hospital. Clinically significant HHV-6 qPCR positivity was defined by >1000 DNA copies/mL.

Results: A total of 368 allo-HSCT were analysed, with 35 cases (9.5%) positive qPCR. Regarding the positive cases, the most common indications for transplant were AML (9 cases; 25.7%), ALL (8; 22.9%) and MDS (7; 20.0%%). A myeloablative conditioning regimen was used in 70.6%. In all but 2 cases the HSC were collected by apheresis, the remaining being harvested from the bone marrow. In 31 patients (88.6%) the HHV-6 DNA was detected within the first 30 days after transplant and 15 (42.9%) were immunosuppressed due to acute GVHD at the time of positive qPCR.

Overall, 27 patients (79.4%) developed acute GVHD, in 10 of which (37.0%) the HHV-6 DNA was detected before the development of acute GVHD, with a median of 10 days between positive qPCR and acute GVHD. Five patients (14.3%) developed chronic GVHD. Two patients (5.7%) developed allograft failure. No patients developed HHV-6-related encephalitis or pneumonia.

Twenty-eight patients (80%) had isolated HHV-6 reactivation (**Table1**), foscarnet was started in 14 patients (50.0%) of which 11 (78.6%) achieved a negative qPCR, and 2 patients (7.1%) started ganciclovir, both (100%) achieving a negative qPCR. QPCR negativity was reached after a median of 7 days of therapy with either drug. In 12 patients (42.9%) no therapy was started after positive qPCR, of which 10 (83.3%) achieved a negative qPCR after a median of 7 days. Of the 5 patients which did not achieve a negative qPCR, 3 (60.0%) died due to other infectious complications and 1 (20.0%) had AML relapse 3 months after transplant.

Seven patients (20.0%) had simultaneous CMV and HHV-6 reactivation: 2 (28.6%) were treated with foscarnet, 2 with ganciclovir, 1 (14.3%) with ganciclovir followed by foscarnet, 1 with ganciclovir followed by foscarnet and cidofovir (both cases due to persistently positive CMV qPCR) and 1 with valganciclovir. Negative HHV-6 qPCR was achieved in all 7 cases. Nine patients (25.7%) had CMV reactivation after HHV-6 reactivation.

Overall, 15 patients (42.9%) died, 10 (66.6%) of which from other infectious complications, 3 (8.6%) from complications due to acute GVHD and 2 (5.7%) from AML relapse.

Table 1 - HHV-6 reactivation therapy

HHV-6 reactivation therapy	N (%)
Isolated HHV-6 reactivation	**28 (80.0)**
Treatment with foscarnet monotherapy	14 (50.0)
Negative HHV-6 qPCR after therapy	11 (78.6)
Treatment with ganciclovir monotherapy	2 (7.1)
Negative HHV-6 qPCR after therapy	2 (100)
No antiviral therapy started	12 (42.9)
Negative HHV-6 qPCR after therapy	10 (83.3)
Simultaneous CMV and HHV-6 reactivation	**7 (20.0)**
Treatment with foscarnet monotherapy	2 (28.6)
Treatment with ganciclovir monotherapy	2 (28.6)
Treatment with ganciclovir followed by foscarnet	1 (14.3)
Treatment with ganciclovir followed by foscarnet and cidofovir	1 (14.3)
Treatment with valganciclovir	1 (14.3)
Negative HHV-6 qPCR after therapy	7 (100)

Conclusions: In our series, HHV-6 reactivation rate was lower than described in literature. We found no cases of encephalitis and the majority of patients developed acute GVHD, of which more than one third had a positive qPCR before acute GVHD. Most cases were treated with foscarnet, but all drugs used were effective.

Disclosure: Nothing to declare.

13 - Infectious Complications

P408

LETERMOVIR PROPHYLAXIS FOR HIGH-RISK ALLOGENIC HEMATOPOIETIC-CELL TRANSPLANT RECIPIENTS: EARLY REAL-LIFE EXPERIENCE AND PARTICULARITIES OF THE SPANISH IMPLEMENTATION

Nuria González[1], Guillermo Ramil[1], Sara Redondo[1], Sara Carbonell[2], Ignacio Arroyo[3], María Suárez-Lledó[2], Sonia Marti[3], Albert Esquirol[1], Carlos Solano[3], Ariadna Pérez[3], Montse Rovira[2], Jose Luis Piñana[3], Jordi Sierra[1], Rodrigo Martino[1], Irene García-Cadenas[1]

Hospital de la Santa Creu i Sant Pau, Institute of Biomedical Research Sant Pau, Universitat Autonoma of Barcelona, Barcelona, Spain, [2]Bone Marow Transplantation Unit, Hospital Clinic, IDIBAPS, Josep Carreras Foundation and Leukemia Research Institute, Barcelona, Spain, Hospital Clínico Universitario-INCLIVA Valencia, University of Valencia, Valencia, Spain

Background: Cytomegalovirus (CMV) infection is a common complication after allogeneic hematopoietic-cell transplant (alloHCT) classically associated with increased mortality. In a pivotal phase 3 trial (Marty F. *et al*, NEJM 2017), letermovir (LET) prophylaxis was shown to reduce the risk of clinically significant CMV infection. In Spain, LET oral formulation is available since August 2021 for high-risk CMV-seropositive alloHCT recipients (HLA mismatched unrelated donor, haploidentical donor, ex-vivo T cell depletion). The aim of this study was to describe the early experiences of using LET prophylaxis in real life particularly focusing on the gastrointestinal tolerability and complications.

Methods: The study cohort contained the first 66 CMV+ high-risk patients who received LET primary prophylaxis from August 2021 to November 2022 at 3 academic spanish institutions with high transplantation activity. Prophylaxis was defined as initiation of LET between day 0 and day +28 post-transplant. Quantitative PCR was used to monitor CMV viremia twice a week during the inpatient period and weekly thereafter.

Results: During the study period, 104 alloHCT were performed in the participating centers. Seventy-one patients (68%) had high-risk features for CMV-related complications and thus were candidates for LET prophylaxis. There were significant differences in the number of high-risk patients among the 3 centers. Baseline characteristics of those receiving LET are presented in **Table 1**. Similar rates of early gastrointestinal alterations were found among centers, including grade 2-4 oral mucositis in 39 patients (59%) and grade 2-4 acute digestive graft vs host disease (GvHD) in 8 (12%).

Five (7%) high-risk patients did not receive LET due to digestive intolerance (3), early CMV reactivation (1) and non-CMV related early death (1). In the remaining 66 patients, the median time from transplant to LET initiation was 7 days (range 5-28), and the median duration of exposure to LET was 100 days (range 5-399), with 15 patients still on treatment at the cutoff date. 6 patients (9%) had prolonged LET exposure due to GvHD or persistent cytopenias.

LET was stopped before day 100 in 9 patients (14%) due to oral mucositis (3, 5%), CMV breakthrough infection (2, 3%) and concurrent human herpesvirus 6 infection (4, 6%). Fifteen patients (23%) started LET after day +7 because of oral mucositis.

Two patients (3%) presented CMV breakthrough infection at days +5 and +75 after LET initiation and 6 (9%) had clinically significant CMV reactivation after LET stop at a median of 38 days from the end (range 13-55). There was one case of CMV gastrointestinal disease.

Table 1. Baseline characteristics and LET use.

	Center 1 (n = 17)	Center 2 (n = 33)	Center 3 (n = 16)	*p*
Age – yr, median (range)	51 (22-71)	51 (18-71)	53 (28-71)	NS
Female sex, n(%)	10 (59%)	10 (30%)	4 (25%)	NS
Diagnosis, n(%)				NS

	Center 1 (n = 17)	Center 2 (n = 33)	Center 3 (n = 16)	p
AML and MDS	10 (59%)	15 (45%)	9 (56%)	
Disease status CR, n(%)	10 (59%)	26 (78%)	9 (56%)	**0.002**
MAC conditioning, n(%)	5 (29%)	14 (42%)	5 (31%)	NS
Haploidentical donor, n(%)	10 (59%)	11 (33%)	7 (44%)	NS
ATG use, n(%)	3 (18%)	2 (6%)	1 (6%)	NS
PTCY-based GvHD prophylaxis n(%)	17 (100%)	29 (88%)	16 (100%)	**<0.001**
PB stem cell source, n(%)	16 (94%)	31 (94%)	16 (100%)	NS
Oral mucositis ≥ G2, n(%)	10 (59%)	18 (55%)	11 (69%)	NS
Acute GI GvHD ≥ G2, n(%)	2 (12%)	4 (12%)	2 (13%)	NS
CMV-seropositive donor, n(%)	15 (88%)	24 (73%)	10 (63%)	NS
LET onset after day + 7, n(%)	14 (82%)	1 (3%)	0	**<0.001**
Stop LET before day + 100, n(%)	2 (12%)	5 (15%)	2 (13%)	NS
Extend LET beyond day + 100, n(%)	3 (18%)	3 (9%)	1 (6%)	NS
CMV breakthrough infection, n(%)	0	1 (3%)	1 (6%)	NS
CMV infection after LET stop, n(%)	1 (6%)	1 (%)	4 (25%)	**0.037**
CMV disease, n(%)	0	1 (3%)	0	NS

Conclusions: Our real-world experience assessing LET prophylaxis in high-risk Spanish alloHCT recipients demonstrates its use in around two thirds of transplants, with significant differences between centers. Therapy adherence is challenging in a significant number of patients affected with typical post-transplant gastrointestinal complications. Efficacy results are in line with previous reports.

Disclosure: Nothing to declare.

13 - Infectious Complications

P409

FLUCONAZOLE PROPHYLAXIS FOR PEDIATRIC ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANT

Amit Jain[1], Rajesh Patil[1], Ratna Sharma[1], Pranoti Kini[1], Ashutosh Walawalkar[1], Pranoti Chiwarkar[1], Mamta Manglani[1]

[1]MCGM - Comprehensive Thalassemia Care, Pediatric Hematology-Oncology & BMT Centre Borivali, Mumbai, India

Background: Invasive fungal infections (IFIs) are an important cause of morbidity and mortality in allogeneic hematopoietic stem cell transplant (HSCT) recipients, affecting 2–16%, depending on transplant characteristics, diagnostic methods, and follow-up, with a mortality rate of 30-50%. Antifungal prophylaxis in this population is extensively reviewed but remains poorly defined and variable. Based on the ECIL guidelines, fluconazole as primary antifungal prophylaxis is recommended only in the pre-engraftment period. We studied the efficacy of fluconazole in post engraftment period.

Methods: This is an observational, retrospective cohort study on the incidence of IFI with fluconazole as primary antifungal prophylaxis in the first 100 days after allogeneic HSCT in patients aged <18 years between July 2018 and June 2022. All patients were admitted in a HEPA filter and positive pressure room from the time of conditioning till engraftment. Fluconazole was used as primary anti-fungal prophylaxis in patients without a history of systemic fungal infection. Patients who received high-dose steroids for acute GVHD were shifted to broad-spectrum antifungal prophylaxis (Liposomal Amphotericin).

Results: A total of 144 allogenic HSCTs were performed on 137 patients. In this cohort, 86 were transplanted with matched donors while 58 with haploidentical family donors. Of these, 111 patients did not have a past history of systemic fungal infection and were eligible for fluconazole as antifungal prophylaxis. Amongst them, 16 patients were shifted to broad-spectrum antifungal in view of acute GVHD. Fungal infection occurred in 7/95 patients. Of these 3 were proven, 1 had probable and 3 had a possible fungal infection. The overall rate of IFI was 7.36% (7/95) with a proven IFI of 3.15% (3/95), consistent with historical data. No mortality due to IFI was observed in this cohort.

Indication	Type of donor	Number (n = 95)	IFI		
			Proven	Probable	Possible
Benign Hematology	Matched donor	53	1	1	2
	Haplo-identical donor	3	-	-	-
Malignancy	Matched donor	9	-	-	-
	Haplo-identical	30	2	-	1

Conclusions: Fluconazole is effective as antifungal prophylaxis in pediatric HSCT recipients without a past history of systemic fungal infection.

Disclosure: None.

13 - Infectious Complications

P410

A SINGLE INSTITUTION PRE-/POST-COMPARISON AFTER THE INTRODUCTION OF SUBCUTANEOUS IMMUNOGLOBULIN REPLACEMENT THERAPY IN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION RECIPIENTS

Makiko Suga[1,2], Shigeo Fuji[1], Yuma Tada[1], Kazuhito Tsutsumi[1,2], Shuhei Kida[1,2], Kumi Shibata[1,2], Ryo Nakata[1], Yasuhiro Shingai[1], Sayako Yuda[1], Takafumi Yokota[1], Jun Ishikawa[1]

Osaka International Cancer Institute, Osaka, Japan, Graduate School of Medicine, Osaka University, Suita, Japan

Background: Infection is the life-threatening complication of allogeneic hematopoietic cell transplantation (allo-HCT) for hematologic malignancies. Immunoglobulin replacement therapy (IgRT) is known to reduce the risk of infection in secondary hypogammaglobulinemia for CLL and MM. However, the benefit of IgRT, especially subcutaneous IgRT (ScIgRT), is not well-established in allo-HCT patients. We analyzed the clinical impact of ScIgRT after allo-HCT.

Methods: This study is a single-center, retrospective analysis. Patients who underwent allo-HCT at our institution from 2011 to

2019 were included in this study. Since SclgRT was available at our institution in April 2017, we grouped patients from January 2011 to March 2017 as the Pre-SclgRT group and those from April 2017 to December 2019 as the Post-SclgRT group. We included the event from 60 days after allo-HCT up to 2 years.

Results: This study included 209 patients (Pre-SclgRT group, n = 118; Post-SclgRT group, n = 91). The median age was 49 years (range, 16-67) and 53 years (range, 19-67), respectively (p = 0.08). AML was the most common indication for allo-HCT in both groups. The 2-year OS rate was 65% in the Pre-SclgRT group and 81% in the Post-SclgRT group (p = 0.02). The cumulative incidence (CI) of relapse at 2 years was 24% and 29% (p = 0.44), whereas that of non-relapse mortality at 2 years was 18% and 7% (p = 0.02). 76 infectious events in 44 patients in the Pre-SclgRT group and 28 events in 19 patients in the Post-SclgRT group were observed. The CI of the documented infection in the observation period was 38% and 21% (p = 0.01). The hazard ratio for the CI of the documented infection in the Post-SclgRT group was 0.47 (p = 0.01) in multivariate analysis using age, sex and revised DRI for adjustment. The median number of intravenous antibacterial therapy days was 4.5 days (range, 0-252) for the Pre-SclgRT group and 0 days (range, 0-228) for the Post-SclgRT group (p < 0.01). The Post-SclgRT group also received significantly fewer days of anti-fungal and anti-viral agents.

Serum IgG level was measured at least once during the observation period in 56% of the Pre-SclgRT group and 98% of the Post-SclgRT group. Among the Post-SclgRT group, 62 received SclgRT continuously for more than 1 month, and 26 started SclgRT after day 30 post-HCT and had both IgG measured before and 1 month after the start of Sclg administration. The changes in serum IgG levels before and after Sclg administration were evaluated, with a mean of 734.6 mg/dL (SD 235.5) before the start of SclgRT and 844.2 mg/dL (SD 276.9) after administration. Furthermore, 26 patients were divided into 2 groups: those whose IgG, measured one month after the start of SclgRT, increased from before the start of SclgRT and those whose IgG decreased. The median mean single dose for the group with increased IgG was 123 mg/kg, while the group with decreased IgG was 71 mg/kg (p < 0.01).

Conclusions: SclgRT possibly reduces infection rates and improves prognosis in the late phase in allo-HCT patients. Larger prospective studies are required to assess the effectiveness of SclgRT in the future adequately.

Disclosure: *CSL Behring:* Research Funding.

13 - Infectious Complications

P411

TREATMENT WITH INTRAVESICAL CIDOFOVIR IN HEMORRHAGIC CYSTITIS DUE TO BK VIRUS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: EXPERIENCE IN OUR CENTER

Ana Maria Mena Santano[1], Carola Lucía Díaz Aizpun[1], Irene Sánchez Bazán[1], María Pérez Raya[1], Sandra Martín Téllez[1], María Ángeles Cuesta Casas[1]

[1]Hospital Regional Universitario de Málaga, Málaga, Spain

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentiall curative option for patients with hematological malignancies, but due to secondary immunosuppression, infections are an important cause of morbidity and mortality. Among viral infections, hemorrhagic cystitis caused by the BK virus (BKV-HC) is worth mentioning. Predisposing factors include: haploidentical transplantation or unrelated donor transplantation, peripheral blood, myeloablative conditioning and the use of cyclophosphamide due to direct damage to the endothelium. Its pharmacological treatment is based on cidofovir presenting clinical and virological efficacy rates between 66 and 86%, but it is also associated with nephrotoxicity in 25-33% of patients.

Methods: This is an observational, descriptive, retrospective,-single-center study. Patients undergoing allo-HSCT who received at least one dose of intravesical cidofovir for the treatment of BKV-HC, between the years 2017 to 2021, were included. The minimum follow-up time was 6 months from the date of transplantation.

Results: Eight patients were included, with a median age at transplantation of 46 years (range 18-68), 4 of whom (50%) were male. Acute leukemia (n = 5, 62%) was the main indication for HSCT, 75% (6) were haploidentical and 50% (4) received reduced intensity conditioning. All patients received post-transplant cyclophosphamide as graft-versus-recipient disease (GVHD) prophylaxis. Despite this, 6 patients (75%) developed GVHD of any grade. The median time to onset of first symptoms of cystitis was 29 days (range 7-48) after allo-HSCT. The most frequent symptom at onset was dysuria, with a severity grade of 3 in 50% (4) of the patients. Before treatment 57.2% (4) of the patients had a BK virus viral load in urine >660,000,000 copies/ml. Patients received a median of 1.5 doses (range 1-4) of intravesical cidofovir, and the treatment dose was 4mg/kg. 3 patients (37.5%) achieved complete response and the median number of days from treatment initiation to response was 16 (range 9-21). Nephrotoxicity of any grade was detected in 25% (2) of patients.

Conclusions: - Our study seems to support the main known risk factors for the development of BKV-HC.

- There is no standard and approved treatment protocol for BKV-HC. In our study the use of intravesical cidofovir appears as a feasible treatment option with efficacy rates comparable to what is reported in the literature and acceptable toxicity profile.

- Prospective randomized studies are required to describe the optimal treatment strategies for this pathology.

Disclosure: Nothing to declare.

13 - Infectious Complications

P412

COVID-19 AFTER ALLO-HSCT: A SINGLE CENTER OBSERVATIONAL STUDY

Daria Mironova[1], Larisa Kuzmina[1], Vera Vasilieva[1], Mikhail Drokov[1], Darya Dubnyak[1], Olga Koroleva[1], Olga Starikova[1], Ulyana Maslikova[1], Maria Dovydenko[1], Feruza Omarova[1], Elena Parovichnikova[1]

[1]National Research Center for Hematology, Moscow, Russian Federation

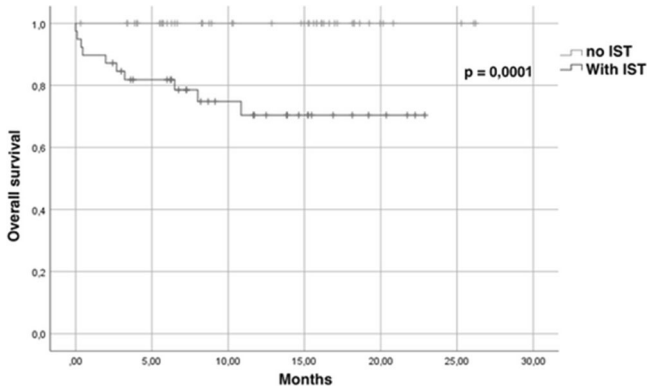
Background: The COVID-19 pandemic brought changes in circumstances of providing medical care to allo-HSCT recipients. Alertness regarding this disease in hematological patients increased and required analysis.

Methods: 87 patients who diagnosed COVID-19 between March 2020 and January 2022 were included in a retrospective single center study of outcomes of COVID-19 after allo-HSCT. All allo-HSCT in these patients were performed between November 2006 and November 2021. Among 87 patients 58,6% patients were female, median age was 42 years (20-72). Reduced intensity conditioning regimen (RIC) was used in 74,7% cases, peripheral hematopoietic stem cells were used in 51,7 % patients. Ex-vivo

TCR-αβ/CD19 + T-cell graft depletion was performed in 13,8% patients.

We analyzed the impact of immunosuppression therapy (IST), severity of COVID-19 disease and GVHD on overall survival after COVID-19.

Results: 81,6 % patients got infected with COVID-19 after 1 year of allo-HSCT, 13,8 % – between 6-12 months after allo-HSCT, 4,6% – on early phase after allo-HSCT (up to 6 months). According to NIH definitions of COVID-19 severity of illness in our study 44,8% patients had mild illness, moderate - 26,4%, severe - 11,5%, critical - 9,2%, asymptomatic - 8%. IST received 44,8% patients due to GVHD treatment or post-transplant GVHD prophylaxis regimen. 31,1 % patients had signs of active GVHD (acute or chronic). Allo-HSCT with ex-vivo TCR-αβ/CD19 + T-cell graft depletion was associated with a milder illness ($p = 0{,}006$). Such factors as immunosuppressive therapy ($p = 0.0001$) (Fig.1) and severe/critical illness ($p = 0.007$) were significantly different in relation to overall survival.



Conclusions: Patients after allo-HSCT are considered to be at high risk for developing severe and critical illness. Although in our experience allo-HSCT recipients did not show expected low overall survival. Furthermore, the use of ex-vivo TCR- αβ/CD19 + T-cell graft depletion is associated with a significant lower risk of critical and severe COVID-19 illness.

Disclosure: Nothing to declare.

13 - Infectious Complications

P413

IMPACT OF FLUOROQUINOLONE (FQP) PROPHYLAXIS ON INFECTIONS INCIDENCE IN AUTOLOGOUS STEM CELL TRANSPLANTATION (AUTO-HSCT) FOR MULTIPLE MYELOMA. A SINGLE CENTER EXPERIENCE

Ilaria Cutini[1], Nicoletta Di Lauria[1], Michele Spinicci[1], Riccardo Boncompagni[1], Antonella Gozzini[1], Chiara Nozzoli[1], Gian Maria Rossolini[1], Alessandro Bartoloni[1], Riccardo Saccardi[1]

[1]Careggi University Hospital, Florence, Italy

Background: Levofloxacin has been widely used as bacteremia prophylaxis during autologous hematopoietic stem cell transplantation (auto-HSCT) over the last decades. Data supporting this practice are controversial due to the possible increasing of both Clostridioides difficile infections and the rate of multidrug resistant organisms (MDRO). This study is aimed to assess the safety and efficacy of levofloxacin as bacterial prophylaxis during Stem Cells mobilization and auto-HSCT.

Methods: We retrospectively evaluated 299 consecutive patients underwent auto-HSCT for multiple myeloma (MM) over the last 10 years (from 2013 to 2022) who received levofloxacin prophylaxis during mobilization and auto-HSCT following High-Dose Melphalan, in order to assess the protective role of FQP. Ninety-three % of patients received Cyclophosphamide (CY) + G-CSF as mobilization therapy, 7% G-CSF associated to Plerixafor in poor-mobilizer patients. Monitoring of infections after CY administration, hospital admission due to neutropenic fever, rate of MDRO colonization after levofloxacin exposure before or after auto-HSCT, neutropenic fever after auto-HSCT, (FUO, sepsis, septic shock), administration of empiric antibacterial therapy, was carried out. Comparison of non-continuous variables was done by Chi-square test.

Results: Patients were divided in two groups based on Levofloxacin administration. After CY, 55 patients (18%) received the prophylaxis. There was no difference between the two groups in the type of induction therapy (standard, lenalidomide based, and antiCD38 based), the response of disease at time of CY, the incidence of either infection complications or hospital admissions (p=ns). No higher incidence of MDRO colonization before auto-HSCT was reported in levofloxacin group (FQP) (p=ns).

After auto-HSCT, 115 patients (38%) received FQP. There was no higher incidence of MDRO colonization before auto-HSCT in FQP pre-exposed patients, (p=ns). The incidence of neutropenic fever after auto-HSCT was lower in FQP ($p < 0.001$) as well as septic events ($p < 0.001$). In FQP, significantly fewer patients needed to start empirical antibiotic therapy ($p < 0.001$); however, the prophylaxis exposure led to higher rate of carbapenem prescriptions ($p < 0.001$). No difference was reported in the incidence of gram negative, gram positive, MDRO, fungal and viral infection between the two groups (p=ns). No Clostridioides infections were reported. There was no higher incidence of acquired MDRO colonization in FQP, (p=ns). A lower incidence of overall mucositis was reported in FQP ($p = 0.001$), with no difference in the severe grade (p=ns). The administration of FQP after both CY and auto-HSCT was found to be protective against neutropenic fever after auto-HSCT ($p < 0.001$) and septic event ($p = 0.007$).

Patients receiving antiCD38 based induction therapy were more prone to develop infections after CY therapy ($p = 0.002$), whilst no difference was seen after auto-HSCT (p=ns). Moreover, a higher incidence of any grade mucositis was reported in antiCD38 based induction therapy.

Conclusions: FQP decreases the incidence of infections during autologous HSCT for MM, without increasing the incidence of MDRO colonization, however, a higher carbapenem prescriptions were reported in FQP group. The administration of FQP is an effective strategy of infection prophylaxis in the autologous setting, especially when the procedure is carried out in an outpatient regimen. A larger, prospective study would provide more conclusive findings on this controversial issue.

Clinical Trial Registry: None

Disclosure: No disclosures.

13 - Infectious Complications

P414

CLINICAL CHARACTERISTICS AND OUTCOMES OF PERI-HSCT COVID-19 INFECTION IN CHILDREN WITH INBORN ERRORS OF IMMUNITY (IEI)

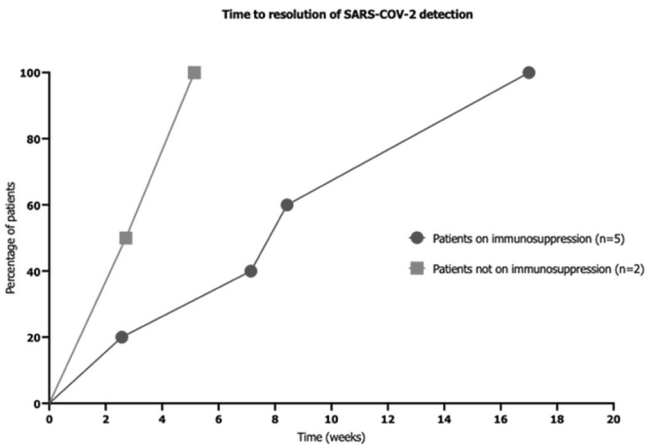
Subramaniam Ramanathan[1], Shirelle Burton-Fanning[2], Sheila Waugh[2], Terence Flood[1], Eleri Williams[1], Sophie Hambleton[1,3], Su Han Lum[1,3], Stephen Owens[1], Andrew Gennery[1,3], Mary Slatter[1,3], Zohreh Nademi[1,3]

North Children's Hospital, Newcastle upon Tyne, United Kingdom, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [3]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom

Background: While the outcome of COVID-19 infection in post-HSCT recipients has been described well, there are paucity of data on the clinical course and treatment strategies in peri-HSCT COVID-19 infection. This is a single centre experience of clinical characteristics and outcomes of COVID-19 infection in patients with COVID-19 infection within 4 weeks of allogeneic HSCT until D + 180 post-HSCT in children with inborn errors of immunity.

Methods: Patient and transplant characteristics, clinical course of COVID-19 infection and treatment strategies were retrospectively collected for HSCTs conducted between December 2021-June 2022. Descriptive statistics were provided for the patient, disease, and HSCT- related variables. COVID-19 diagnosis was established by polymerase chain reaction (PCR) on nose/throat swabs. The severity of COVID-19 was determined as mild/asymptomatic (not requiring oxygen supplementation), moderate (requiring oxygen supplementation), and severe (requiring mechanical ventilation).

Results: Seven patients (4 girls) were included, median age 4.51 years (range: 1.3 – 14.7) at HSCT. Primary diagnoses were primary haemophagocytic lymphohistiocytosis (HLH, n = 2), hypomorphic RAG1 combined immunodeficiency (n = 2) MHC class II deficiency (n = 2), Chediak Higashi syndrome (n = 1) and chronic granulomatous disease (CGD, n = 1). All patients received Fludarabine-Treosulfan-Thiotepa and Alemtuzumab (n = 4) or ATG+Rituximab (n = 3). Donor and stem cell source were TCRab/CD19 depleted haploidentical parental grafts (n = 3), matched unrelated donor PBSC (n = 3), matched sibling donor PBSC (n = 1) and marrow (n = 1). Median duration of SARS COV-2 RNA detection was 7.14 weeks (range: 2.5 – 17), with 5 patients having persistent detection (> 4weeks). Three had COVID-19 infection for a median duration of 2.5 weeks (range: 2 – 3) before HSCT; 2 patients were COVID-19 positive 13 and 15 weeks pre-HSCT respectively, and remained COVID-19+ve for 4 and 2 weeks respectively post-HSCT; 2 patients were Covid-19 +ve at 7 and 24 weeks post-HSCT respectively. Only 1 patient had active Stage II acute skin graft versus host disease (GVHD) and none had chronic GVHD. Five patients were on immunosuppression (steroids and/or cyclosporine) during the course of their illness (Figure 1). All patients received remdesivir (1 patient received 2 courses) and 6 patients received COVID-19 directed monoclonal antibody (Sotrovimab=5; Regdanvimab=1). Two patients received pre-planned CD45RA-depleted memory donor T-cell addbacks (donors had recovered from COVID-19). While 5 patients had mild infection, 2 patients needed supplemental O2. None needed mechanical ventilation and all recovered from infection successfully.



Conclusions: In countries where restrictions have been relaxed, leading to relative endemicity of the virus, concomitant SARS-CoV-2 infection in children embarking on HSCT or with significant immunosuppression is expected to become commonplace, highlighting the importance of novel strategies. Our small cohort shows a favourable outcome in paediatric patients with pre-HSCT and persistent COVID-19 infection in children with IEI.

Disclosure: The authors have no conflict of interest.

13 - Infectious Complications

P415

DOES PROPHYLACTIC GRANULOCYTE TRANSFUSION IMPROVE OUTCOMES IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS? A STUDY IN A TERTIARY CARE CENTER IN INDIA

Shruti Dabhade[1], Vijaykumar Shirure[1], Manthan Kathrotiya[1], Mayur Mundhe[1], Kazi Wajid Hussain[1], Sandip Kheni[1], Jayani Patel[1], Ankitkumar Jitani[1], Hemant Menghani[1], Velu Nair[1]

[1]Apollo International Hospital, Ahmedabad, India

Background: Severe neutropenia and consequential sepsis pose the biggest challenge in hematopoietic stem cell transplant (HCT). The neutrophil engraftment usually occurs at a mean of 14 to 15 days in allogeneic HCT and takes even longer in cord blood transplants. In an attempt to minimize this neutropenic period, various groups have resorted to granulocyte transfusion (GTX). However, data is limited on the accrued benefits of GTX. We conducted a prospective study using prophylactic GTX in patients during the first 2 weeks following HCT.

Methods: Between December 2020- September 2022, Thirty-four patients having severe neutropenia post HCT were treated with 78 prophylactic GTX until neutrophil engraftment. Granulocyte was collected from same-blood group donors after priming with Granulocyte colony-stimulating factor and Dexamethasone. No adverse events were observed during the Granulocyte infusion. On the development of febrile neutropenia, they were given antimicrobial therapy as per institutional protocol. The outcomes were measured as, the incidence of infection (either blood culture or CRP, or procalcitonin positivity), duration of fever (fever defined according to the CTCAE V grading), duration of antimicrobials used, the median time to neutrophil engraftment, Overall Survival (OS) and Non-Relapse Mortality (NRM) at 100 days post HCT, the incidence of CMV viremia and incidence of acute and chronic GVHD. These outcomes were then compared amongst the GTX recipients and a retrospective control group of HCT patients from our center who did not receive GTX during the peri-transplant period.

Results: Among 78 GTX, the median number of GTX received per patient was 2 (1 to 5) units and the average dose of granulocytes transfused was 0.124 (0.04 to 1.24) $\times 10^9$/kg. The median neutrophil increment at 24 hrs after GTX was 734.5 (− 267 to 9764) /µl and it showed a strong positive correlation with the dose of granulocytes given (p = 0.031). As compared to the cases, the control group needed a longer duration of antimicrobial therapy (9 (6-14) days vs 12 (9-14) days, p = 0.002). Among the cases and controls, the median duration of fever (5 (2- 10) days vs 4 (2-12) days, p = 0.40) and median time to neutrophil engraftment (11 (8-17) days vs 12 (9-14) days, p = 0.12) was comparable. Median CRP and procalcitonin were significantly higher in the control group patients as compared to the cases (50 mg/dl vs 71 mg/dL and 0.33 ng/ml vs 11.74 ng/ml respectively, p = 0.026). Blood culture was positive in two cases and in none from the control group. The incidence of CMV viremia was

significantly higher among the cases as compared to the controls (38% vs 7%, p = 0.03). Among the cases and controls, OS and NRM at 100 days were 97% vs 93% (p = 0.89), and 2.9 % vs 7% (p = 0.89), respectively. Acute and chronic GVHD was seen in 2.9% vs 14% (p = 0.41), and 2.9% vs 7% (p = 0.41) respectively.

Conclusions: Prophylactic GTX during peri transplant severe neutropenia, ameliorated sepsis related parameters, thus benefitting the benefits. However, the frequency of CMV reactivation was higher in the GTX group which offsets the economic benefits accrued.

Disclosure: Nothing to declare.

13 - Infectious Complications

P416

INFECTIOUS COMPLICATIONS IN RUXOLITINIB-TREATED PATIENTS WITH CORTICOSTEROID-REFRACTORY GRAFT VERSUS HOST DISEASE AFTER HEMATOPOIETIC CELL TRANSPLANTATION: EXPERIENCE OF A SINGLE CENTRE

Isabel Izquierdo Garcia[1], Ana Gomez Martinez[1], Eduardo Gonzalez Gomez[2], Marta Moreno Carbonell[3], Pilar Delgado Beltran[1]

[1]Hospital Miguel Servet, Zaragoza, Spain, [2]Hospital del Mar, Barcelona, Spain, [3]Hospital Gregorio Marañon, Madrid, Spain

Background: The JAK 1/2 inhibitor Ruxolitinib has been approved for the treatment of adults and paediatric patients >12 years with steroid refractory graft-versus-host disease (GvHD) based on the REACH-2 and 3 studies. Ruxolitinib is emerging as the treatment of choicein this patients but there is relatively little real-world data published on ruxolitinib for this indication. We wanted to evaluate the safety (analyzing infectous events) of ruxolitinib in cGVHD patients in our center.

Methods: For this descriptive, retrospective, single centre analysis, we included 14 adult patients who received Ruxolitinib at a starting dose of 10 mg twice daily for chronic GVHD in our centre from 2020 to 2022.

Results: Among all patients (n = 14), 9 patients (64%) developed at least 1 documented infection while on ruxolitinib. Only one patient died related to infectious complications (COVID-19). Viral infections were the most common, with a total of 9 viral events detected. Four patients (28%) developed CMV viremia. No CMV organ involvement was seen. One patient (7%) had VHS. Finally, 2 patients (14%) developed an upper respiratory infection due to Influenza A, detected on PCR-based respiratory viral screening. We identified a total of 12 bacterial infections. No bacteriemia was founded. Three patients (21%) developed an E. coli urinary tract infection; 2 caused by E. Coli and 1 by Klebsiella Pneumoniae, and 1 patient (7%) a Pseudomonas sp. soft tissue infection. Seven patients (50%) developed respiratory tract infections. 3 of them suffered pneumococcal pneumonia and the other 4 bronchitis without microbiological documentation but with respiratory symptoms and fever. We observed one patient with Campylobacter Yeyuni gastrointestinal infection. Finally, 2 patients were diagnosed with pulmonary aspergillus infection. They were not on any antifungal prophylaxis at time of infection.

Conclusions: Infections represent a common complication after ruxolitinib initiation in patients with GVHD. We reviewed all viral, bacterial, and fungal events among our cohort of patients treated with chronic GVHD. Overall, we found that 64% of patients developed an infection after ruxolitinib initiation. Only one event was fatal. Ruxolitinib was confirmed to be a safe and effective option as salvage treatment for chronic GvHD but demonstrates the necessity for careful infectious prophylaxis and monitoring.

Disclosure: Nothing to declare.

13 - Infectious Complications

P417

EBV REACTIVATION AND PTLD AFTER ALLO-HSCT. A SINGLE CENTER EXPERIENCE IN T-CELL DEPLETED TRANSPLANTS WITH ADOPTIVE IMMUNOTHERAPY AND IN UNMANIPULATED TRANSPLANTS WITH POST-TRANSPLANT GVHD PROPHYLAXIS

Valerio Viglione[1], Loredana Ruggeri[2], Antonio Pierini[1], Adelmo Terenzi[2], Sara Tricarico[1], Alessandra Cipiciani[1], Rebecca Sembenico[1], Mattia Mariannelli[1], Sara De Santis[1], Francesco Zorutti[1], Roberto Castronari[2], Silvia Bozza[1], Cristina Mecucci[1], Antonella Mencacci[1], Alessandra Carotti[2]

[1]University of Perugia, Perugia, Italy, [2]Santa Maria della Misericordia Hospital, Perugia, Italy

Background: Post-transplant EBV-reactivation is still a threat after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Post-transplant lymphoproliferative disorders (PTLD) are largely associated to EBV infection and represent a significant cause of mortality and morbidity in patients who undergo HSCT. Incidence ranges from 1% to 11% and it varies according to different conditioning regimens and types of donor. Median onset is 2 months. The monoclonal antibody directed against CD20, Rituximab, and the lightening of immunosuppression constitute the backbone of its prophylaxis, while treatment relies mainly on intense immune-chemotherapy protocols. To date, there is lacking of evidence on which patient needs to be treated and when it is time to start the treatment.

Methods: We retrospectively analyzed a total of 106 consecutive first allo-HSCT from January 2019 to September 2022, with an observational period ranging from 3 months to over 3 years. 41 patients (38%) underwent unmanipulated allo-HSCT with different protocols of GvHD prophylaxis and 65 (61%) patients underwent T-deplete HSCT with adoptive immunotherapy with conventional and regulatory T cells (Treg/Tcon allo-HSCT) and no pharmacologic post-transplant immunosuppression. In the unmanipulated transplant, we administered prophylactic Rituximab only when the donor was haploidentical (35 cases, 85%). No Rituximab prophylaxis was administered in Treg/Tcon allo-HSCT.

EBV DNAemia was assessed by quantitative PCR on whole blood weekly in the first 3 months and less frequently thereafter.

Results: EBV DNA was detected in the peripheral blood (PB) of 50/65 in the Treg/Tcon allo-HSCT (76%) versus 9/41 in the unmanipulated allo-HSCT group (21%). EBV presence lasted longer in Treg/Tcon than in unmanipulated allo-HSCT (8 months, range 1-28 versus 5 months, range 1-11). Only one patient developed PTLD (0.94%). Eleven patients, all in the Treg/Tcon allo-HSCT group, received Rituximab as pre-emptive therapy in presence of increasing symptomatic viremia. At +60 days from transplant, patients after Treg/Tcon allo-HSCT had a mean of 189 B-cells/uL (range 0-882) versus 7/uL (range 0-195) after unmanipulated transplants who received prophylactic Rituximab and 61/uL (range 0-94) after unmanipulated transplant who did not receive Rituximab. Better B-cell rebuilding was also associated with higher production of Immunoglobulins (IgG and IgM). T-cell number were similar in the different groups of patients we analyzed.

Early CD4 and CD8 T-cell pathogen specific responses were detectable against EBV in Treg/Tcon allo-HSCT patients starting from the first two months after transplant. In contrast, in unmanipulated transplant such responses were not detectable until 6 months from transplant.

Conclusions: B-cells, which represents the cell target of EBV infection and proliferation, were 10 times more in Treg/Tcon allo-HSCT than in unmanipulated allo-HSCT. This finding may explain the high frequency of EBV reactivation. Despite prolonged positivity of the DNAemia in the group who did not received prophylaxis, we observed only 1 PTLD who required treatment. Fast T-cell rebuilding due to Treg/Tcon adoptive immunotherapy without immune suppression in such group of transplants may favor an EBV-specific immune control that prevented PTLD in the vast majority of patients.

Finally, as expected, the use of rituximab as pre-emptive therapy in patients at high risk to develop PTLD was effective.

Disclosure: Nothing to declare.

13 - Infectious Complications

P418

THE ROLE OF CHEST RADIOGRAPHY IN THE EVALUATION OF FIRST FEBRILE NEUTROPENIA IN PATIENTS UNDERGOING HSCT

Lucía Medina de Alba[1], Adolfo Jesús Sáez Marín[1], Jose María Sánchez Pina[1], María del Pilar Martínez Sánchez[1], Magdalena Corona de la Puerta[1], Tycho Stephan Baumann[1], Reyes Mas Babio[1], Andrea Tamayo Soto[1], Guillermo Ramos Moreno[1], Esther Parra Virto[1], Alberto Blanco Sánchez[1], Rodrigo Gil Manso[1], Rafael Colmenares Gil[1], Daniel Gil Alos[1], Joaquín Martínez López[1], María Calbacho Robles[1]

[1]*Hospital Universitario 12 de Octubre, Madrid, Spain*

Background: Febrile neutropenia (FN) is a common complication in hematopoietic stem cell transplantation (HSCT). Chest X-ray (CRX) is a diagnostic test routinely performed within the first 24 hours even though patients are usually asymptomatic and pneumonia findings are rare. The endpoint of this study was to clarify the utility of CRX during the first episode of FN in adult patients undergoing HSCT.

Methods: Single-center retrospective study that analyzed electronic clinical records of 197 adult patients that underwent autologous (n = 103), allogenic with reduced intensity (n = 57), or allogenic myeloablative HSCT (n = 37) between July 2020 and September 2022 (Table 1). All the patients received appropriated antifungal and antiherpetic prophylaxis. CRXs obtained within the first 48 hours of FN were examined for radiologic features of pneumonia, the presence of clinical symptoms or an altered physical examination was assessed. We used Stata® for the statistical analysis.

Variables	Autologous HSCT	Allogenic HSCT	
		Myeloablative	Reduced Intensity
Age	53.96 (16.92–71.44)	44.83 (18.97–64.88)	53.75 (19.67–67.50)
Sex (W/M)	48/55	21/16	28/29
N	103	37	57
Malignant disease			
- Hodgkin Lymphoma	8 (7.77%)	1 (2.70%)	4 (7.02%)
- Non-Hodgkin Lymphoma	24 (23.30%)	1 (2.70%)	13 (22.81%)
- Multiple Myeloma	51 (49.51%)	0 (0%)	1 (1.75%)
	2 (1.94%)	20 (54.05%)	14 (24.56%)
- Acute Myeloid Leukemia			
- Acute Lymphoblastic Leukemia	1 (0.97%)	5 (13.51%)	7 (12.28%)
- Bone Marrow Aplasia	0 (0%)	4 (10.81%)	0 (0%)
- Germ Cell Tumor	13 (12.62%)	0 (0%)	0 (0%)
- Myelodysplastic Syndrome	0 (0%)	6 (16.22%)	14 (24.56%)
- Plasma Cell Leukemia	1 (0.97%)	0 (0%)	2 (3.51%)
- Other (Amyloidosis, Systemic Lupus Erythematosus, Sarcoma, Chronic Lymphocytic Leukemia, Medulloblastoma)	3 (2.91%)	0 (0%)	2 (3.51%)
Previous pulmonary disease	25 (24.27%)	3 (8.11%)	13 (22.81%)
Symptoms or altered physical examination	10 (11.24%)	1 (2.78%)	6 (10.53%)
Pneumonia	2 (2.27%)	1 (2.78%)	1 (1.79%)
Number of CRX	86	36	57

Single-center retrospective study that analyzed electronic clinical records of 197 adult patients that underwent autologous (n = 103), allogenic with reduced intensity (n = 57), or allogenic myeloablative HSCT (n = 37) between July 2020 and September 2022 (Table 1). All the patients received appropriated antifungal and antiherpetic prophylaxis. CRXs obtained within the first 48 hours of FN were examined for radiologic features of pneumonia, the presence of clinical symptoms or an altered physical examination was assessed. We used Stata® for the statistical analysis.

Results: A total of 182 (92.4%) patients had a FN episode; 179 (90.82%) of them had CRX and 17 (8.62%) had respiratory symptoms. 14 patients had pathological findings on their CRX (7.95%) with only 4 being associated to radiographic features of pneumonia (2.23%). 2 patients were asymptomatic (2 of 162) and 2 had respiratory symptoms or an altered physical examination (2 of 17). In our sample there's a 9.53 (IC95%: 1.43 – 63.41) times higher probability to diagnose a pneumonia by CRX in a patient with symptoms than without. Therefore, we found that CRX in symptomatic patients had a positive predictive value of 50% and a negative predictive value of 91.43%.

Conclusions: Routine CRX at the time of first neutropenic fever in asymptomatic adults undergoing autologous or allogenic HSCT seems unlikely to reveal an underlying pulmonary infectious disease in our sample. It appears to be useful in symptomatic patients.

Disclosure: Nothing to declare.

13 - Infectious Complications

P419

VIRAL INFECTION PROFILE AFTER HEMATOPOETIC STEM CELL TRANSPLANTATION IN A REFERENCE HOSPITAL IN BRAZIL

Sarah Campos[1], Karine Barroso[1], Beariz Araujo[1], João Leitão[1], Livia Gurgel[1], Fernando Duarte[1]

[1]Walter Cantídio University Hospital, Fortaleza, Brazil

Background: Despite recent advances in the field of allogeneic hematopoietic stem cell transplantation (HSCT), viral infections are still a significant complication during the period of immune suppression that follows the procedure and remain a frequent cause of morbidity. The most epidemiologically relevant viruses in this context are CMV, EBV, BKV and HV6, and their post-transplant screening is essential.

Methods: This is a retrospective, descriptive, analytical and quantitative study with analysis of exam results and medical records. Allogeneic transplants performed in the last 5 years, in patients aged 16 years or older, were analyzed. The objective was to evaluate the profile of viral infection in patients undergoing Allogeneic Hematopoietic Stem Cell Transplantation in a Brazilian reference hospital.

Results: From January 2017 until December 2021, 341 transplants were performed, of which 126 were allogeneic. Nine patients (5 related and 4 unrelated) were excluded from the series due to the absence of viral screening records in the files, remaining 117 patients in the study (68 related, 15 unrelated and 20 haploidentical). Of these, 50.43% were women and 49.57% were men, with a median age of 37.9 years (ranging from 16 to 70 years). Regarding the diagnosis, most patients had AML (30%), followed by ALL (27%), aplastic anemia (14%), CML (9%) and MDS (9%), followed by other less frequent diseases. The investigation of viral reactivation was performed by PCR and screening for CMV, EBV, BKV and HV6 were evaluated. A cutoff points of 1000 copies was used for CMV and EBV. 81.75% of the patients had some virus detected (in any value) during the post-BMT period. In line with the literature, there was a prevalence of viral reactivation in transplantations from alternative donors, having the haploidenticals 90.91% of detection. CMV reactivation was the most frequent. Among the 117 patients, 70.94% had detectable values for CMV, 17.95% <1,000 copies and 52.99% >1,000 copies. Next are the EBV numbers: among the tested patients, 40.28% had >1000 copies and 26.39% <1000 copies. Among all detectable patients, 53.26% had more than one virus and 6.52% had detection of all 4.

Conclusions: Viral reactivation is frequent in allogeneic HSCT, especially with the use of alternative donors, with emphasis on CMV reactivation. Knowing the viral reactivation profile of each transplantation center is essential to guide screening strategies and preemptive treatment.

Disclosure: Nothing to declare.

13 - Infectious Complications

P420

WEST-NILE VIRUS MENINGOENCEPHALITIS IN IMMUNOCOMPROMISED HOST AFTER ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION – A PEDIATRIC CASE REPORT

Marta Adavastro[1,2], Giacomo Gotti[2], Sonia Bonanomi[2], Francesca Vendemini[2], Guglielmo Migliorino[3], Sergio Malandrin[3], Adriana Balduzzi[1,2]

[1]Universitiy of Milano-Bicocca, Milano, Italy, [2]MBBM Foundation, San Gerardo Hospital, Monza, Italy, [3]San Gerardo Hospital, Monza, Italy

Background: West Nile virus (WNV) infection is a zoonotic disease that can lead to a wide spectrum of manifestations in immunocompromised host, from asymptomatic disease to potentially fatal encephalitis. Symptomatic cases represent approximately 25% of the infections, with neuroinvasive disease affecting <1% of cases. WNV infection is endemic in Italy, with summer outbreaks. Infection mostly occurs via mosquito.

Nowadays there is no approved therapy for symptomatic invasive WNV infection and only supportive treatment is recommended. Different approaches with immunomodulant therapies as polyclonal or monoclonal immunoglobulins, interferon and corticosteroids have been reported with no significant benefit.

Methods: We report a case of a 4 years-old child who underwent allogeneic bone marrow transplantation (BMT) from his matched sibling donor for transfusion-dependent thalassemia with severe iron overload, after a conditioning regimen consisting of treosulfan (14 g/m^2, d-7 to d-5), fludarabine (30 mg/m^2, d-7 to d-3), thiotepa (5 mg/kg q12h, d-2) and graft-versus host disease prophylaxis including cyclosporine, antihuman thymocyte immunoglobulin (15 mg/kg d-4 to d-2), methotrexate 10 mg/m^2 d + 1, + 3, + 6.

Results: The patient had an uneventful early post-BMT course, ANC and platelet engraftments occurred on d + 21 and d + 26, respectively. At d + 23, the child developed neurological symptoms with severe headache, vomit, irritability, photophobia, refusal to walk and play, fever not responsive to antipyretics. Brain MRI resulted negative for PRES. Electroencephalography showed slow waves with occipital focal asymmetry, not consistent with typical manifestation of viral encephalitis. Moderate pleocytosis (13 leucocytes/μL), with polymorphonuclears prevalence, and normal glucose (69 mg/dL, range 60-80) and proteins (31 mg/dL, range 15-45) were detected in the CSF. Molecular analyses with PCR for viral herpetic, parvovirus, enterovirus, adenovirus, BK and JC virus tested negative. Based on the recent WNV outbreak in Northern/Eastern Italy, WNV analysis was performed on his CSF and PCR detected 500 copies/mL. Additional sampling on plasma and urine tested positive as well, with 735 copies/mL and 2,853,216 copies/mL, respectively, confirming the diagnosis of WNV-related meningoencephalitis.

Intravenous immunoglobulins (Ig, 400 mg/kg/day for 5 days) and supportive therapy were provided. After 5 days after symptom onset and after the Ig 1st infusion, fever resolved, his general status frankly improved, and his neurological symptoms decreased in the following two days and completely recovered in 10 days. Serial EEG revealed slow but progressive improvement. Moreover, an additional spinal and brain MRI showed persistent normal findings. Patient was discharged on day +46 and he is alive with no significant complication after 3 months.

Conclusions: This case highlights that WNV infection needs to be considered in immunocompromised patients with meningoencephalitis symptoms, both living in endemic areas and in Countries with frequent outbreaks. Our case suggests that patient may benefit from the rapid detection of the infection and administration of intravenous immunoglobulins. Due to the long incubation period in immunocompromised hosts, screening for WNV-serology in BMT-recipients should be considered before conditioning, as active infections in immunocompromised hosts has shown to be fatal in most cases and no curative therapy is still available.

Disclosure: Nothing to declare.

13 - Infectious Complications

P421

HUMAN-HERPES-VIRUS-6 B ENCEPHALITIS AFTER HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Nina Kristin Steckel[1], Deepak B. Vangala[1], Matthias Eckhardt[1], Philipp Aurich[2], Britta Maecker-Kolhoff[3], Britta Eiz-Vesper[4], Roland Schroers[1]

[1]Universityhospital Knappschaftskrankenhaus Bochum, Bochum, Germany, [2]Universityhospital Knappschaftskrankenhaus Bochum, Bochum, Germany, Hannover Medical School, Hannover, Germany, [4]Institute of Transfusion Medicine and Transplant Engineering, Hannover Medical School, Hannover, Germany

Background: Viral encephalitis is still a very rare complication after autologous stem cell transplantation (aSCT) and is often fatal due to small therapeutic options. The most common culprits are Herpes simplex (HSV)-, Cytomegalo (CMV)-, and Poliomavirus (JCV). Diagnosis is often difficult, and brain biopsy are needed to confirm etiology. We here present a case of encephalitis caused by Human-Herpes-Virus-6 B in an adult patient after aHSCT for secondary central nervous diffuse large B-Cell-Lymphoma (DLBCL), which has been successfully treated with antiviral therapy and virus-specific T-Cells.

Methods: Case Report

Results: A 55-year-old patient was diagnosed with DLBCL of the right testis in October 2014. He underwent chemotherapy with 6 cycles of R-CHOP-14 and 2 cycles of R-Methotrexate resulting in complete remission. In addition, an orchiectomy was carried out and the left testis was radiated. In April 2022 a cerebral relapse was diagnosed after epileptic seizure with cerebral right frontal manifestation but without systemic lymphoma manifestation. Chemoimmunotherapy with rituximab, methotrexate, cytarabine, and thiotepa (MATRIx protocol) was started with stem cell harvest after the first cycle. After 4 cycles, a complete remission was documented, and consolidation using high-dose chemotherapy with rituximab, carmustin, and thiotepa followed by autologous stem cell support was performed in August 2022. The early post-transplant period was complicated by neutropenic fever and enteritis with nausea and emesis as well as pneumonia and liver toxicity. After hematological reconstitution the clinical condition improved, and the patient was planned to be discharged.

Suddenly he presented with fast progressive loss of consciousness resembling catatonia with apathy and epileptic status ensued. He fell into coma and had to be artificially ventilated. In MRI-scans typically signs for viral encephalitis were described. In addition, (HHV6-B) was detected in the cerebrospinal fluid leading to the diagnosis of HHV6-B associated encephalitis. An antiviral therapy with foscarnet and intravenous immunoglobulins (IVIG) as well as complex anticonvulsive medication was initiated. In addition to this, virus-specific T-cell therapy of an HLA-adapted unrelated healthy donor was processed (alloCell, Hannover) and could be administered 18 days after first symptoms. The neurological symptoms declined, and the patient could be weaned after dilatative tracheostomy from mechanical ventilation. Due to a fungal infection and the necessity of liposomal amphotericin B treatment, the antiviral therapy had to changed into ganciclovir after three weeks of treatment. Decannulation was possible seven weeks after first symptoms. The patient was weak and still had failure in usual orientation including strong restrictions in short term memory. In MRI-scan the signs of viral encephalitis improved and the cerebrospinal fluid remained negative for HHV6-B DNA. Discharge to a rehabilitation facility was possible 8 weeks after first symptoms.

Conclusions: This case report demonstrates that in patients with severe immunodeficiency after aHSCT a HHV6-B infection can be associated with encephalitis. It is an acute life-threatening disease, which can be successfully treated with a combination of adequate antiviral therapy, immunoglobulins, and virus-specific T-cells.

Disclosure: Nothing to declare.

13 - Infectious Complications

P422

A CASE REPORT OF DIGESTIVE CRYPTOSPORIDIOSIS: A CHALLENGING DIAGNOSIS

María Pérez Raya[1], Carola Lucía Díaz Aizpún[1], Kati Hurst[1], Jesús González García[1], María Cuesta Casas[1]

[1]Hospital Regional Universitario de Málaga, Málaga, Spain

Background: Cryptosporidium is an intestinal parasite that may be found in water or contaminated food and causes diarrheal disease. In allogeneic hematopoietic stem cell transplantation (HSCT) recipients, with profound T-cell immunosuppression, it can lead to severe disseminated cryptosporidiosis, presenting with diarrhea, abdominal pain, anorexia, nausea and vomiting. Differential diagnosis proves a challenge due to clinical similarities with acute intestinal graft-versus-host disease (aGVHD).

Optimal treatment strategies are still unclear, although combined therapy with Azithromycin and Nitazoxanide for several weeks, in addition to inmune restoration, seems to be an effective option.

Methods: We report a case of digestive cryptosporidiosis after allogeneic HSCT.

Results: We present the case of a 59 years old male patient, diagnosed with unfavorable-risk AML (ASXL1, RUNX1) in December 2021.

He began treatment according to the PETHEMA LMA-FLOW protocol, achieving first complete remission with positive MDR after induction and consolidation treatment. Allogeneic HSCT from an identical related donor after a sequential conditioning regimen was performed in May 2022. Post-transplant complications included intestinal aGVHD (MAGIC II) at day +21 and subsequent hepatic GVHD (MAGIC IIIB) at day +74, both resolved with steroids. In addition, he developed intestinal Citomegalovirus disease, requiring prolonged antiviral treatment.

He later presented with diarrhea, rectal bleeding and fever, requiring hospital admission for management. On admission, broad-spectrum antimicrobial coverage was administered and immunosuppressive treatment was deepened after pathological studies were suggestive of intestinal GVHD, requiring association of up to 3 lines of immunosuppressive treatment due to torpid clinical course.

Despite an initial improvement of digestive symptoms, he developed oral intolerance, persistent nausea and intractable bilious vomiting as well as diarrheal stools. Intense inflammation and subsequent wall thickening generated episodes of intestinal pseudo-obstruction with torpid progress after conservative management, associating severe malnutrition. A gastroscopy performed to rule out upper gastrointestinal GVHD, CMV or adenovirus disease, showed ovoid structures in the gastric lumen with negative GIEMSA, PAS and methenamine silver staining, initially suggestive of Microsporidium involvement. Cryptosporidium was finally confirmed in a stool culture with Kinyoun staining and PCR on day +132. Targeted treatment with Nitazoxanide 1g every 12 hours and oral Azithromycin 500mg every 24 hours was initiated, in addition to reducing immunosuppressive treatment, maintaining Ruxolitinib 5mg every 12 hours.

He developed necrotizing myositis with unfavorable progress despite antibiotic therapy, broad-spectrum antifungals and surgical debridement. Isolation of abundant fungal structures was later confirmed.

Finally, after 12 days of antiparasitic treatment without observing clinical improvement, the necrotizing myositis remained uncontrolled, despite several surgical debridements and extensive antimicrobial treatment, resulting in death.

Conclusions: - Disseminated cryptoporidiosis is an entity that most commonly occurs in immunocompromised patients, such as those undergoing allogeneic HSCT, causing diarrheal disease.

- Diagnosis is often difficult and delayed, due to low incidence and clinical similarities with other entities such as intestinal GVHD.
- Given its severity, systematic screening for Cryptosporidium should be included in the study of diarrheal syndrome in allogeneic HSCT recipients, especially if they develop or have previously developed GVHD.
- The early initiation of treatment with combined therapies together with restoration of cellular immunity show effective results.

Disclosure: Nothing to declare.

13 - Infectious Complications

P423

BACTEREMIA IN BONE MARROW TRANSPLANTATION PATIENTS: INCIDENCE AND CLINICAL RISK FACTORS IN A MIDDLE-INCOME COUNTRY TRANSPLANTATION UNIT

Jorge Cuervo-Sierra[1], German Velasquez-Quintero[1], Sebastian Hoyos[1], Juan Felipe Jaramillo-Alvarez[2], Jurany Marin-Montoya[1], Maira Mesa-Giraldo[1], Maria Camila Villegas-Osorio[1], Deisy J. Giraldo-Gomez[1], Luisa F. Castro-Quintero[1]

[1]Clinica Somer, Bone Marrow Transplantation Unit, Rionegro, Colombia, [2]Clinica Somer Hematology, Rionegro, Colombia

Background: Despite universal precautions and antibiotic prophylaxis bacteremia is a common complication and an early cause of death in bone marrow transplantation patients. Our aim was to describe bacteremia incidence, main bacteria involved, clinical risks factor associated with positive blood cultures and 30- and 100-days survival according to bacteremia.

Methods: We retrospectively reviewed clinical records of a cohort of patients who received a bone marrow transplantation from January 2017 to October 2022, microbiology laboratory registry was checked for every patient. First 100 days post-transplant bloodstream infections were included

Coagulase-negative Staphylococci were taken in count if were isolated from two or more cultures.

Numerical variables were reported as means or medians. Categorical variables were reported as frequencies and percentages. A bivariate analysis was done, Chi-squared test was used for categorical variables, Mann Whitney U test was used for continuous variables.

A survival analysis using the Kaplan-Meier estimator was used to compare survival at 30- and 100-days post-transplant according to the presence of bacteremia.

Results: Between January 2017 and October 2022 205 transplant were done, 124 (60,7 %) autologous, 27 (13,7%) identical related allogenic and 54 (26,2 %) haploidentical; the main indications were plasma cells neoplasms (30,73 %), non-Hodgkin's lymphoma (22,43%), acute lymphoblastic leukemia (13,6%), acute myeloid leukemia (15,12%) and Hodgkin's lymphoma (7,8%).

Febrile neutropenia occurred in 81,6% of transplants. Bacteremia was detected in 48 patients, gram-negative bacilli bacteremia accounted for 31 (64,6%) of episodes, *Escherichia coli* was the most common germ isolated from 23 (47,9%) patients, gram-positive cocci were isolated from 16 (33,3%) patients (8 coagulase-negative Staphylococci and 8 Streptococci). Two mixed bacteremic episodes occurred.

ESBL - producing gram negative Enterobacteriaceae were isolated in 8 patients (E. *coli*: 6, *K. pneumoniae*: 2) corresponding to 28,6% and 40% of *E. coli* and *K. pneumoniae* bacteremia respectively. All but one (87,5%) of coagulase-negative Staphylococci were methicillin-resistant.

Fluoroquinolone resistance was detected in 93,5% of gram-negative bacilli.

Carbapenemase-producing (KPC-positive) corresponded to 9,6 % of gram-negative bacilli isolates.

Bacteremia incidence was associated with the time length to myeloid engraftment (Mann-Whitney U, $p < 0{,}001$), being 60 years or older was also associated with bacteremia ($p = 0.005$, relative risk: 2,21; CI 95%: 1.32-3.69). There was no difference in bacteremia incidence between allogenic and autologous transplants.

There was no difference in mortality at 30- and 100-days post-transplant between patients with positive and negative blood cultures. Globally, mortality was 1,5 % and 5,8 % at 30 and 100 days respectively.

Conclusions: Bacteremia is common in patients going to bone marrow transplantation, gram negative bacilli are still the main cause of bacteremia in our unit. Being older than 60 years and the time length to myeloid engraftment were associated with bacteremia. An increase in mortality at 30 and 100 days were found in patients with bacteremia. Antibiotic resistance is an increasing problem.

Disclosure: nothing to disclosure.

13 - Infectious Complications

P424

EFFICACY COMPARISON OF LEVOFLOXACIN AND RIFAXIMIN PROPHYLAXIS IN PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION

Gülşah Akyol[1], Yakup Patat[1], Ali Ünal[1], Muzaffer Keklik[1], Leylagül Kaynar[2]

[1]Erciyes University, Kayseri, Turkey, [2]Medipol University, Istanbul, Turkey

Background: Opportunistic infections in the post-allogeneic stem cell transplant period pose a high risk for recipients, either before or during the first 100-day period after engraftment. The most common ones are bacteria and fungi in the early period, then fungus, opportunistic pathogens such as CMV. The most commonly recommended for bacterial prophylaxis in international guidelines are quinolone antibiotics. In this study, our aim is to determine whether there is a protective difference between rifaximin and levofloxacin prophylaxis after allo-transplantation.

Methods: A total of 116 patients, 58 of whom were given prophylaxis with rifaximin and 58 with levofloxacin, were included. 63 were male and 53 were female. The mean age was 41 (Min: 17, Max: 67) 56 AML, 29 ALL, 7 aplastic anemia, 6 NHL, 4 hodgkin lymphoma, 4 myelofibrosis, 3 CML, 3 SCA, 1 PNH, 1 myeloma, 1 ITP and 1 histiocytosis patient were included in the study.

Results: Levofloxacin prophylaxis was found to be superior to rifaximin prophylaxis with a lower rate of switching to broad-spectrum antibiotics (p:0.008). It was determined that there was no significant difference between the two prophylaxis for switching to broad-spectrum antibiotics in AML patients (p:0.086) and ALL patients (p:0.622). In the other patient groups consisting of a total of 30 patients, it was observed that switching to antibiotic use after levofloxacin prophylaxis was less common. (p:0.031).

It revealed that there was no difference between the prophylaxis of the two drugs in the development of fever after AHSCT. It was revealed that levofloxacin caused less fever development in AML patients (p:0.017). It showed that the two drugs were not superior to each other on the development of fever after AHSCT in ALL patients (p:0.62). It was observed that the rate of fever development after levofloxacin prophylaxis was lower in other patient groups other than leucemia (p:0.031).

It was determined that there was a lower readmission rate with levofloxacin (p:0.004). However, when separately AML were evaluated, no significant difference was found between the two drugs. In ALL patients, levofloxacin was found to be superior in terms of readmission. (Re-hospitalization levofloxacin 33%; rifaximin 83%) (p:0.027). No significant difference was found in others.

Of 116 patients, 54 were hospitalized within the first 100 days. In 27 patients, the most common cause was infection, the second most common cause was GVHD.

There was no significant difference in mortality among prophylaxis. Lower mortality rates were detected in AML patients who were given prophylaxis with levofloxacin. (p:0.011).

Conclusions: There is no study in the literature comparing levofloxacin and rifaximin one-to-one.

In a study, it was found low rate of transplant-related mortality and a similar rate of infectious complications when compared with rifaximin and ciprofloxacin. In another study, similar mortality, fever, rehospitalization for infection, and infections were observed with cefpodoxime and levofloxacin prophylaxis.

In our study levofloxacin was found to be superior to rifaximin prophylaxis with less conversion to broad-spectrum antibiotics. Levofloxacin caused lower rate fever in AML patients. In ALL patients, levofloxacin was found to be superior in terms of readmission. (33% vs 83%).

Disclosure: All authors declare that there is no conflict of interest.

13 - Infectious Complications

P425

CASPOFUNGIN PROPHYLAXIS IN THE PRE-ENGRAFTMENT PERIOD IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC TRANSPLANTATION: A SINGLE CENTER EXPERIENCE

Annamaria Vincenzi[1], Francesco D'Agostino[1], Alessia Fiore[1], Raffaella Iannotta[1], Francesco Grimaldi[1], Lucia Ammirati[2], Catello Califano[2], Andrea Camera[3], Luigiana Luciano[1], Simona Avilia[1], Alessandro Severino[1], Marco Picardi[1], Fabrizio Pane[1], Giorgia Battipaglia[1]

[1]Federico II University of Naples, Naples, Italy, [2]Onco-Ematologia Ospedale Pagani, Pagani, Italy, [3]Hematology Unit, Sant'Anna e San Sebastiano Hospital, Caserta, Italy

Background: Caspofungin, an echinocandin with a manageable pharmacologic profile, may provide a helpful alternative for prophylaxis of invasive fungal infections (IFIs) to the azoles that show wide pharmacological interactions and hepatic toxicity.

Methods: We retrospectively analyzed the outcomes of a cohort of consecutive patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) in our institution and receiving caspofungin, at the loading dose of 70 mg/die on the first day, followed by 50 mg/die (or 70 mg/die in cases with body weight >80 kgs), as antifungal prophylaxis during pre-engraftment period (from neutropenia until engraftment).

Results: Here we report the results of the 25 patients (16 females, 9 males) transplanted during the period July 2020 to June 2022, for acute myeloid leukemia (n = 17), acute lymphoblastic leukemia (n = 4), myelodysplastic syndrome (n = 1), myelodysplastic/myeloproliferative syndrome (n = 1), Hodgkin lymphoma (n = 1), severe combined immunodeficiency with non Hodgkin lymphoma (n = 1). Median age at transplant was 51 (range 26-70) years, and median interval from diagnosis to transplant was 8 (IQR 6-15) months. Seventeen patients were transplanted in complete remission, whereas 6 underwent allo-HSCT with active disease, and 2 with positive minimal residual disease. Three patients had a Sorror >2. Donors were HLA-identical siblings in 9, unrelated in 10 (10/10, n = 8; 9/10 n = 2) or haploidentical in 6 cases. Stem cell source was peripheral blood in 13 and bone marrow in 12 cases. Conditioning regimen was myeloablative or reduced-intensity in 10 and 12 patients, respectively. In 3 patients a sequential conditioning regimen was adopted. Graft-versus-host disease (GVHD) prevention consisted of Cyclosporine A alone (n = 1) or with either methotrexate (n = 8) or mycophenolate mofetil (n = 16). Antithymocyte globulin or post-transplant cyclophosphamide were used in 15 and 10 patients, respectively. Demographics are summarized in table 1. Median duration of hospitalization for allo-HSCT was 30 days (range 15-56). All but one patient engrafted. Median time to neutrophil and platelet engraftment were 15 (range 9-23) and 17 (range 8-44) days. Median duration of caspofungin prophylaxis was 16 (range 8-26) days with no toxicities and no need to switch to other antifungal agents. One patient developed a possible IFI (radiological findings) at 36 days after allo-HSCT, successfully treated with antibiotics and voriconazole. Three patients experienced grade II-IV acute GVHD (2 grade II, 1 grade IV), resolutive in all but one patient. Cumulative incidence of relapse at 1 year accounted for 15% while non-relapse mortality at 100 days and 1 year accounted for 4% and 8%, respectively. Main causes of death were disease recurrence (n = 2), veno-occlusive disease (n = 1) and GVHD (n = 1). Three patients experienced molecular relapse. Donor lymphocyte infusions were used either as preemptive (n = 3) or curative (n = 2) treatment in association with systemic treatments. One patient underwent a second allo-HSCT after achieving a second complete remission. With a median follow-up of 13 (range 5-28) months, 12-months overall and progression free survival were 84 ± 8% and 70 ± 10%, respectively, while GVHD/relapse-free survival was 70 ± 10%.

Characteristics (%)	**n = 25**
Sex, M/F	9 (36) / 16 (64)
Median age at transplant, years (range)	51 (26-70)
Median interval from diagnosis to transplant, months (IQR)	8 (6-15)
Transplant indications	
AML / ALL	17 (68) / 4 (16)
MDS	1 (4)
MDS/MPN	1 (4)
HL	1 (4)
NHL/SCID	1 (4)
Disease status at transplantation, Complete remission / Active disease / MRD pos	17 (68) / 6 (24) / 2 (8)
Stem cell source, PB / BM	13 (52) /12 (48)
Donor, HLA-identical sibiling / UD / Haploidentical	9 (36) / 10 (40) / 6 (24)
Conditioning regimen, MAC / RIC / Sequential	10 (40) / 12 (48) / 3 (12)
Cyclosporine alone	1 (4)
Cyclosporine + Methotrexate	8 (32)
Cyclosporine + Mycophenolate mofetil	16 (64)
Post-transplant Cyclophosphamide	10 (40)
ATG	15 (60)

Abbreviations: *M* male; *F* female; *IQR* interquartile range; *AML* acute myeloid leukemia; *ALL* acute lymphoid leukemia; *MDS* myelodysplastic syndrome; *MDS/MPN* myelodisplastic syndrome/myeloprolipherative neoplasm; *HL* Hodgkin lymphoma; *NHL* non Hodgkin lymphoma; *SCID* severe combined immudodeficiency; *MRD pos* positive Minimal Residual Disease; *PB* periphereal blood; *BM* bone marrow; *UD* unrelated donor; *MAC* myeloablative conditioning; *RIC* reduced intensity regimen; *ATG* antithymocyte globulin.

Conclusions: Prophylaxis with caspofungin is feasible, with low toxicity and only one possible IFI during the pre-engraftment period in our single-center experience.

Disclosure: Nothing to declare.

13 - Infectious Complications

P426

SUCCESSFUL EXPERIENCE OF USING GRANULOCYTE CONCENTRATE IN PATIENTS WITH SEVERE APLASTIC ANEMIA NCSH «OHMATDYT», KYIV, UKRAINE

Andrii Budzyn[1], Olena Nesterenko[1], Oleksandr Lysytsia[1], Dmytro Peretyatko[1], Alina Volkova[1], Mariia Babaskina[1], Olha Dashchakovska[1], Natalia Stryha[1], Oleksandr Istomin[1]

[1]NCSH "Ohmatdyt", Kyiv, Ukraine

Background: Severe neutropenia, which is observed in patients with vSAA is the cause of the development of bacterial and fungal life-threatening complications. In order to control infectious complications in pre- and post transplantation period HSCT, together with systemic antibacterial and antimycotic therapy, the introduction of G-CSF, management tactics involve the use of a high-tech treatment method - transfusion of donor granulocytes.

Methods: Case report - A 5-year-old girl was hospitalized with a diagnosis of vSAA (ANC < 500/microL). HSCT was absolutely indicated to the patient. Before HSCT, we inserted a tunneled CVC (Broviac 4,2 Fr). Despite prophylactic a/b therapy with ceftriaxone, febrillitis was recorded 2 days later, which required increased therapy with amikacin and vancomycin. Against the background of a/b therapy, hyperemia and swelling appeared at the point of entry of Broviak and subcutaneous Dacron cuff. Later, phlegmon formed in the subclavian region.

We decided to change the first line of antibiotics to Imipinem, Colomycin, Dalacin, and Posaconazole to Caspofungin (according to the results of microbiological screening). Additionaly, we decided to start therapy of donor granulocite transfusions. The patient received at all 14 GT (from 7 donors), prepared by the apheresis method with 6% hexosoethyl starch (HES 6%). Donors were examined according to the national standard of infectious screening, CMV status and phenotype were additionally also needed to be considered. Donors of Granulocytes, Apheresis were pre-treated with G-CSF in dose of 0.5 mg/kg subcutaneously, 12 hours before apheresis. Prepared doses of GC (400 ml from one donor) were irradiated and divided into smaller doses (200 ml each) for two consecutive administrations.

The following quality control lab results were received:

- Absolute granulocytes count at unit: from 24.09 to 211.165 $\times 10^8$/unit - target granulocyte clinical content was achieve in each unit.

- Absolute granulocytes count at unit per 1 kg of recepient body weight: from 1.015 to 8.445 $\times 10^8$/kg.

Results: After second GT, normalization of body temperature, reduction of phlegmon in the subclavian region was observed. The Broviac catheter was removed and a new CVC (Certafix Duo) was inserted. We noted: decreasing inflammatory marker levels after fourth GT, wound was healed by secondary tension after seventh GT.

After that, Alo-HSCT from an HLA-identical (10/10) family donor was successfully performed, without any infectious complications.

Conclusions: The use of GT on the background of combined antibacterial and antifungal therapy contributes to resolving infectious lesions in patients with severe neutropenia.

Disclosure: All authors declare no conflict of interest.

13 - Infectious Complications

P427

CLOSTRIDIUM DIFFICILE INFECTION, CYTOMEGALOVIRUS REACTIVATION AND GASTROINTESTINAL GRAFT VERSUS HOST DISEASE IN RECIPIENTS OF ALLOGENEIC STEM CELL TRANSPLANTATION

Mane Gizhlaryan[1], Lusine Krmoyan[1], Inga Khalatyan[1], Narine Ghazaryan1[1], Dianna Soghomonyan[1], Taguhi Hovhannisyan[1], Emma Tadevosyan[1,2], Gevorg Tamamyan[1,3], Karen Meliksetyan[1]

[1]Hematology Center after Prof R. H. Yeolyan, Yerevan, Armenia, [2]City of Smile Charitable Foundation, Yerevan, Armenia, [3]Yerevan State Medical University after M. Heratsi, Yerevan, Armenia

Background: Clostridium difficile infection (CDI) and Cytomegalovirus (CMV) are common infections in patients undergoing allogeneic stem cell transplantation (SCT). We retrospective evaluated a Sickle cell disease (SCD) patient case of an allogeneic stem cell transplant recipient to ascertain the risk factors, and outcome of infection with CMV and CDI.

Methods: Retrospective Case report of SCD patient with GI acute GVDH, CMV reactivation, and CDI.

Results: In the case of this report, the patient was 10 years old boy, who underwent allogeneic hematopoietic stem cell transplantation (HSCT) with a donation from his brother, and the procedure appeared to go well, with no clinical manifestations of SCD following the transplant. On day +20 full engraftment and chimerism >99%, with Hg electrophoresis Hg S wasn't detected. However, on day +28 had a fever up to 38.5°C, severe diarrhea, more than >2000 mL/day, abdominal pain, anorexia, dyspepsia, food intolerance, nausea, and vomiting. At the same time, the CDI test (GDH, ToxA, and ToxB) and CMV PCR tests were positive. According to clinical guidelines diagnosed upper and lower gastrointestinal tract (GIT) acute graft versus host disease (aGVHD), CMV reactivation, and CDI. Treatment of CDI started with oral Vancomycin and Metronidazole, for CMV with oral Valganciclovir, and for Gastrointestinal (GI) aGVHD except cyclosporine A (CsA) added mycophenolate mofetil (MMF), budesonide, and steroid. From day +35 clinical symptoms were relieved, diarrhea volume was reduced, and CMV detection by PCR methods was negative, but CDI was positive. Due to immunosuppressive therapy, CMV reactivated the second time, and ganciclovir started, leading to pancytopenia, and developed sepsis. Antibacterial treatment CDI made it unmanageable. Fidaxomicin has been used to treat CDI, unfortunately, it hasn't been effective. GI aGVHD clinical symptoms developed a second time, which was uncontrollable. Unfortunately, on day +98 patient died.

Conclusions: One of the mechanisms of GVHD includes tissue inflammation leading to the release of cytokines prominent to the triggering of the immune system. Our hypothesis is that CDI or CMV are instigated worsening tissue injury in the gut raising the risk for GI GVHD, and decreased microbial variety, which is typical for the patients with CDI, CMV and with GI GVHD.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P428

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IS EFFECTIVE FOR PATIENTS WITH ADULT T CELL LEUKEMIA/

444

LYMPHOMA AND CAN ERADICATE HTLV-1 INFECTION: A RETROSPECTIVE MONOCENTRIC STUDY

Ambroise Marçais[1], Clemence Loiseau[1], Adrien Gilbert[1], Maya Belhadj[1], Clarisse Cazelles[1], Philippe Renaudier[2], Philippe Helias[3], Florin Santa[4], Ludovic Lhermitte[1], Amani Ouedrani[1], Veronique Avettand Fenoel[5], Vahid Asnafi[1], Felipe Suarez[1], Olivier Hermine[1]

[1]Hopital Necker Enfants Malades, APHP, Paris, France, [2]Centre Hospitalier Universitaire de la Martinique, Fort de France, France, [3]Centre Hospitalier Universitaire de la Guadeloupe, Pointe à Pitre, France, [4]Centre Hospitalier de Cayenne, Cayenne, French Guiana, [5]Hopital Cochin, APHP, Paris, France

Background: Adult T-cell leukemia/lymphoma (ATL) is associated with a poor prognosis in aggressive subtypes with a median overall survival (OS) inferior to one year. Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) has been reported to be the only curative treatment for patients responding to chemotherapy. Here, in addition to outcome we report integrative studies of the HTLV-1 virus and immunological response following allo-HSCT.

Methods: We conducted a monocentric, retrospective study at the ATL national reference center in Necker Hospital (Paris, France). All consecutive patients over the age of 18 years, with ATL diagnosed between 2016 and 2021 were included. Objectives of this study were to determine the feasibility and the outcome of allo-HSCT. Chimerism, HTLV-1 proviral load (PvL), viral integration architecture assessed with high throughput sequencing and immunological response against the HTLV-1 virus were also carried out.

Results: Among the 60 patients treated for an ATL between 2016 and 2021, only 20 of them could be allografted. The main cause that prevented performance of allo-HSCT was lack of disease control. All allografted patients had an aggressive subtype (8 acute and 12 lymphoma subtypes). Fifteen (75%) of patients were allografted after a first line chemotherapy with CHOP like regimen. All patients received high-dose methotrexate chemotherapy for central nervous system as prophylaxis or curative treatment.

At time of allo-HSCT, 11 patients were in complete remission (CR,) 4 in partial response (PR) and 5 in stable/progressive disease (SD/PD). All patients received a reduced toxicity conditioning TBF (Thiotepa/Busulfan/Fluadarabine) regimen. The median age at transplant was 49 years (36-65). The donor was matched related for 6 (30 %), haplo-identical for 12 (60 %) and matched or mismatch unrelated for 2 (10 %). Two related donors were infected with the HTLV-1 virus. Four patients died from transplantation toxicity (acute GvHD, n = 2, acute conditioning injury, n = 2). Three patients presented mild or severe chronic GvHD. Six patients relapsed with a median of 1.5 months and then died.

After a median follow-up of 32 months (10-64 months), the progression-free survival (PFS) and OS rates at 24 months were of 72.7% and 72.7% (median not reached) in CR patients, 50.0% and 75% (median 3 and 28 months respectively) in PR patients and 0% and 0% (median=3 months) in SD/PD patients.

All of the 9 patients allografted with a HTLV-1 seronegative donor and who were alive without relapsing at one-year post allo-HSCT had a rapid decrease of the PvL which became negative with a median of 30 days post alloHSCT. Two patients reverted to positive PvL at 12 and 30 months, respectively while sustaining full donor chimerism. Architecture of viral integration showed the disappearance of the tumor viral clone in assessable patients in remission. Moreover, five of 7 analyzed patients developed T immunological response against HTLV-1 with the detection of cytotoxic T lymphocytes targeting of the viral oncoprotein TAX and were all in remission.

Transplant characteristics	
ATL subtype	Acute (n = 8, 40%)
	Lymphoma (n = 12, 60%)
Disease status at time of alloHSCT	CR (n = 11, 55%)
	PR (n = 4, 20%)
	SD/PD (n = 5, 25%)
Donor type	MSD (n = 6, 30%)
	Haplo (n = 12, 60%)
	MUD (n = 2, 10%)
Conditioning	T1B2F (n = 7, 35%)
	T2B2F (n = 13, 65%)
Stem cells source	BM (n = 9, 45%)
	PBSC (n = 11, 55%)
T cell depletion/repletion	ATG (n = 8, 40%)
	PTCy (n = 12, 60%)

Conclusions: Allo-HSCT should be performed in ATL patients when possible only in patients in CR or PR. Immune response against the virus may participate to the prevention of relapse.

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P429

VENETOCLAX, CHIDAMIDE, AND DECITABINE AS A BRIDGING THERAPY IN RELAPSED/REFRACTORY T LYMPHOBLASTIC CELL LYMPHOMAS WITH LARGE MEDIASTINAL MASSES PRIOR TO CD7 CAR-T CELL THERAPY

Lefu Huang[1,2,3], Xian Zhang[2,3], Peihua Lu[2,3]

Tsinghua University School of Medicine, Beijing, China, [2]Lu Daopei Institute of Hematology, Beijing, China, [3]Hebei Yanda Lu Daopei Hospital, Beijing, China

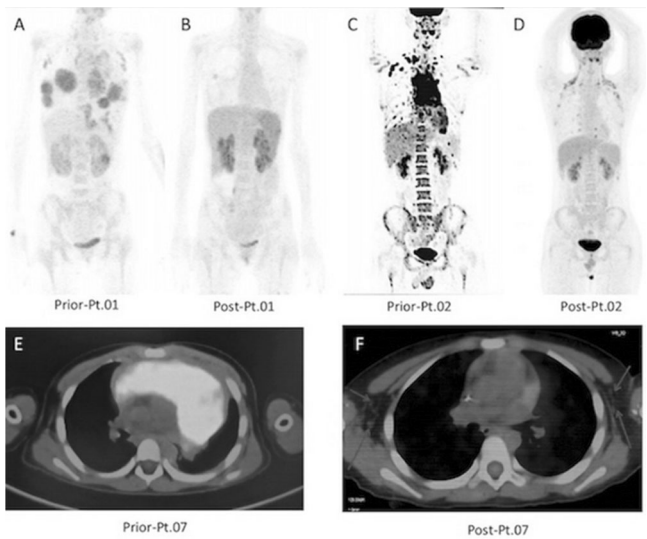
Background: T-cell lymphoblastic lymphoma (T-LBL) is a highly aggressive T-type malignancy, especially with mediastinal masses. Effective treatment has been elusive, long-term survival in relapsed/refractory (R/R) T-LBL patients remains poor. In our previous study, we described CD7 CAR-T cell therapy yielded 70% of complete remission (CR) rate in R/R T-LBL patients and maintained MRD-negative status and alive after transplantation. However, the safety, such as Cytokine release syndrome (CRS) level, was associated with the patient's tumor burden before infusion.

Methods: A single-arm, prospective clinical trial was designed to further explore the efficacy of Venetoclax, Chidamide, and Decitabine as a bridging therapy in R/R T-LBL with large mediastinal masses prior to CD7 CAR-T cell therapy. Eligible R/R T-LBL patients were enrolled, receiving Venetoclax (100mg-200mg/d) Chidamide (5mg/10kg, BIW), and Decitabine (10mg d1-d5) followed by CD7 CAR-T cell infusion. PET-CT was performed to evaluate the response rate.

Results: A total of 7 eligible patients received Venetoclax, Chidamide, and Decitabine followed by CD7 CAR-T cell infusion with a median age of 14 years old (8-46) and a median of 3 prior lines of therapies (2-5 lines). All 7 T-LBL patients had large mediastinal mass, with the maximum can reach 18cm in diameter

Patient No.	Age (years)	Gender	Maximum diameter of mass (cm)	Prior lines of chemotherapy	High risk factors of Genetic	Efficacy of bridging therapy	Efficacy on Day 28	CRS Grade	peak levels of CAR7 cells
Pt.01	35	F	8	3	Yes	CR	CR	2	81.69%
Pt.02	14	M	11	2	Yes	CR	CR	1	92.8%
Pt.03	14	M	6	5	NO	PR	CR	0	39.54%
Pt.04	14	F	9	2	Yes	SD	PR	3	81.92%
Pt.05	46	M	7.5	3	NO	NR	NR	2	76.73%
Pt.06	12	F	12	3	Yes	PR	CR	1	86.93%
Pt.07	8	M	8	3	Yes	PR	CR	0	95.11%

(Pt.07). Of 7 patients, 5 patients had genetic risk factors, such as TP53 mutation positive, MYC and TRA/D fusion genes positive, CDKN2A biallele loss, multiple multiple chromosome karyotype abnormalities, especially Pt.01 had multiple risk factors, such as t (8; 14) (q24.1; q11.2), MYC+ and TRA/D fusion gene positive and IKZF gene mutation positive, which predicts an extremely poor prognosis(Table 1). Similarly, 3 patients cohld be diagnosed with double hit T-LBL with MYC and BCL-2 or BCL-6 positive. In addition, four patients were accompanied by large pleural effusion, indicating advanced disease and possibly severe CRS reactions, such as hypoxemia. The best overall response rate was 71.43% (5/7), including 28.57% (2/7) CR) and 42.86% (3/7) partial remission (PR). Furthermore 57.14% (4/7) patients were able to successfully bridge to the intended CD 7 CAR-T cell therapy without additional chemotherapy in addition to FC chemotherapy, which further resulted in a 3-month PFS of 57.14% (4/7) calculated from bridging therapy initiation. Then, 6 patients received the CD7 CAR-T cells at a fixed dose of 1×10^6/kg, except for one patient who received CAR-T cells at a dose of 2×10^6/kg2×10^6/kg due to rapid disease progression. At the day 28 assessment, 85.71% (6/7) patients achieved overall response, including 71.43% (5/7) CR and 14.29% (1/7) PR, respectively. Among of them, All 3 patients (Pt.01, Pt.02, Pt.07) with extremely high risk and large mediastinal mass achieved remission achieved CR (Figure 1). Despite impressive CR rates were achieved, majority of patients had mild CRS (grade 0-2). Only 1 patients experienced grade 3 CRS, and no patient developed neurotoxicity.



Conclusions: This clinical trial demonstrates promising efficacy of Venetoclax, Chidamide, and Decitabine as a bridging therapy in relapsed/refractory T-LBL with large mediastinal masses, although this not a randomized trial.

Clinical Trial Registry: NCT04572308

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P430

EXCELLENT SURVIVAL AFTER ALLOGENEIC HAEMATOPOIETIC CELL TRANSPLANTATION IN PATIENTS WITH RELAPSED OR REFRACTORY HOGDKIN LYMPHOMA IN THE ERA OF IMMUNOTHERAPY

Anna Czyz[1], Kateryna Filonenko[2], Anna Kopinska[3], Grzegorz Helbig[3], Anna Lojko[4], Lidia Gil[4], Maciej Majcherek[1], Tomasz Wrobel[1], Malgorzata Ociepa[5], Tomasz Czerw[5], Agnieszka Piekarska[2], Magdalena Dutka[2], Maria Bieniaszewska[2], Sywia Bartyzel-Palinska[6], Patrycja Mensah-Glanowska[6], Sebastian Giebel[5], Jan Maciej Zaucha[2]

[1]Wroclaw Medical University, Wroclaw, Poland, [2]Gdansk Medical University, Gdansk, Poland, [3]Silesian Medical University, Katowice, Poland, [4]Poznan University of Medical Sciences, Poznan, Poland, [5]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch, Gliwice, Poland, [6]Jagiellonian University Collegium Medicum, Krakow, Poland

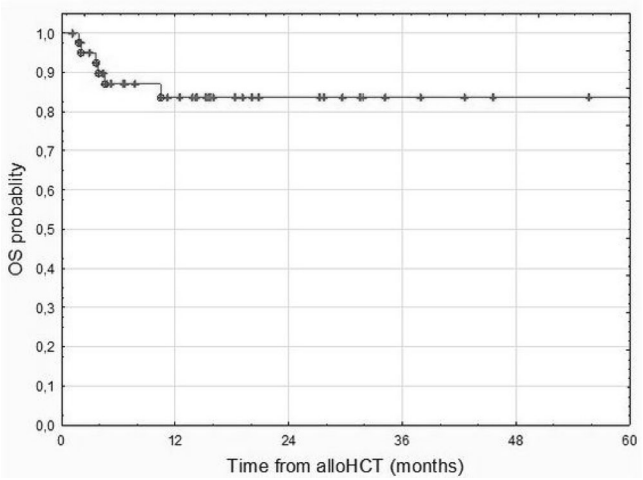
Background: Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative option for patients with refractory or relapsed (r/r) Hodgkin lymphoma (HL). The use of new and potent agents in r/rHL such as brentuximab vedotin (BV) and immune checkpoint inhibitors (CPIs) improves the response rate before transplantation, however, it is not clear if this translates to better outcomes, mainly due to concerns about CPI increased risk of graft-versus-host disease (GvHD) and non-relapse mortality (NRM). The study aimed to evaluate outcomes in r/rHL patients who received BV and/or CPIs before allo-HCT.

Methods: All consecutive adult HL patients who received BV and/or CPIs before allo-HCT from matched related donor (MRD), matched (10/10) unrelated donor (MUD), mismatched (9/10) unrelated donor (mMUD) or haploidentical donor at the Polish Lymphoma Research Group allied centers were identified.

Results: Forty one patients (median age at allo-HCT 33 years, range 20-56; 14/41 females) transplanted between 2013 and 2022 were included in the analysis. All but one of the analyzed patients relapsed after auto-HCT. The median time between auto-HCT and relapse was 5 months (1-104). Patients received a median of 2 lines of chemotherapy (2-8) before auto-HCT and a median of 1 line (0-2) after auto-HCT. Of the total 41 patients, 12 (29%) were treated with BV before allo-HCT, 14 (34%) with nivolumab, and 15 (37%) first with BV and then with nivolumab. Finally, at the time of allo-HCT, 22 patients (54%) achieved complete response and 16 (39%) partial response. In nivolumab-treated patients, the median

time from the end of immunotherapy to allo-HCT was 13 weeks (2-152). Patients received MAC (18; 44%), RIC (20; 49%) or non-myeloablative conditioning (3; 7%) and graft from either MRD (12; 29%), MUD (20; 49%), mMUD (2; 0.5%), or haploidentical donor (7; 17%). GvHD prophylaxis was based on post-transplant cyclophosphamide (22; 54%) or consisted of cyclosporine combined with MTX (with or without ATG) in transplants from MRD or MUD (19, 46%). Grade 3-4 acute GvHD occurred in 6/41 patients (14%), all of whom were treated with nivolumab prior to allo-HCT, but the difference in GvHD rate compared to those who were not treated with nivolumab was not significant (21% vs 0%, $p = 0.16$). Moderate or severe chronic GvHD occurred in 3 of 37 evaluable patients (8%), and similarly, all of these patients were treated with nivolumab (12% vs 0%, $p = 0.54$). After the median follow-up of 16 months (1-98), the 2-year LFS and OS was 81% (95%CI65-90) and 84% (95%CI68-92), respectively. In univariate analysis, there were no significant differences in survival regarding prior nivolumab treatment, disease status at transplant, donor type, conditioning or GvHD prophylaxis. The 2-year NRM and relapse incidence (RI) in the whole study group was 13.5% (95%CI6-31) and 5.5% (95%CI1-21), respectively, with no significant differences found between patients treated or not with nivolumab before allo-HCT.

Conclusions: Our findings confirm that allo-HCT is highly curative option for heavily pretreated HL patients in the era of immunotherapy. It provides excellent survival with low RI, acceptable NRM, and acceptable acute and chronic GvHD rates.



Clinical Trial Registry: not applicable

Disclosure: AC reports honoraria for lectures from Takeda and BMS.
GH reports honoraria for lectures from Takeda and BMS
LG reports honoraria for lectures from Takeda and BMS
TC reports honoraria for lectures from Takeda and BMS
TW reports honoraria for lectures from Takeda and BMS
MB reports honoraria for lectures from Takeda and BMS
SG reports honoraria for lectures from Takeda and BMS
JMZ reports honoraria for lectures from Takeda and BMS

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P431

IDENTIFICATION OF PULMONARY AND CLINICAL RISK FACTORS IN PATIENTS WITH LYMPHOMA CONDITIONED WITH BEAM AND TEAM BEFORE AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Radu-Florian Gherman[1], Sophie Ewald[1], Gabriele Ihorst[1], Tim Strüssmann[1], Robert Zeiser[1], Ralph Wäsch[1], Hartmut Bertz[1], Daiana Stolz[1], Justus Duyster[1], Jürgen Finke[1], Reinhard Marks[1], Monika Engelhardt[1], Jesus Duque-Afonso[1]

[1]University of Freiburg, Freiburg, Germany

Background: Organ dysfunction, including pulmonary function impairment and coexistent comorbidities, plays a key role in the use of high-dose chemotherapy prior to autologous hematopoietic stem cell transplantation (auto-HSCT) in patients with lymphoma. In order to reduce pulmonary toxicity, efforts have been made to replace BCNU/carmustine from BEAM (BCNU/carmustine, etoposide, cytarabine, melphalan) conditioning by other non-pulmonary substances such as thiotepa (TEAM). We retrospectively analyzed the impact of pulmonary function and other clinical characteristics on outcome in patients conditioned with BEAM or TEAM prior to auto-HSCT at our institution.

Methods: 354 patients with lymphoma undergoing auto-HSCT (305 conditioned with BEAM and 49 with TEAM) at our institution between 2008 and 2020 were included in this study. In patients treated with BEAM, the median follow-up was 47 months (range: 0.5-163), whereas with TEAM were followed up for a median of 22 months (range:0.5-149). We applied the Cox proportional hazards regression model to calculate HR and confidence intervals (CI) for overall survival (OS) and progression-free survival (PFS) for uni- und multivariate analyses; and the Fine and Gray model to determine cumulative incidence rates and sub-distribution hazard ratios (SHR) for relapse incidence and non-relapse-mortality (NRM) rates.

Results: Clinical characteristics of the patients in both cohorts were similar. However, a higher proportion of patients conditioned with TEAM had a decreased Karnofsky-performance-score (KPS) ≤ 80% (50% vs 27%; p-value < 0.001) and a reduced median diffusion capacity of carbon monoxide corrected for hemoglobin (DLCOcSB) (median values 66% vs. 78% of predicted; p-value < 0.001) compared to patients treated with BEAM.

In the univariate analysis, conditioning with BEAM provided a longer PFS (HR 1.74; CI 1.07, 2.83; p-value 0.025) and lower relapse rate (SHR 1.76; CI 1.07, 2.92; p-value 0.026) but similar OS (HR 1.58; CI 0.88, 2.82; p-value 0.12) and NRM (HR 1.44; CI 0.42, 4.88; p-value 0.56) compared to TEAM. In the multivariate analysis, DLCOcSB ≤60% of predicted, progressive disease status (PD) prior auto-HSCT, KPS ≤ 80% and a Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) score ≥5 were associated with decreased OS in patients treated with BEAM, but only PD prior to auto-HSCT could be also identified in patients treated with TEAM.

Impaired lung function defined as DLCOcSB ≤60% was associated with lower OS (HR 4.10; CI 2.38, 7.05; p-value < 0.001) and PFS (HR 2.62; CI 1.58, 4.34; p-value < 0.001) and higher NRM (SHR 5.91; CI 2.07, 16.87; p-value < 0.001) in patients conditioned with BEAM. In contrast, no association between lung function impairment and worse outcomes could be demonstrated in patients conditioned with TEAM. In subgroup analysis including only patients with clinical features such as age≥65 or HCT-CI ≥ 5 or DLCOcSB≤60%, no significant differences on outcome were found between patients conditioned with BEAM vs TEAM.

Conclusions: In summary, we have identified clinical risk factors and abnormalities in pulmonary function tests associated with worse outcome in patients conditioned with BEAM compared to TEAM before auto-HSCT. Our data suggest TEAM conditioning as a valid alternative for patients with DLCOcSB ≤60% of predicted, age >65 years old, HCT-CI score ≥5 and/or KPS ≤ 80%.

Disclosure: JD-A has received speaker's honoraria from Roche, Amgen, AstraZeneca, Riemser, Lilly, Ipsen and Sobi and travel support from AstraZeneca, Gilead and Sobi.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P432

LIQUID BIOPSY BY ULTRA-DEEP SEQUENCING MONITORING IMPROVES EARLY RELAPSE DETECTION AFTER CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN FOLLICULAR LYMPHOMA PATIENTS

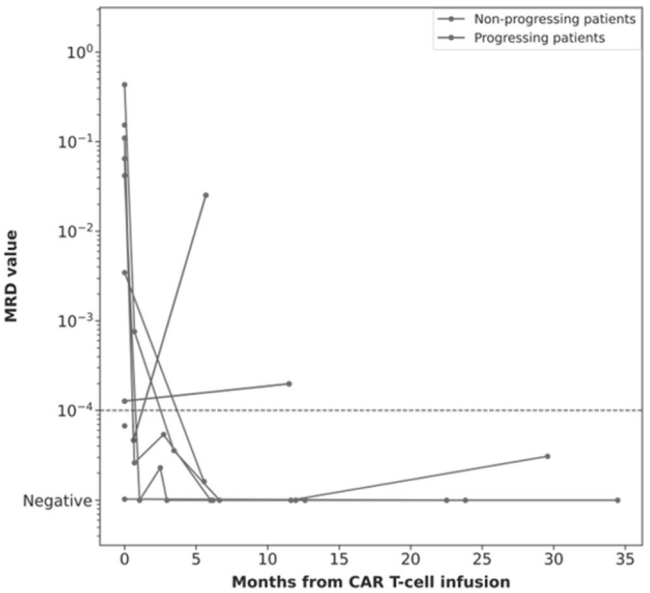
Ana Jimenez Ubieto[1], Alejandro Martin[2], María Poza[1], Yanira Ruiz-Heredia[2], Sara Dorado[2], Antonia Rodriguez[1], Tycho Baumann[1], José María Sánchez Pina[1], María Calbacho[1], Laura Rufian[1], Pilar Martinez[2], Pilar Sarandeses[1], Enrique Revilla[1], Margarita Rodriguez[1], Inmaculada Rapado[1], Miguel Gallardo[3], Rosa Ayala[1], Joaquín Martinez López[1], Santiago Barrio[1]

[1]Hospital 12 de Octubre, Madrid, Spain, [2]Altum sequencing Co, Madrid, Spain, [3]CNIO, Madrid, Spain

Background: Despite Follicular lymphoma (FL) is considered an indolent disorder with a relatively favorable course, some patients have a more aggressive course and a poorer outcome. Chimeric antigen receptor (CAR) T-cell therapy has improved outcomes for relapse/refractory patients. However, nearly 40% of the CAR T-cell treated patients will either fail to respond or relapse after therapy. Currently, PET/CT scans are used to assess response in FL. The prognostic value of circulating tumor DNA (ctDNA) after CAR-T cell therapy in FL has never been explored.

Methods: A total of 12 FL patients treated with CAR-T cell therapy were included (10 Tisa-cel, 2 Liso-cel). Genomic profiling was performed before starting lymphodepleting chemotherapy to identify somatic mutations suitable for liquid Biopsy MRD monitoring (LiqBio-MRD) as previously reported (Jiménez Ubieto et al; Leukemia 2022). The screening was performed on gDNA from FFPE lymph node biopsies and ct DNA from plasma samples. Then, the LiqBio-MRD method was applied to 70 follow-up plasma samples. PET/CT examinations were performed on day 90, 180, 365 and every six months after that.

Results: After a median follow-up is 33 (13-42) months, eight patients (73%) achieved complete (CR), two partial response (PR) and one progression (PD). In total three patients progressed after infusion (3-12 months). We found trackable mutations in all the patients (100% lymph node and 63 % liquid biopsy baseline samples). A median of 2.3 (1-8) mutations were detected at baseline, been the most frequently mutated genes CREB, KMT2D and EP300. No differences between the number of mutations or genes affected between long-term CR patients and relapse/refractory were observed. All the progressing patients were MRD-positive before progression. All durably responding patients had undetectable ct DNA at or before three months after infusion. Dynamics of ct DNA LiqBio-MRD are shown in figure 1. At day +28, patients with detectable ct DNA compared with those with undetectable c tDNA had a median PFS of 6 months vs not reached (P = .0009). Besides the 3 progressing patients, 4 additionally patients (33%) presented a positive PET/TC test during follow-up (8, 9, 18 and 31 months after infusion). A biopsy was confirmatory of "necrosis" without lymphoma viability in 2 patients, other was diagnosed with breast cancer and the other presented a rectal abscess. Interestingly, ct DNA LiqBio-MRD In these patients was constanstelly negative (figure 1).



Conclusions: Noninvasive MRD evaluation in liquid biopsy permits the risk stratification and outcome prediction of patients undergoing CAR-T cell therapy for treating FL. It could be also used to detect false positives PET/TC assessments during follow-up. These results provide a rationale for designing ct DNA-based risk-adaptive clinical trials.

Disclosure: Financial support: 2022/0101/PROGRAMA CRIS DE TALENTO CLÍNICO 2021 and 2022/0010/INSTITUTO DE SALUD CARLOS III FIS PROJECT.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P433

OUTCOME OF HIGH DOSE CHEMOTHERAPY FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION IN RELAPSED/ REFRACTORY HODGKIN LYMPHOMA ACHIEVING DISEASE RESPONSE AFTER DIFFERENT NUMBERS OF SALVAGE REGIMENS

jacopo Mariotti[1], Francesca Ricci[1], Chiara De Philippis[1], Daniele Mannina[1], Barbara Sarina[1], Daniela Taurino[1], Carmelo Carlo-Stella[1], Armando Santoro[1], Stefania Bramanti[1]

[1]IRCCS Humanitas Research Hospital, Rozzano, Italy

Background: In the last few years, brentuximab vedotin (BV) and immune checkpoint inhibitors (CPI) have offered new treatment opportunities for patients with relapsed/refractory Hodgkin lymphoma (R/R HL). Up to now, the standard of care for patients responsive to either BV or CPI is generally represented by a consolidation with allogeneic stem cell transplantation (Allo-SCT) (De Philippis C, Blood Adv 2020). More recently, autologous transplantation (Auto-Tx) has been employed as consolidation strategy also for patient refractory to more than 2 lines of therapy, if a response has previously been achieved by BV (Lucchini E, Hematol Reports 2021) or CPI (Merryman RW, Blood Adv 2021). This is a retrospective study aiming to compare the outcome of patients receiving high-dose-chemotherapy (HDC) and Auto-Tx as consolidation treatment after complete remission (CR) or very good partial remission (PR) independently by the line of therapy utilized.

Methods: Between January 1998 and December 2021, 92 subjects with R/R HL were selected for the purpose of analysis: 80

treated with second line salvage chemotherapy, either IGEV (n = 41) or BEGEV (n = 39), and 12 receiving BV as third line or CPI as third/fourth line of treatment, respectively. We analyzed the 2 cohorts of patients: those responsive to standard second line therapy (IGEV and BeGEV) and responsive to third (BV) and fourth (CPI) salvage therapy.

Results: All patients had responsive disease and were either in CR (n = 70) or PR (n = 10). Of note, 8 (2 in the BV/CPI and 6 in the IGEV/BEGEV cohort) out of 10 patients converted to CR after transplant. The two cohorts were comparable in terms of refractory vs relapsed disease, time to relapse (≤12 vs > 12 months) and extranodal involvement at relapse. Median follow-up was 47,9 months for patients transplanted after IGEV/BEGEV and 32,2 months for new drugs cohort. Twenty-one patients had relapsed or progressed, 13 after IGEV, 7 after BEGEV and 1 in the new drugs cohort, at a median of 8,9 months (range 0.9-55.6). The amount of infused CD34+ cells was slightly higher for IGEV/BEGEV relative to BV/CPI cohort (median CD34+ cells 5,95 and 5,25x10^6/Kg), with no difference in terms of time of engraftment (median day 14 and 15). Side effects were similar in terms of infections (all patients developed at least one infectious episode) and mucositis (G3 or higher, 56% vs 50%).

Three-year overall (OS), progression free survival (PFS) and cumulative incidence (CI) of relapse for IGEV/BEGEV and new drugs cohorts were 84% and 88% (p = 0.668), 75% and 91% (p = 0.238) and 27% and 9% (p = 0.247), respectively. In particular, patients in CR had similar outcomes in terms of 3-year OS (85% and 86%, p = 0.832), PFS (78% and 89%, p = 0.395) and CI of relapse (25% and 11%, p = 0.421).

Conclusions: Even with the limit of the small sample size, our results suggest that HDC and Auto-Tx, rather that Allo-SCT, may be considered the standard consolidation treatment for R/R HL when disease response is achieved by BV or CPI even beyond 2nd line of treatment.

Disclosure: The authors have no conflict of interest to disclose.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P434

ENCOURAGING OUTCOMES IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR RELAPSED/REFRACTORY LYMPHOMA PATIENTS: EFFICACY OF A NEW INTENSIFIED APPROACH USING LYMPHOMA-ORIENTED CHEMOTHERAPY AND REDUCED-INTENSITY CONDITIONING REGIMEN

Mizuki Watanabe[1,2], Sung-Won Kim[1], Wataru Takeda[1], Takashi Tanaka[1], Ayumu Ito[1], Yoshihiro Inamoto[1], Takahiro Fukuda[1]

[1]National Cancer Center Hospital of Japan, Tokyo, Japan, [2]Kyoto University Hospital, Kyoto, Japan

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) for patients with relapsed/refractory non-Hodgkin lymphomas (NHLs) remains challenging. In the current climate where reduced-intensity conditioning (RIC) regimens are preferred, approaches to intensify anti-lymphoma effects by adding lymphoma-oriented chemotherapies to RIC should be addressed. We retrospectively examined the outcomes of allo-HSCT using a sequential approach consisting of lymphoma-oriented chemotherapies followed by allo-HSCT using RIC regimens (sequential intensified-RIC allo-HSCT).

Methods: Between 2014 and 2021, 54 patients with refractory/relapsed lymphomas (aggressive B-NHL: n = 25, indolent B-NHL: n = 4, extranodal NK/T-cell lymphoma [ENKTL]: n = 4, peripheral T-cell lymphomas [PTCLs]: n = 21) received sequential intensified-RIC allo-HSCT. In all cases, the conditioning regimen was initiated before complete neutrophil recovery from the prior chemotherapy. Overall survival (OS) and relapse/progression-free survival (PFS) was assessed utilizing the Cox proportional hazard multivariate model, using variables selected manually in the preceding univariate analysis with $P < 0.05$.

Results: Median age was 56 years (range, 19-69) and median follow-up period for survivors was 2 years (range, 0-7). RIC regimens were Fludarabine (Flu)-Busulfan (Bu) in 18 patients, Flu-Melphalan (Mel) based regimens in 28 and Flu-Bu-Mel in 7. Low-dose TBI was used in 24 patients and the focal radiation to the involved sites was concurrently used in 11. Lymphoma status before the initiation of chemotherapy was stable disease/progressive disease (SD/PD) in 30, partial response (PR) in 20, and complete response (CR) in 4, respectively.

Two-year OS and PFS were 48.8% and 38.9%, respectively. Cumulative incidence of progression/relapse and non-progression/relapse mortality (NRM) at 2 years was 39.1% and 23.3%, respectively. OS stratified by lymphoma status before the preceding chemotherapy were 66.7% in CR, 48.1% in PR and 48.9% in SD/PD patients. Patients with SD/PD or PR lymphoma status showed frequent disease progression within 1 year (SD/PD: 48.5%, PR: 30.0%), while no progression was observed beyond 2 years after the transplant. Indolent B-NHL and ENKL showed no relapse/progression after allo-HSCT.

In multivariate analysis, male gender and the history of autologous HSCT negatively affected OS (vs female: HR 2.43, p = 0.049; vs no history of auto-HSCT: HR 4.12, p = 0.005) and PFS (vs no history of auto-HSCT: HR 2.58, p = 0.042). Lymphoma status of PR and SD/PD showed comparable outcomes (vs SD/PD, OS: HR 0.82, p = 0.629; PFS: HR 0.87, p = 0.712; progression/relapse: OS: HR 0.61, p = 0.284; NRM: HR 2.02, p = 0.271). Age over 50 was strongly associated with a higher risk of mortality: all 11 patients who died of non-progression/relapse causes were over 50 years old at transplantation.

Conclusions: Allo-HSCT using sequential intensified-RIC for refractory/relapsed NHLs showed acceptable outcomes even in patients with PR or SD/PD lymphoma status. This strategic approach potentially could be a key to improving poor outcomes in this difficult-to cure population, although high frequencies of progression/relapse remain issues. Elderly patients (over 50 years of age) might not be a good candidates for this approach due to the high risk of NRM. Since this is a retrospective study in a small cohort, future prospective studies in larger cohorts should be encouraged.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P435

AUTOLOGOUS VERSUS ALLOGENEIC STEM CELL TRANSPLANTATION IN PATIENTS WITH ANGIO-IMMUNOBLASTIC T-CELL LYMPHOMA

Mesire Aydin[1], Man Wai Tang[1], Bart J. Biemond[1], Marie José Kersten[1], Joost S. P. Vermaat[2], Erfan Nur[1]

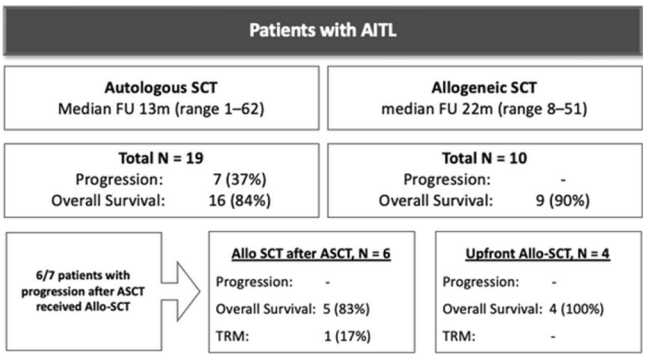
[1]Amsterdam University Medical Centers, Amsterdam, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands

Background: Angio immunoblastic T-cell lymphoma (AITL) is an uncommon type of peripheral T-cell lymphoma. One of the key characteristics of AITL is abnormal immune reactions and inflammation. Transplant eligible and chemotherapy sensitive AITL patients are often treated with induction chemotherapy followed by high dose chemotherapy and autologous stem cell transplantation (ASCT) as first-line therapy. The 5-year overall

survival (OS) of patients with T-cell lymphoma undergoing consolidation with ASCT was superior to that of patients receiving induction chemotherapy only (78% vs 45%) (Brink et al., 2022). Treatment of refractory/relapsed disease remains challenging. Recent studies show a good disease-free survival (DFS) after allogeneic stem cell transplantation (Allo-SCT) in patients with refractory/relapsed AITL. However, most of these studies reported single arm small cohorts or case reports, which are difficult to compare. We questioned whether Allo-SCT might result in improved DFS compared to ASCT in patients with AITL. As AITL seems to be an immunogenic disease, Allo-SCT could potentially be used as a first-line treatment in transplant eligible patients with AITL. In this study, we retrospectively compared the survival outcomes of transplantation eligible patients with AITL who underwent either ASCT or Allo-SCT.

Methods: Patients with histologically confirmed diagnosis of AITL and treated with either ASCT or Allo-SCT between 2010 and 2020 were included. Eligible allogeneic donor grafts included both related and unrelated donors. The primary endpoint was DFS, while secondary endpoints included relapse incidence and treatment related mortality (TRM).

Results: Twenty-three patients with AITL treated with ASCT and/or Allo-SCT were included in this study. There were 12 male and 11 female patients with the median age at transplantation of 58 years. A total of 19 patients underwent ASCT as first-line treatment. Six of these patients received a subsequent Allo-SCT due to relapsed disease. Four other patients had refractory disease after induction therapy and were treated with reduced intensity conditioning and upfront Allo-SCT. At 2 years, the DFS was 51% for ASCT and 90% for Allo-SCT ($p = 0.026$). Relapse rate was 44% in the ASCT group compared to 0% in the Allo-SCT group ($p = 0.019$). One patient in the Allo-SCT group died of TRM (10%).



Conclusions: In this (retrospective)exploratory study, allogeneic stem cell transplantation resulted in improved disease-free survival as compared to autologous stem cell transplantation in patients with AITL. Additionally, to improve the power of this study, more patients from other academic centers in the Netherlands will be included. More studies are needed to elucidate whether Allo-SCT should be considered as an adequate alternative to ASCT as first-line consolidation treatment in transplant-eligible patients. The omission of the myeloablative chemotherapy prior to ASCT might reduce the risk of toxicity of subsequent Allo-SCT, potentially further improving the outcomes of Allo-SCT.

Disclosure: **Kersten:** *BMS/Celgene:* Honoraria, Research Funding; *Kite, a Gilead Company:*Honoraria, Research Funding; *Miltenyi Biotech:* Honoraria; *Novartis:* Honoraria; *Roche:* Honoraria, Research Funding; *Takeda:*Honoraria; *Adicet Bio:* Honoraria.

Biemond: *Modus Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Chiesi:* Membership on an entity's Board of Directors or advisory committees; *Novo Nordisk:* Membership on an entity's Board of Directors or advisory committees; *Celgene:* Membership on an entity's Board of Directors or advisory committees; *CSL Behring:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Bluebird Bio:* Membership on an entity's Board of Directors or advisory committees; *BMS:*Research Funding; *GBT:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Sanquin:*Research Funding.

Nur: *Novartis:* Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P436

IMPACT OF THIOTEPA DOSE-INTENSITY IN PATIENTS WITH PRIMARY LARGE B-CELL LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM (PCNSL) UNDERGOING AUTOLOGOUS TRANSPLANTATION (AUTOHCT) WITH THIOTEPA/ CARMUSTINE (TT-BCNU) CONDITIONING

Shanze Arshad[1], Fang Xi[2], Kwang Ahn[2], Manmeet Kaur[2], Michael Scordo[3], Craig Sauter[4], Mehdi Hamadani[2]

[1]University of Kentucky, Lexington, United States, [2]Medical College of Wisconsin, Milwaukee, United States, [3]Memorial Sloan Kettering Cancer Center, New York, United States, [4]Cleveland Clinic Foundation, Cleveland, United States

Background: AutoHCT is an accepted consolidation strategy for patients with PCNSL. We recently showed that the two common conditioning regimens used for autoHCT in PCNSL, thiotepa/busulfan/cyclophosphamide (TBC) and TT-BCNU, provide comparable outcomes (Scordo. JAMA Onc 2021). Among TT-BCNU recipients the total thiotepa dose varies, with some centers administering a total dose of 20mg/kg (Ferreri. Lancet Haematology 2017), while others 10mg/kg (Khurana. BBMT 2017). The impact of thiotepa dose-intensity on autoHCT outcomes in not known. Using publicly available CIBMTR data, we retrospectively compared outcomes for PCNSL patients undergoing autoHCT following TT-BCNU conditioning using either the 10mg/kg or the 20mg/kg total thiotepa dose.

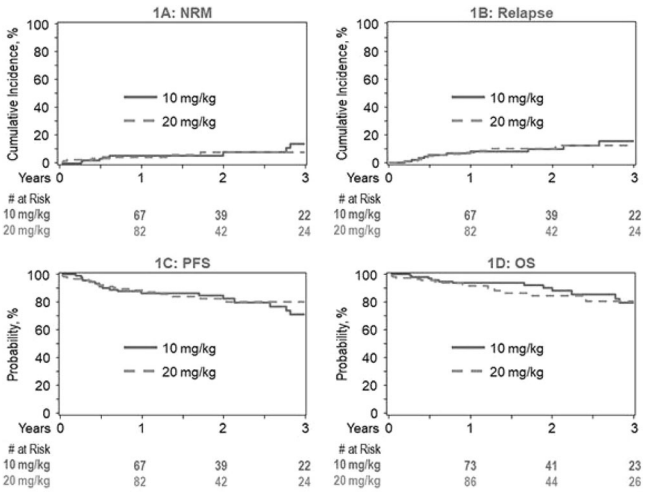
Methods: Two hundred and eighteen adult PCNSL patients who underwent a first autoHCT with TT-BCNU condition between 2011–2018 were included. 90 patients received total thiotepa dose of 10mg/kg (TT-10 group), while 128 received the 20mg/kg total thiotepa dose (TT-20 group). The endpoint analyzed included (a) time to hematopoietic recovery, (b) relapse/progression, (c) non-relapse mortality (NRM), (d) progression-free survival (PFS) and (e) overall survival (OS). Cox proportional hazard analysis was used to identify prognostic factors for relapse, NRM, PFS, and OS. Variables considered in regression model include patient age, sex, race, performance status, HCT-comorbidity index (HCT-CI), rituximab use during conditioning, interval between diagnosis and HCT, and remission status. Covariates with a $p < 0.05$ were considered significant.

Results: Baseline characteristics are presented in **Table 1**. The median follow-up of survivors was 22 (range 5-72) months. The cumulative incidence of neutrophil recovery at 1-month for the two groups were: TT-10 99% (95%CI = 88-100%) and TT-20 99% (95%CI = 88-100%), respectively ($p = 0.88$). The cumulative incidence of 1-year NRM for TT-10 and TT-20 cohorts were 6% (95% CI = 2-12%) vs. 4% (95%CI = 1-8%), respectively ($p = 0.66$). The 3-year cumulative incidence of relapse (15% vs. 13%; $p = 0.67$), PFS (71% vs 80%; $p = 0.25$) and OS (79% vs 83%; $p = 0.56$; **Figure 1**) were not significantly different in the TT-10 and TT-20 groups,

respectively. On multivariable regression analysis compared to TT-10, the TT-20 cohort was not associated with significantly different risk of NRM (Hazard ration [HR] = 0.79; 95%CI = 0.28-2.2; p = 0.64), relapse/progression (HR = 0.87; 95%CI = 0.38-1.98; p = 0.74), PFS (HR = 0.80; 95%CI = 0.42-1.5; p = 0.48) or OS (HR = 1.10; 95% CI = 0.51-2.4; p = 0.80). Male sex was associated with a significantly lower of mortality (HR = 0.41; p = 0.03), while HCT-CI of 3 or more, predicted for a higher risk of mortality (HR = 3.39; p = 0.03). Relapse of primary disease was the most common cause of death in both cohorts: TT-10 11.1% (n = 10) and TT-20 7% (n = 9).

Table 1

	Thiotepa 10mg/kg (N = 90)	Thiotepa 20mg/kg (N = 128)
Median Age, years (range)	62 (25-76)	60 (23-78)
Male Sex (%)	43 (47.8%)	79 (61.7%)
KPS 90-100, (%)	37 (41.1%)	54 (42.2%)
Patient Race		
White	76 (84.4%)	105 (82%)
Non-White	10 (11.1%)	16 (12.5%)
Missing	4 (4.4%)	7 (5.5%)
Remission status		
CR1	59 (65.6%)	75 (58.6%)
CR2+	19 (21.1%)	13 (10.2%)
PR	12 (13.3%)	40 (31.3%)
HCT-CT 3 or more (%)	46 (51.1%)	61 (47.7%)
Median lines of therapy (range)	1 (1-3)	1 (1-3)



Conclusions: In this registry analysis in patients with PCNSL undergoing TT-BCNU conditioning, we found no statistically significant advantage of higher thiotepa dose-intensity (20mg/kg), when compared to 10mg/kg dose in terms of NRM, relapse, PFS or OS. These findings have potential pharmacoeconomic implications for HCT centers.

Disclosure: Mehdi Hamadani reports: **Research Support/ Funding:** ADC Therapeutics; Spectrum Pharmaceuticals. **Consultancy:** Incyte Corporation, MorphoSys, SeaGen, Gamida Cell, Novartis, Legend Biotech, Kadmon, ADC Therapeutics; Omeros, Abbvie, Caribou, CRISPR, Genmab, Kite.

Speaker's Bureau: 2022 = Sanofi Genzyme, AstraZeneca, BeiGene, ADC Therapeutics, Kite.

DMC: Myeloid Therapeutics. M. Scordo reports: Clinical trial research support to institution: Angiocrine Bioscience, Inc.; Omeros Corporation; Amgen, Inc. Consultancy: Omeros Corporation; Angiocrine Bioscience, Inc. (past); McKinsey & Company (past). Ad-hoc advisory board: Kite – A Gilead Company (past) CME activity honorarium: i3Health; Medscape, LLC. (past).

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P437

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION FOR MARGINAL ZONE LYMPHOMAS – MULTICENTER ANALYSIS BY THE POLISH LYMPHOMA RESEARCH GROUP

Joanna Drozd-Sokolowska[1], Małgorzata Sobczyk-Kruszelnicka[2], Anna Kopińska[3], Elżbieta Sienkiewicz[4], Joanna Romejko-Jarosińska[5], Mariola Sędzimirska[6], Agnieszka Tomaszewska[1], Kateryna Filonenko[7], Grzegorz Helbig[3], Jan Maciej Zaucha[7], Grzegorz Basak[1], Sebastian Giebel[2], Tomasz Czerw[2]

[1]Medical University of Warsaw, Warsaw, Poland, [2]Maria Sklodowska-Curie Institute-Cancer Center, Gliwice Branch, Gliwice, Poland, [3]Medical University of Silesia, Katowice, Poland, [4]Warsaw University of Technology, Warsaw, Poland, [5]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland, [6]Lower Silesian Center for Cellular Transplantation with National Bone Marrow Donor Registry, Wroclaw, Poland, [7]Medical University of Gdansk, Gdansk, Poland

Background: Marginal zone lymphomas (MZL) are a rare subtype of indolent mature B-cell lymphomas. According to the World Health Organization (WHO) 2016 classification they were subdivided into three entities, i.e., extranodal MZL (EMZL) of mucosa-associated lymphoid tissue, splenic MZL (SMZL), and nodal MZL (NMZL). All three entities, although reorganized, were retained in the 5th edition of the WHO classification.

Despite significant progress in the treatment of indolent lymphomas, treatment options for MZL are still limited, including CAR-T-cell therapy showing only modest efficacy. Additionally, there is an inherent risk of progression of MZL to more aggressive lymphomas (transformed MZL, t-MZL), which require a more intensive therapeutic approach.

Here we analyze the results of autologous hematopoietic cell transplantation (auto-HCT), still considered an option for relapsed/refractory disease, performed for either MZL or t-MZL.

Methods: Retrospective analysis of all consecutive patients diagnosed with MZL/t-MZL who underwent auto-HCT as part of their treatment.

Results: Forty-five patients were included (35 MZL, 10 t-MZL), 20 (44%) were females, and the median age at auto-HCT was 54 years (range, 32-71). EMZL was the most predominant subtype at diagnosis (25/42, 60%), with NMZL and SMZL constituting 26% and 14%. The median time from the first diagnosis to auto-HCT was 2.2 years (range, 0.6-11.4). The median number of lines of therapy received for MZL was 2 (range, 1-4), while for t-MZL 1 (range, 1-2).

Thirty-two (71%) patients were in complete (CR), and 12 (27%) in partial (PR) remission at the time of auto-HCT. Twenty-four (53%) patients experienced POD24.

The performance status according to ECOG was 0-1 in 42 (93%), and the HCT-CI comorbidity index was 0-1 in 42/43 (98%) patients.

The conditioning included TBI 12 Gy in 4 (9%) patients, while in others it was only chemotherapy based (41, 91%), most frequently BEAM (21, 47%), BeEAM (12, 27%), and CBV (5, 11%).

All but one patient, who died 13 days after auto-HCT due to infectious complications, engrafted. The median time to ANC > $0.5x10^9$/L was 10 days (range, 7-21), the median time to PLT >$20x10^9$/L 12 days (range, 7-21).

For 42 evaluable patients, the best response assessed after auto-HCT was CR in 38 (90%) patients.

The 4-year overall survival (OS) after auto-HCT was 83% (95%CI, 63-92%) for MZL, while the 2-year OS was 69% (95%CI, 31-88%) for t-MZL, p = 0.5. The respective values for progression-free survival (PFS) were 75% (95%CI, 55-86%) and 69% (95%CI, 31-88%), p = 0.6.

The 2-year cumulative incidence of relapse (CIR) was 11.5% (95%CI, 10-13%), and the 4-year 17% (95%CI, 15-19). There was no statistical difference in CIR between MZL and t-MZL (p = 0.78). Three (6.7%) patients died within 100 days from auto-HCT, translating into 100-day non-relapse mortality of 6.7% (95%CI, 5.6%-7.8%).

Three (7%) patients developed second primary malignancies (SPM), translating into a 4-year cumulative incidence of SPM of 6.4% (95%CI, 5.1-7.7).

Conclusions: Auto-HCT can still be considered a valuable option for carefully selected patients with MZL or t-MZL, allowing for long-term disease control in a significant proportion of patients, including patients with POD24. The risk of SPM is within the range reported for auto-HCT.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P438

THE OUTCOME OF PATIENTS WITH MANTLE CELL LYMPHOMA AFTER HIGH DOSE CHEMOTHERAPY FOLLOWED AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION AT A SINGLE INSTITUTION BETWEEN 2005-2021

Joanna Romejko Jarosinska[1], Ewa Paszkiewicz-Kozik[1], Anna Dabrowska-Iwanicka[1], Martyna Kotarska[1], Monika Swierkowska[1], Anna Borawska[1], Katarzyna Domanska-Czyz[1], Agnieszka Druzd-Sitek[1], Robert Konecki[1], Elzbieta Lampka[1], Ewa Mroz-Zycinska[1], Wlodzimierz Osiadacz[1], Beata Ostrowska[1], Lidia Poplawska[1], Marcin Szymanski[1], Joanna Tajer[1], Lukasz Targonski[1], Grzegorz Rymkiewicz[1], Jan Walewski[1]

[1]Maria Sklodowska-Curie National Research Institute of Oncology, Warszawa, Poland

Background: The induction immunochemotherapy with high-dose cytarabine consolidated by autologous hematopoietic cell transplantation (auto-HCT) has been still standard treatment for fit, transplant-eligible patients with mantle cell lymphoma (MCL). The aim of our retrospective study was to evaluate the outcome of patients who underwent auto-HCT as the consolidation of the first line treatment and to investigate risk factors.

Methods: Between 2005-2021, a total of 126 consecutive patients with a newly diagnosed MCL (classic variant - 104, pleomorphic variant - 13, blastoid variant - 9,) were treated with the induction chemotherapy: R-CHOP/R-DHAP-like (n = 74), R-CHOP/R-IVAC (n = 44) or other chemotherapy regimens (n = 11). Median age was 55 (range: 28-71). Complete remission (CR) before auto-HCT was confirmed in 62 (80%) patients.

Results: Of 126 patients, 104 were proceeded to high dose therapy (HDT) and auto-HCT after first line treatment. The remaining 22 patients (17.5%) received the second line therapy before auto-HCT because of partial response (PR) or stable disease (SD). At a median follow-up of 70 months from auto-HCT, the 5-year progression free survival (PFS) and the 5 year overall survival (OS) for 104 patients who received one line of induction therapy before auto-HCT were 66% (95%CI: 56%, 76%) and 78% (95%C.I.: 70%, 86%), respectively. The 5 year PFS and the 5 year OS for a total 126 patients were 62% (95%CI.: 53%, 71%) and 75% (95%CI: 67%, 83%), respectively. Age more than 60, and disease status before auto-HCT (CR versus PR or SD) were significant risk factors for death and progression. The HR (Hazard Ratio) for death and progression for patients who did not achieve CR before auto-HCT was 2,13 (95%CI: 1.18, 3.18), p = 0.01 and 1.79 (95%CI: 1.06, 3.00), p = 0.02, respectively. The HR for death and progression for patients at age more than 60 were: 1.85 (95%CI: 1.03, 3.34), p = 0.04 and 1.71 (95%CI: 1.01, 2.88), p = 0.04, respectively. Morphologic variants, Ki67 index, type of induction therapy, number of lines before HCT had no significant impact on OS and PFS. We recorded 10 cases of second primary cancer (8%). The main reasons of death were progressive disease (63%), second cancer (9%) and comorbidities (28%).

Conclusions: More than 65 % of patients with new diagnosed MCL benefit from immunochemotherapy with high dose cytarabine consolidated by auto-HCT. MCL variants, Ki67 index, type of induction therapy do not affect outcomes post auto-HCT. Complete remission before auto-HCT is the most important factor resulting in longer OS and PFS than in case of active disease (PR or SD). Older patients benefit from auto-HCT but the outcomes is worse than in younger patients.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P439

T DEPLETE ALLOGENEIC HAEMATOPOETIC STEM CELL TRANSPLANT FOR RELAPSED/REFRACTORY HODGKIN'S LYMPHOMA: HIGH RATES OF RESPONSE POST TRANSPLANT EVEN IN THE SETTING OF PRE TRANSPLANT RESIDUAL DISEASE

Shima Ismail[1], Farheen Mir[1], Chloe Anthias[1,2], Sandra Easdale[1], Mike Potter[1], Mark Ethell[1], Carlos Arias[1], Bhupinder Sharma[1,2], David Cunningham[1,2], Ian Chau[1,2], Sunil Iyengar[1,2], Dima El-Sharkawi[1,2], Emma Nicholson[1,2]

[1]Royal Marsden Hospital, London, United Kingdom, [2]Institute of Cancer Research, Sutton, United Kingdom

Background: Whilst the predictive impact of PET positive disease prior to Autologous haematopoetic stem cell transplant (HSCT) is well established, there is less evidence prior to Allogeneic HSCT, particularly in the era of targeted therapies. This is a single centre experience of reduced intensity allogeneic HSCT in a heavily pretreated Hodgkin's Lymphoma (HL) cohort, the majority receiving T cell depletion.

Methods: This retrospective study analysed outcomes of 45 consecutive patients who underwent allogeneic HSCT at our centre for Relapsed/Refractory HL between January 2004 and December 2020 with PET-CT assessment pre and post HSCT. Data was collected from patient records and Promise Database. Probability of Overall Survival(OS), Progression Free Survival(PFS) were calculated by Kaplan Meier method and log rank test performed. Cumulative Incidence(CI) of relapse risk(RR), non-relapse mortality(NRM) was calculated using competing risk analysis.

Results: Median age at HSCT was 28 years (18-62) and median prior lines of therapy was 4 (2-8). 56% of patients had a prior autologous HSCT and 18% had had prior checkpoint inhibition. 42%, 22%, 20%, 9% and 7% had a sibling, MUD, MMUD, umbilical

cord or haploidentical donor respectively. 58% were conditioned with Flu-Mel-Alemtuzumab, 17% with LEAM-Alemtuzumab +/-Flu, 2% with Flu-LEAM and 2% with Flu-Cy-Etoposide. For cord blood transplants (9%), conditioning was Flu-Mel-ATG (n = 1) or T replete Flu-Cy-2Gy TBI (n = 3) and Haploidentical transplants (7%), all received Flu-Cy-2Gy TBI plus post transplant Cyclophosphamide. 33% of patients received donor lymphocyte infusion post HSCT for Mixed T cell chimerism and/or Relapse. 57% were in complete metabolic remission (CMR) at a median of 24 days prior to HSCT. 78% were in CMR at median of 87 days post HSCT.

With a median follow up of 5.2 years [DCA1], 5 year OS and PFS were 61% (43-74) and 57% (40-70) respectively. 2 year NRM and RR were 19% (9-32) and 19% (4-23) respectively. Donor type had a significant impact on PFS ($p = 0.001$) with cord blood HSCT having inferior outcomes compared to other donor types. Of 21 patients not in CMR pre-HSCT, 12 converted to CMR post-HSCT. Those in CMR prior to HSCT had superior 5 year PFS(66% (43-82)) compared to those not in CMR (43% (20-64, $p = 0.05$)) but there was no difference in 5 year OS (67% (44-82) vs 50% (25-71, $p = 0.27$)). CMR post-HSCT was associated with superior 5 year PFS (69%(50-82)) compared to those not in CMR post HSCT (11% (1-39, $p < 0.001$)) but again no OS benefit was seen(66% (47-80) and 38% (9-67, $p = 0.16$)). [DCA2] There was no significant impact on OS or PFS by age at HSCT, prior lines of therapy, time of HSCT, history of prior Auto HSCT or checkpoint inhibition, conditioning type or use of T cell depletion.

PATIENT CHARACTERISTICS		N(%)
Total		45
Median Age: 28 (18-62)	Age <28	21(47%)
	Age >/= 28	24 (53%)
Sex	Male	28 (62%)
	Female	17 (38%)
Median Lines of therapy: 4 (2-8)	<4 lines of therapy	24 (53%)
	>/= 4 lines of therapy	21 (47%)
CMV Positive Recipient	Yes	18 (40%)
	No	27 (60%)
Donor Type	Sibling	19 (42%)
	MUD	10 (22%)
	MMUD	9 (20%)
	Cord	4 (9%)
	Haploidentical	3 (7%)
Conditioning	Flu-Mel-Alemtuzumab	26 (58%) (MUD = 6; Sibling=14, MMUD = 6)
	Flu-LEAM-Alemtuzumab	7 ((15%) (MUD = 2, Sibling=2, MMUD = 3)
	Flu-LEAM	1 (2%) (MUD = 1)
	Flu-Cy-Etoposide	1(2%) (MUD = 1)
	LEAM-Alemtuzumab	3 (7%) (Sibling=3)
	Flu-Mel-ATG	1 (2%) (Cord=1)
	Flu-Cy-2Gy TBI	3 (7%) (Cord=3)
	Flu-Cy-2Gy TBI and Post Transplant Cy	3 (7%) (Haploidentical=3)
Donor Lymphocyte Infusion	Yes	15 (33%)
	No	30 (67%)
Previous Autologous HSCT	Yes	25 (56%)
	No	20 (44%)
	Yes	8 (18%)
Previous Checkpoint inhibition	No	37 (82%)
Date of Transplant	2005-2012	15 (33%)
	2013-2020	30 (67%)
PET status prior to Allogeneic HSCT	CMR (Deauville 1-3)	
	No CMR (Deauville 4/5)	26 (57%)
		19 (43%)
PET status post Allogeneic HSCT	CMR	35 (78%)
	No CMR (Deauville 4/5)	10 (22%)
Median time from PET-CT to HSCT	24 days (9-186 days)	
Median time from HSCT to PET-CT	87 days (26-138 days)	

Conclusions: Outcomes in this cohort was impacted by donor source with patients with cord donors having inferior PFS compared to other donor types. Whilst achievement of CMR prior to Allogeneic HSCT was associated with superior PFS long-term, a significant proportion of patients not in CMR prior to HSCT were converted to CMR post with the majority maintaining long term remission. This supports the efficacy of Allogeneic HSCT for high risk relapsed/refractory HL even in patients with residual disease prior to HSCT.

Disclosure: No conflict of interest.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P440

INTERIM REPORT OF A STUDY OF SAFETY AND EFFICACY OF PET-ADAPTED TREATMENT WITH NICE-40 IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA (NCT04981899)

Andrey Chekalov[1], Yuriy Kuznetsov[1], Kirill Lepik[1], Liudmila Fedorova[1], Sergey Shalaev[2], Ilya Zyuzgin[2], Maria Grigoreva[3], Marina Demchenkova[3], Elena Kondakova[1], Vadim Baykov[1], Artem Gusak[1], Ivan Moiseev[1], Natalia Mikhailova[1], Alexander Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation, [2]N.N. Petrov National Medical Research Center of Oncology Ministry of Health of the Russian Federation, St. Petersburg, Russian Federation, [3]Irkutsk Regional Cancer Center, Irkutsk, Russian Federation

Background: Published data have demonstrated the high efficacy of PD-1 inhibitor nivolumab monotherapy or in combination with ifosfamide, carboplatin, and etoposide (NICE) as first salvage treatment and bridge to ASCT for relapsed/refractory classical Hodgkin lymphoma (r/r cHL) (Herrera et al, 2022). The efficacy of nivolumab 40 mg was previously demonstrated in patients with r/r cHL (Lepik KV, 2020). The introduction of lower dose nivolumab in PET-adapted second line treatment may help to avoid salvage chemotherapy before ASCT with minimal financial burden.

Methods: Interim report of multicenter study included 20 patients with r/r cHL after the first-line of treatment (table 1).

Median age was 34 years (22-63), median follow-up was 9 months (3-21). Patients received 6 cycles of nivolumab at the fixed dose of 40 mg (Nivo), with subsequent assessment of response by PET-CT. Patients with complete response (CR) proceeded to ASCT. Patients with <CR after nivolumab monotherapy were treated with 2 cycles of a combination of nivolumab at the fixed dose 40 mg, ifosfamide, carboplatin and etoposide (NICE-40), with subsequent PET-CT assessment. Patients with CR and PR proceeded to ASCT. The response was evaluated according to the LYRIC criteria. Interim report assessed overall response rate (ORR), adverse events (AEs) according NCI CTCAE 5.0, 1-year overall survival (OS) and progression-free survival (PFS).

Table 1. Patient characteristics (n = 20)

Characteristics	n (%)
Median age, range	34 (22-63)
Sex male/female	10/10 (50/50)
Prior radiation therapy	7 (35)
First-line therapy	
ABVD	13 (65)
BEACOPP	7 (35)
Primary refractory	15 (75)
Early relapse	3 (15)
Late relapse	2 (10)
B-symptoms at Nivo initiation	6 (30)
Bulky disease	7 (35)
Disease stage at Nivo initiation	
I	1 (5)
II	9 (45)
III	2 (10)
IV	8 (40)

Results: ORR after 6 cycles of Nivo was 55% (CR-25%, PR-30%), indeterminate response (IR) was 45%. Five (25%) and 15 (75%) patients received ASCT after Nivo and 2 cycles of NICE-40 respectively. ORR after NICE-40 was 77% (CR-46%, PR-31%). ASCT after NICE-40 was performed in 11 patients. No grade 3-4 immune-mediated AEs were reported prior to ASCT. Immune-related thyroiditis grade 2 was observed in 1 patient (5%) on Nivo. One patient died due to cardiac toxicity of the conditioning regimen. Best response on study treatment protocol: ORR- 85% with CR-55% and PR-30%, IR-15%. Median OS and PFS was not reached, 1-year OS and PFS was 93% (95% CI: 80-100) and 69% (95% CI: 47-100), respectively.

Conclusions: The interim analysis supports the proposed therapeutic approach as both effective and safe, allowing some patients with r/r cHL to avoid the toxicity of standard second-line therapy. Continuation of the study with longer follow up is needed for further analysis.

Clinical Trial Registry: **(NCT04981899)**, https://clinicaltrials.gov/ct2/show/study/NCT04981899

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P441

ALLOGENEIC TRANSPLANTATION AFTER ADOPTIVE IMMUNOTHERAPY AND CHECKPOINT INHIBITOR FOR RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMA

Humanitas Center[1], Cristina Zucchinetti[1], Laura Giordano[1], Chiara De Philipis[1], Daniele Mannina[1], Barbara Sarina[1], Daniela Taurino[1], Rachele Carbon[1], Carmelo Carlo-Stella[1], Armando Santoro[1], Stefania Bramanti[1]

[1]IRCCS Humanitas Research Hospital, Rozzano, Italy

Background: Immunomodulating drugs are currently used as salvage strategies for relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL), such as primary mediastinal (PML), diffuse large B cell (DLBCL) or follicular NHL (FL). These drugs comprise, for instance, monoclonal antibodies targeting programmed cell-death (PD-1) (Zinzani, JCO 2019), bispecific antibodies, such as glofitamab (Hutchings, JCO 2021), and antibody-drug conjugates, such as loncastuximab (Kahl, Clin Canc Res 2019). For these patients, in the pre-CART era, allogeneic stem cell transplantation (Allo-HSCT) as consolidation therapy was the only potential curative strategy. The increased use of such new drugs in the management of R/R NHL raised the issue of improving our understanding on long-term outcome and toxicities. Therefore, we asked whether the usage of these new strategies before Allo-HSCT may be associated with an increased risk of complications for patients with NHL. We retrospectively analyzed a cohort of 22 patients treated at our center.

Methods: The primary objective of our study was to evaluate the major outcomes in terms of side effects and long-term results of patients with a R/R NHL receiving an Allo-HSCT at our center after achieving disease response, either complete (CR) or partial remission (PR), with new immunomodulatory drugs. The primary endpoint was GVHD/relapse free survival (GRFS). Secondary endpoints comprised overall survival (OS), non-relapse mortality (NRM), acute and chronic GVHD. Between July 2018 and June 2022, 35 patients with R/R NHL were evaluated for Allo-HSCT: of these 22 were transplanted in CR or PR, whereas 13 were not eligible to Allo-HSCT because of quickly progressive disease.

Results: Eleven patients had DLBCL (2 double expressor and 3 transformed), 6 GZL, 3 FL and 2 PML. Median age was 49 years old, 14 were male, median number of treatments was 4 (range 3-8), 8 have received brentuximab+nivolumab, 8 glofitamab, 2 pembrolizumab and 7 loncastuximab. Donor type was represented by haploidentical relative (n = 13), matched related (n = 6) and unrelated (n = 3) donor. Eighteen patients were in CR and 4 in PR. All patients received peripheral blood stem cells as graft source after a reduced intensity (n = 17) or non-myeloablative (n = 5) conditioning regimen. With a median follow-up of 27,7 months, 17 patients are alive, 5 have died because of toxicity (n = 4: pneumonia, neurologic, GVHD, septic shock) or PD (n = 1) or. Three-year OS and GRFS were 76% and 59%, respectively. Three-year NRM was 18%, while relapse incidence was 6% (n = 1). Six-months cumulative incidence (CI) of grade II-IV and III-IV acute GVHD was 18% and 10%, respectively. Two-year CI of moderate-severe chronic GVHD was 19%. Other relevant side effects comprised: CMV reactivation (n = 8) for 1-year CI of 41%, Aspergillus probable lung infection (n = 4) for 1-year CI of in invasive fungal infection of 10%, BK virus (n = 3) and EBV reactivation (n = 1), VOD (n = 1).

Conclusions: Allo-HSCT as consolidative strategy in R/R DLBCL achieving disease response after new immunomodulatory strategy was safe and effective in the pre-CART era. These results suggest its potential use as curative strategy without unexpected toxicity for patients relapsing after CART and rescued with immunomodulatory therapies.

Disclosure: We have no conflict of interests to disclose.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P442

FLUDARABINE-MELPHALAN-CAMPATH FOLLOWED BY UNMANIPULATED PERIPHERAL-BLOOD HAEMATOPOIETIC STEM CELLS CAN STILL CURE LYMPHOMA. THE KING'S COLLEGE HOSPITAL 10 YEARS' EXPERIENCE IN RELAPSED AND REFRACTORY LYMPHOMAS

Daniele Avenoso[1], Amal Alabdulwahab[1], Michelle Kenyon[1], Varun Mehra[1], Pramila Krishnamurthy[1], Francesco Dazzi[1], Ye Ting Leung[1], Sandra Anteh[1], Mili Naresh Shah[1], Andrea Kuhnl[1], Robin Sanderson[1], Piers Patten[1], Deborah Yallop[1], Antonio Pagliuca[1], Victoria Potter[1]

[1]King's College Hospital NHS Foundation Trust, London, United Kingdom

Background: The second decade of this millennium was characterized by a widespread availability of chimeric antigen receptor T-cell (CAR-T)therapies to treat relapsed and refractory lymphomas.

As expected, the role and indication of allogeneic haematopoietic stem cell transplant(allo-HSCT)in the management of lymphoma changed and it is currently redefining its role in the treatment pathway of our patients. Currently a not unneglectable proportion of patients will be considered candidate for an allo-HSCT and the debate of which transplant platform should be offered is still active.

Herein we report the outcome of patients affected with relapsed/refractory lymphoma and transplanted following reduced intensity conditioning at King's College Hospital, London, between January 2009 and April 2021.

Methods: HSCT was performed using GCSF mobilized peripheral blood stem cells as consolidative strategy for patients in partial or complete response after salvage therapy. Conditioning protocol fludarabine150 mg/m2, melphalan140mg/m^2. Graft-versus-host disease (GVHD)prophylaxis consisted of pre-transplant campath at the total dose of 60mg in unrelated donors and 30mg in fully matched sibling donors, and ciclosporin3mg/Kg from day -1(therapeutic level of150-200)until d + 56 and then tapered in absence of GVHD aiming to stop it on day+90.

Probabilities of overall survival(OS) was calculated using the Kaplan-Meier method. Relapse incidence(RI) and transplant related mortality(TRM) rates were estimated using cumulative incidence(CI) functions and considered as competing risks. For GvHD, death and relapse were considered competing events. Statistical analyses were performed with GraphPad Prism Version9.4.1.

Results: Table 1 summarize the demographic of the population and allo-HSCT details. A median of 7x10^6 CD34 + /Kg was infused(range1.8 – 11.2). Median time to neutrophil >1000/mL was 12days(10-24), and 11 days (8-29) to platelet >20.000/mL. No deaths before the engraftment were recorded. Two cases of primary graft failure occurred. Median unfractionated, CD3+ and CD15 chimerism at 365days after transplant were 99%, 99% and 99%, respectively. One year and five years OS were87% and79.9%, respectively and median OS was not reached. One year and five years GFRS were 69%and 61%, respectively, with median GRFS were not reached. The global CI of relapse was 16%with no late relapses seen beyond 24 months after transplant. Incidence of acute GVHD was 48%(only grade I/II); no cases of grade III/IV were diagnosed. Chronic GVHD occurred in 39% of patients; within this group moderate and severe cases were noted in 4 and 3 patients, respectively. TRM was 12%, with no cases developed within day 100 and 18 months after the procedure. The main causes of deaths were infections (3 cases) and disease progression (1 case). CMV reactivation occurred in 41%with a median time to first CMV reactivation of 28 days (range -6 – 251). No case of CMV disease occurred.

Patients Characteristics	N (%)
Total	33 (100)
Male	24 (72)
Female	9 (28)
Median age (range)	43 (25–64)
Median line of therapy (range)	4 (3–6)
Diagnosis	
Hodgkin Lymphoma	10 (30)
Follicular Lymphoma	9 (27)
Large B-cell Lymphoma	5 (15)
Mantle cell lymphoma	3 (9)
T cell lymphoma	6 (18)
Previous auto-HSCT	19 (58)
Previous CAR-T	1 (3%)
PET negative pre allo-HSCT	22 (66)
PET positive pre allo-HSCT	11 (34)
Partial Response	*6*
Active disease	*5*
Full matched sibling donor	13
Matched unrelated donor	22
Primary graft failure	2
Secondary graft failure	0
VOD/SOS	2
Months of median follow up (range)	49 (-)
Median days to Neutrophil engraftment (range)	12 (10–24)
Median days to Platelets engraftment (range)	11 (8-29)
Median Chimerism at day 100 (UF/CD3/CD15)	98/94.5/99
Median Chimerism at 1 year (UF/CD3/CD15)	99/99/99
Median Days to first CMV reactivation	28
Median Days to first EBV detectable	108

Conclusions: The outcomes of heavily pretreated lymphoma patients are favorable with median OS and GFRS survival not reached after a median of 49months. These encouraging results are a further proof of the curative effect of *graft-versus-lymphoma* and the use of PBSC didn't increase the TRM or the rate of moderate/severe chronic GVHD.

In conclusion, even if some lymphoma subgroups can't be treated (yet) with advanced cellular therapies, this study confirms the role of allo-HSCT as a safe and curative strategy.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P443

HAPLOIDENTICAL STEM CELL TRANSPLANTATION IN CUTANEOUS T-CELL LYMPHOMAS: A MONOCENTRIC RETROSPECTIVE STUDY

Fabio Serpenti[1], Francesca Cavallaro[1], Giorgia Saporiti[1], Maria Goldaniga[1], Giulia Galassi[1], Filippo Bagnoli[1], Silvia Alberti-

Violetti[2], Kordelia Barbullushi[1], Giulio Cassanello[1], Wilma Barcellini[1], Emilio Berti[2], Francesco Onida[1]

[1]Hematology Unit, Fondazione IRCCS Ca Granda Policlinico di Milano, Milan, Italy, [2]Dermatology Unit, Fondazione IRCCS Ca Granda Policlinico di Milano, Milan, Italy

Background: Allogeneic stem cell transplantation (HSCT) is the only curative option for advanced stage Mycosis Fungoides (MF) and Sézary Syndrome (SS) patients. With the recent improvements in the transplant procedure, haploidentical (haplo-) HSCT can be performed safely, when a matched donor is not available. We hereby report clinical data and outcomes of a series of nine patients who were treated with haplo-HSCT for MF/SS at our centre and their outcomes compared to matched transplants.

Methods: We retrospectively analysed clinical characteristics and outcomes of all patients treated with haplo-HSCT for MF/SS at our centre between Jan 2016 and Jun 2022. We then compared their outcomes to those of patients receiving HLA-identical or MUD transplant for MF/SS in the same period.

Results: A total of 23 MF/SS patients received HSCT at our Institution between Jan 2016 and Jun 2022. Donors were HLA-identical siblings in 6 cases (26,1%), MUD in 8 (34,8%), and haplo in 9 (39,1%) – table 1.

Focusing on the haplo cohort, 5 patients received haplo-HSCT for SS and 4 for MF. Median age at transplant was 55y (20-67), and median time from diagnosis to transplant was 22 months (18-134). Previous lines of therapy included steroids, PUVA, single or multi-agent chemotherapy, alemtuzumab and brentuximab vedotin and median number of previous lines of therapy was 5 (3-11). All patients were in PR at time of transplant, except for one SS patient in CR. Conditioning regimen consisted of thiotepa-cyclophosphamide-fludarabine plus TBI 2Gy. Post-transplant cyclophosphamide was given as GvHD prophylaxis, together with CSA-MMF in 7 patients and CSA-MTX in 2. ATG was added in 3 patients. Stem cell source was PBSC in 7 cases and BM in 2. All patients achieved CR after transplant. After a median follow-up of 26 months, 7 out of 9 (78%) patients were still alive and in CR. Grade III-IV Acute GvHD occurred in 2 patients (22%), while moderate/severe chronic GvHD in 1 (11%). Relapse rate was 44,4%, and all relapses occurred less than 6 months after HSCT. 2y-overall survival was 88,8%. Two patients died due to progressive disease at +5 and +30 months after transplant; there was no case of transplant-related mortality.

After a median follow-up of 571 days, in the whole cohort, 2-yr overall survival (OS) and disease-free survival (DFS) were respectively 77.7% and 50,2%. According to donor type, 2-yr OS was 83.3%, 62,5% and 88,9% and DFS 62,5%, 50% and 44,4% for HLA-identical sibling, MUD and Haplo, respectively.

	SIB = 6	MUD = 8	HAPLO = 9	TOT = 23
Sex (M/F)	3 / 3	3 / 5	5 / 4	11 / 12
Median age (range)	49 (34-60)	52 (36–59)	52 (18-60)	51 (18-60)
Disease (MF/SS)	3 / 3	3 / 5	4 / 5	10 / 13
Status at transplant (CR/PR/SD-PD)	2 / 3 / 1	1 / 6 / 1	1 / 8 / 0	4 / 17 / 2
Conditioning (RIC/NMA)	5 / 1	8 / 0	9 / 0	22 / 1
TBI 2 Gy (yes/no)	1 / 5	0 / 8	9 / 0	10 / 13
Median Sorror (range)	1 (0-3)	2,5 (0-4)	0 (0-6)	1 (0-6)
Stem cell source (PBSC/BM)	6 / 0	8 / 0	7 / 2	21 / 2
G III-IV aGvHD	1	1	2	4
Mod/Sev cGvHD	0	1	2	3

Conclusions: Haplo-HCT outcomes is feasible in the setting of cutaneous T cell lymphomas; conditioning chemotherapy and low dose TBI made all patients reach a CR status after transplant. Outcomes were non-inferior when compared to HLA-identical and MUD transplants in our centre. Overall, our results support the use of Haplo-HSCT in the absence of a matched donor.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P444

AUTO-HSCT AND ALLO-HSCT IN THE TREATMENT OF PATIENTS WITH PERIPHERAL T-CELL LYMPHOMAS: MULTICENTER EXPERIENCE OF RUSSIA AND KAZAKHSTAN

Elena Lepik[1], Vladislav Kovalik[1], Andrey Kozlov[1], Evgenia Borzenkova[1], Kirill Lepik[1], Elena Kondakova[1], Vadim Baykov[1], Marina Popova[1], Ivan Moiseev[1], Tatiana Shneider[2], Olga Uspenskaya[2], Marina Demchenkova[3], Vera Sergeevicheva[4], Vadim Keimakin[5], Gayane Tumyan[6], Anastasia Semenova[6], Ilya Zyuzgin[7], Natalia Mikhaylova[1], Alexander Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation, [2]Leningrad Regional Clinical Hospital, St. Petersburg, Russian Federation, [3]Irkutsk Regional Cancer Center, Irkutsk, Russian Federation, [4]Federal State Budgetary Scientific Institution Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation, [5]National Research Oncology Center, Nur-Sultan, Kazakhstan, [6]Federal State Budgetary Institution National Medical Research Center of Oncology named after N.N. Blokhin, Moscow, Russian Federation, [7]Federal State Budgetary Institution National Medical Research Center of Oncology named after N.N. Petrov, St. Petersburg, Russian Federation

Background: Mature T/NK-cell lymphomas (TCL) are a group of rare, predominantly aggressive non-Hodgkin's lymphomas, which are also characterized by the development of a refractory or relapsing course of the disease in case of first line failure. Hematopoietic stem cell transplantation (HSCT) is a therapeutic approach that improves the prognosis of this group in patients. We analyzed the results of HSCT performed in several centers in Russia and Kazakhstan.

Methods: We analyzed clinical data in 86 patients with TCL, who undergone HSCT in 7 clinical centers in Russia and Kazakhstan from 2005 to 2022. Histological subtypes included: peripheral T-cell lymphoma, NOS (n = 23); ALK-positive anaplastic large cell lymphoma (n = 23); ALK-negative anaplastic large cell lymphoma (n = 11); nodal TFH cell lymphoma, angioimmunoblastic-type (n = 16) (WHO Classification, 2022). The remaining patients (n = 13) have more rare forms of PTCL. The median age was 43 years (1-66). 72 (62%) patients had primary resistant disease or relapsed after first-line therapy. Auto-HSCT was performed in 70 patients as a consolidation of the 1st remission (n = 27), after the 2nd (n = 32), after the 3rd (n = 10) and 4th line therapy (n = 1). Allo-HSCT was performed in 24 patients with more aggressive PTCL. The conditioning regimens used prior to allo-HSCT were low intensity regimens (FluBe n = 22; FluMel n = 1; FluCy n = 1). In all patients, the GVHD prophylaxis regimen was based on posttransplant cyclophosphamide.

Results: With a median follow-up of 27 months. 55 patients were alive at the time of analysis. The median overall survival (OS) after auto-HSCT and allo-HSCT was not reached; the 3-year survival rate was 58% and 72%, respectively. Three-year PFS after auto-HSCT and allo-HSCT was 46% and 50%, respectively. PFS in patients with auto-HSCT in the 1st line was non-statistically better than in patients who received auto-HSCT after 1st line (41% vs 23%, $p = 0.07$). The subgroup analysis showed that patients who underwent allo-HSCT in a complete response (CR) have an advantage over patients who underwent allo-HSCT with a partial response or with an active disease status (SD/PD) - (PFS 3-year 73% vs 20% vs 0%, $p = 0.019$). The cumulative incidence (CI) of acute GVHD grade II-IV and severe GVHD grade III-IV was 25% and 21%, respectively. The CI of chronic GVHD was 26%. Eleven patients has relapsed or progression TCL. Six out of eleven patients underwent anti-relapse treatment after allo-HSCT, 5 patients achieved CR which persists until the last follow up. Treatment in the post-transplant period was based on stimulation of the graft-versus-lymphoma (GVL) effects (donor lymphocyte infusion ($n = 3$), nivolumab ($n = 1$)) or on targeted treatment (brentuximab vedotin ($n = 2$); crizotinib/ceritinib ($n = 3$)). The CI of achieving remission of TCL with relapse after allo-HSCT was 45%.

Conclusions: Our data provide additional evidence that auto-HSCT as 1st line consolidation is associated with better results than in relapse. Allo-HSCT is an effective treatment option for patients with r/r TCL. Conducting allo-HSCT in CR is associated with a better prognosis for patients with TCL. In our analysis, we also observed the feasibility of treating relapses after allo-HSCT using targeted antitumor effects and/or stimulation of GVL effects.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P445

RELAPSED OR REFRACTORY DOUBLE-EXPESSOR DIFFUSE LARGE B-CELL LYMPHOMAS ARE ASSOCIATED WITH INFERIOR SURVIVAL OUTCOMES AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION - A SINGLE CENTRE EXPERIENCE

Cindy Krisnadi[1], Jing Yuan Tan[1], Lawrence Cheng Kiat Ng[1], Melinda Si Yuan Tan[1], Francesca Wei Inng Lim[1], Shin Yeu Ong[1], Chandramouli Nagarajan[1], Yeow Tee Goh[1], Yeh Ching Linn[1], Jeffrey Kim Siang Quek[1], Hein Than[1], Tertius Tuy[1], Jordan Chung Cheng Hwang[1], Nicholas Grigoropoulos[1], William Ying Khee Hwang[1,2], Aloysius Yew Leng Ho[1], Yunxin Chen[1]

[1]Singapore General Hospital, Singapore, Singapore, [2]National Cancer Centre Singapore, Singapore, Singapore

Background: Double-expressor lymphomas (DELs) are diffuse large B-cell lymphomas (DLBCL) with co-expression of the C-MYC and BCL2 proteins. Poorer outcomes have been demonstrated in DELs standard R-CHOP induction therapy, including shorter overall survival and disease-free interval. Autologous stem cell transplantation (auto-SCT) is commonly used as a potentially curative treatment in relapsed/refractory DLBCLs (R/R DLBCL). However, data regarding the prognostic impact of DEL status on auto-SCT outcomes in R/R DLBCL is limited. We retrospectively studied the outcomes of auto-HSCT in patients with relapsed/refractory DEL.

Methods: Records of patients who underwent auto-SCT for R/R DLBCL from 2010 to 2022 were reviewed. Patients with double/triple-hit lymphoma, transformed indolent B-cell lymphoma, primary mediastinal B-cell lymphoma, primary CNS lymphoma, or richter transformation of chronic lymphocytic leukaemia were excluded. Double-expressor status was defined by overexpression of C-MYC and BCL2 proteins on immunohistochemistry of ≥40% and ≥50% respectively, without concomitant chromosomal rearrangements involving MYC and BCL2/BCL6 genes. Disease response assessment was evaluated via PET-CT or CT scan. Overall survival (OS) and progression free survival (PFS) were estimated using the Kaplan-Meier method and compared via DEL status.

Results: A total of 34 patients were included in this analysis. At initial diagnosis, 9 (26.5%) were DEL and 25 (73.5%) were non-DEL. Both groups achieved ≥80% complete response (CR) rates after 1st line chemoimmunotherapy. Median time to relapse/progression was 12 months in both groups with similar incidence of refractory or early relapse (< 12 months), 55.6% in DEL vs 52% in non-DEL. At relapse, patient demographics and disease characteristics were similar in both groups. 66.7% of DEL vs 76% of non-DEL achieved CR after salvage chemotherapy, prior to transplant. Despite both groups showing good post-transplant outcomes (88.9% complete remission in DEL, 84% in non-DEL), DELs had a higher incidence of relapse as compared to non-DELs, 88.9% vs 40%, $p = 0.033$. Patients with DEL also had inferior PFS post-transplant, with median of 16 months, while median PFS was not reached in the non-DEL group. The 5-year PFS in patients with DEL was 11.1% compared to 55.2% in non-DEL group ($P = .031$). We did not observe a significant difference in terms of OS between both groups. Median OS was 59 months in the DEL group vs 61 months in the non-DEL group. 5-year OS was 22.2% and 48.4% respectively ($P = .431$). In patients who relapsed post auto-HSCT, 7 out of 8 DEL patients and 8 out of 10 non-DEL patients received 3rd line therapy. Median PFS after 3rd line therapy was shorter in the DEL group (18 months vs 48 months), though not statistically significant ($p = 0.123$).

Table 1: Patient and disease characteristics at first relapse prior to salvage chemotherapy with auto-HSCT

	Non-DEL No. (%) n = 25	DEL No. (%) n = 9	P-value
Male	15 (60)	4 (44.4)	0.679
Female	10 (40)	5 (55.6)	
Median age in years (range)	59 (40–73)	59 (40–66)	0.611
Primary refractory or early relapse (≤ 12 months)	13(52)	5 (55.6)	1.000
Ann Arbor stage 3-4	22 (88)	7(77.8)	0.846
saaIPI 2-3	21 (84)	7 (77.8)	1.000
Conditioning regimen			
Non-thiotepa based	14 (56)	5 (55.6)	1.000
Thiotepa based	11 (44)	4 (44.4)	
CR rate post salvage chemotherapy	19 (76)	6 (66.7)	0.917
CR rate post-transplant	21 (84)	8 (88.9)	1.000
Relapse post-transplant	10 (40)	8 (88.9)	0.033
Early relapse post-transplant (≤ 12 months)	9 (36)	4 (44.4)	0.962
PFS from transplant in months, median (range)	Not reached	16 (1–32)	0.031
OS from transplant in months, median (range)	61 (49–96)	59 (26–78)	0.431
Received third line therapy and beyond	8 (80)	7 (87.5)	-
Small molecule based therapy*	3 (37.5)	4 (57.1)	-
CAR-T or Bi-specific T-cell engager	2 (25)	1 (14.2)	-

*small molecule based therapy included either ibrutinib, lenalidomide or polatuzumab. *saaIPI* second-line age-adjusted international prognostic index, *PFS* progression-free survival, *OS* overall survival, *CR* complete remission, *PR* partial response, *SD* stable disease, *PD* progressive disease

Conclusions: Patients with relapsed/refractory double-expressor DLBCL were associated with inferior outcomes after auto-SCT in this limited series. Considerations for improving outcomes including intensification of upfront treatment with consolidative auto-SCT, addition of novel therapies to upfront therapy as well as the use of novel targeting therapies to achieve a deeper response prior to transplant may be further explored.

Disclosure: The authors declare no conflict of interest.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P446

ALLOGENEIC HEMATOPOETIC STEM CELL TRANSPLANT FOR PATIENTS WITH ADVANCED T-CELL-NON-HODGKIN LYMPHOMAS

Hassan Naim[1], Radwan Massoud[1], Gaby Zeck[1], Dietlinde Janson[1], Christine Wolschke[1], Francis Ayuk[1], Nicolaus Kröger[1]

University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: T-cell non-Hodgkin lymphomas (T-NHL) are rare diseases, which are associated with worse outcome in comparison to their B-cell counterparts. Allogeneic stem cell transplantation (allo-SCT) may have a curative potential for these patients due to the graft versus lymphoma effect.

Methods: Fifty-five consecutive patients with T-NHL underwent allo-SCT between the years 1990-2021 at University Medical Center Hamburg. Sixteen patients had peripheral T-cell Lymphoma not otherwise specified (PTCL-NOS) (29%), n = 11 (20%) angioimmunoblastic T-cell lymphoma (AITL), n = 8 (15%) anaplastic large-cell lymphoma (ALCL), n = 6 (11%) adult T-cell leukemia/lymphoma (ATLL), n = 5 (9%) enteropathy associated T-cell lymphoma (EATL), n = 4 (7%) hepatosplenic gamma/delta T-cell lymphoma (HSTL), n = 2 (4%) T-cell-prolymphocytic leukemia (T-PLL), n = 2 (4%) Mycosis fungoides (MF), n = 1 (2%) each extranodal T/NK- cell lymphoma (ENKTL). Fifty-three percent of patients were transplanted in chemosensitive disease (CS-T-NHL) and 47% with refractory disease (ref-T-NHL).

Results: In the CS-TNHL group 27% were transplanted in CR1, 17% CR2, 17% in PR1 and 24% in PR2. All patients were heavily pretreated with 27% patients relapsing post auto-SCT (45% CS-T-NHL, 54% ref-T-NHL, p = 0.7) and two patients in the ref-T-NHL post allo-SCT. There were no significant differences in disease subtypes and age at transplant between the two groups.

In the CS-TNHL group 12 patients (41%) had matched related donor and 17 patients (59%) had unrelated donors (MUD 35% MMUD 24%), compared to 8 patients from MSD (31%) and 12 patients from unrelated donor (MUD 46% MMUD 23%) in the Ref-T-NHL group (p = 0.6).

Fifty-three Patients (96%) had leukocyte engraftment with a median of 13 days (range, 9-36) and 45 (82%) achieved platelet engraftment after a median of 15 days (range, 8-72) At day 100, the cumulative incidences of grade II-IV and grade III-IV acute GVHD were 28% and 14% respectively with no difference between the two groups.

The 3-year relapse incidence (RI) was 25% (CS-TNHL 19% vs 34% ref-TNHL, p = 0.33). The cumulative incidence of non-relapse mortality (NRM) at 3 years was 26% (CS-TNHL 22% vs 28% ref-TNHL group, p = 0.52). Female patients and a previous auto-SCT was associated with decreased RI (3-year RI Female vs Male Patients 35% vs 10% p = 0.045, previous auto-SCT vs no auto-SCT 3 Year RI 11% vs 40%, p = 0.003). none of the other patients, donor and transplant characteristics affected RI and NRM.

The median OS for the entire population was 15 months (70 months for CS-T-NHL vs 6 months for ref-TNHL), with 3-year OS of 48% (56% for CS-T-NHL vs 39% for ref-TNHL, p = 0.15). The median PFS for the overall population was 15 months (63 months for CS-T-NHL vs 5 months for ref-TNHL), with a 3-year PFS of 44% (60% for CS-T-NHL vs 30 months for ref-TNHL, p = 0.075).

Conclusions: Acknowledging the retrospective nature of our study, and the small sample size, our results indicate that allo-SCT have a curative potential in patients with T-NHL even in refractory status.

Disclosure: nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P447

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN RELAPS/REFRACTORY LYMPHOMA PATIENTS: A SINGLE CENTER EXPERIENCE

Bülent Karakaya[1], Hülya Yilmaz[1], Gül Yavuz Ermiş[1], Güldane Cengiz Seval[1], Sinem Civriz Bozdağ[1], Selami Koçak Toprak[1], Meltem Kurt Yüksel[1], Önder Arslan[1], Muhit Özcan[1], Taner Demirer[1], Günhan Gürman[1], Meral Beksaç[1], Pervin Topçuoğlu[1]

[1]Ankara University, Ankara, Turkey

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered as a potentially curative option in relapse and/or refractory patients. In our study, we aimed to evaluate our lymphoma patients who underwent allo-HSCT.

Methods: Seventy-six patients with lymphoma who underwent consecutive allo-HSCT between 1996 and 2020 were included in the study. Forty-nine were diagnosed as Non-Hodgkin Lymphoma (NHL) and 27 patients with Hodgkin Lymphoma (HL). Patients with NHL were grouped as Aggressive B, Indolent B and T-cell NHL based on disease behavior patterns. Parameters such as demographic data, transplant characteristics, post-transplant progression-free survival (PFS) and overall survival (OS) rates were evaluated into four groups. Data were analyzed using SPSS v.25.0. The p value < 0.05 was considered as significant.

Patients and Characteristics: The characteristics of all the patients are summarized in Table 1. Median follow-up was 8.1 months (range: 0.3-210.6 months) after transplantation. Most of HL patients underwent transplantation with stable/active disease and unrelated donors were used more frequently than other lymphomas (p = 0.004). In T cell-NHL group, myeloablative (MA) regimen was mostly preferred.

Table 1. Demographic and transplant characteristics

Variables	All patients: n:76	Aggressive B NHL (group 1) n:21	Indolent B NHL (group 2) n:14	T NHL (Group 3) n:14	HL (Group 4) n:27
Median age, years (range)	39.5 (18–65)	40 (22–61)	45 (37-63)	50.5 (19-65)	27 (18-59)
Gender, Female (n, %)	27 (35.5)	3 (14.3)	3 (21.4)	4 (28.6)	17 (63)
Disease status at transplant, stable/active (n, %)	52 (68.4)	13 (61.9)	7 (50)	9 (64.3)	23 (85.2)
Donor type (Matched-related) (n, %)	59 (77.6)	18 (85.7)	12 (85.7)	13 (92.9)	16 (59.3)
Priming regimen, myeloablative (n, %)	34 (44.7)	11 (52.4)	4 (28.6)	12 (85.7)	7 (25.9)
		20 (95.2)	13 (92.9)	14 (100)	

Variables	All patients: n:76	Aggressive B NHL (group 1) n:21	Indolent B NHL (group 2) n:14	T NHL (Group 3) n:14	HL (Group 4) n:27
Stem cell source (PB) (n, %) (1 cord blood lost data)	70/75 (92.1)				23 (88.5)
TBI Usage (n, %)	29 (38.2)	8 (38.1)	8 (57.1)	9 (64.3)	4 (14.8)
Oto-HSCT (n, %)	40 (52.6)	14 (66.7)	1 (7.1)	5 (35.7)	20 (74.1)
Tandem transplant (n, %)	12 (15.8)	4 (19)	1 (7.1)	2 (14.3)	5 (18.5)
Between Oto-HSCT and Allo-HSCT, less than 12 months (n, %)	19/40 (47.5)	8/14 (57.1)	1/1 (100)	3/5 (60)	7/20 (35)
Neutrophil Engraftment, median (days) (range)	14 (5-23)	13.5 (10-22)	14 (5-20)	13 (8-23)	15 (10-21)
Platelet Engraftment, median (days) (range)	13 (7-38)	13 (8-21)	15.5 (7-38)	11.5 (9-21)	13 (9-37)
Transplant response, partial and greater (n, %)	46/60 (76.7)	14/17 (77.8)	8/10 (80)	12/12 (100)	12/20 (60)
Stable/active disease in remission (n, %)	22/60 (36.7)	6/18 (33.3)	1/10 (10)	7/12 (58.3)	8/20 (40)
CMV reactivation (n, %)	41 (53.9)	13 (61.9)	7 (50)	6 (42.9)	15 (55.6)
Primary graft failure (n, %)	26 (34.2)	9 (42.9)	6 (42.9)	2 (14.3)	9 (33.3)
Acute GvHD, Grade 2-4 (n, %)	32/68 (47.1)	11/18 (61.1)	7 (50)	2/13 (15.4)	12/23 (52.2)
Chronic GvHD (n, %)	34/52 (65.4)	8/14 (57.1)	5/9 (55.6)	9/12 (75)	12/17 (70.6)
Transplant-related death (n, %)	30/68 (44.1)	10/20 (50)	6/11 (54.5)	5/13 (38.5)	9/24 (37.5)

Results: The post-transplant response rate was the highest rate in T-NHL and lowest rate in HL ($p = 0.014$). Despite of more stable/active disease prior to transplantation in T-NHL group, the remission rate after transplantation was higher than other groups. Engraftment times were similar in all groups. The incidence of acute GvHD was significantly lower in T-NHL than both aggressive B-NHL ($p = 0.011$) and HL group ($p = 0.03$). Chronic GvHD was similar in all groups. Relapse rate was lowest in indolent B-NHL and highest in HL, but relapse was seen in similar rate of aggressive B and T lymphomas. All transplant-related deaths were similar among all groups. In HL, median PFS was less than other groups, but not statistically significant. In univariate analysis, stable/active disease status at transplant, stem cell source (bone marrow) and no-response to transplant were independent risk factors for PFS. In multivariate analysis, only stable/active disease at transplant and stem cell source decreased PFS.

The median OS was similar among groups ($p = 0.47$). In univariate analysis, while stable/active disease at transplant, primary graft failure, acute GvHD were risk factors for OS as multivariate analysis, stable/active disease status at transplant and acute GvHD were independent risk factors for death.

Conclusions: Most patients with T-NHL were not in remission before transplantation. However, the remission rate after transplantation was higher than indolent NHL. In T-NHL group, MA conditioning regimen was mostly preferred, therefore, MA regimen might have been favorable effect on the remission. Acute GvHD was less frequent in T-NHL compared with indolent, aggressive B NHL and HL. Our data suggest that common risk factors for PFS and OS in uni- and multivariate analysis were disease status at transplantation.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P448

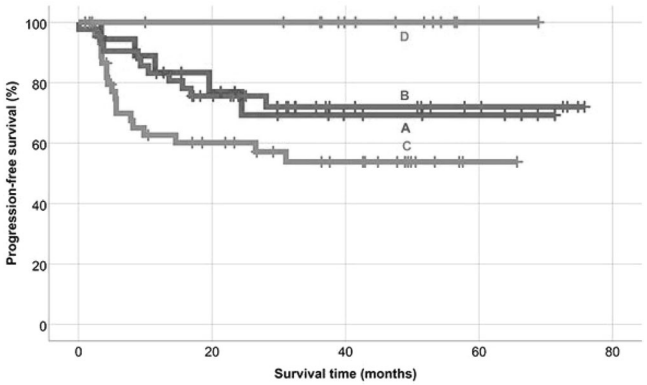
IMPROVED SURVIVAL OUTCOMES OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN RELAPSED/REFRACTER HODGKIN'S LYMPHOMA IN THE BRENTUXIMAB VEDOTIN ERA REAL WORLD DATA FROM HUNGARY

Zsófia Miltényi[1], Kata Husi[1], Roxána Szabó[1], László Imre Pinczés[1], Dóra Földeák[2], Réka Dudley[3], Árpád Szomor[3], Beáta Koller[4], László Gopcsa[4], Árpád Illés[1]

[1]University of Debrecen, Debrecen, Hungary, [2]University of Szeged, Szeged, Hungary, [3]University of Pécs, Pécs, Hungary, [4]Central Hospital of Southern Pest National Institute of Hematology and Infectious Diseases, Budapest, Hungary

Background: Nowadays, 20-30% of Hodgkin lymphoma patients are refractory to firstline treatment or relapse. Autologous stem cell transplantation (AHSCT) is the standard treatment in these cases, which can provide a cure rate of about 50%.

Methods: The aim of our present study was to assess progression- and overall survival (OS) in patients who underwent AHSCT in Hungary between 01.01.2016-31.12.2020, and to investigate the prognostic role of PET/CT performed before transplantation and how survival was improved by the brentuximab vedotin (BV) treatment.



Results: 126 HL patients underwent AHSCT during the examined period. The mean age at disease diagnosis was 33 (15-61) years, majority of patients (57 %) were males. Nodular sclerosis was the most common histological subtype (68 %). The median follow-up time from AHSCT was 39 (1-76) months, 107 patients are still alive, 11 died and eight were lost to follow-up. 68% of the patients received two or more salvage treatments (so they received BV treatment before AHSCT). PET/CT was negative (PET-) in 76% and PET/CT was positive (PET +) in 24% of the patients before AHSCT. The 5-year OS comparing PET- and PET+ patients was 90% v. 74% ($p = 0.039$), and 5-year PFS was 75% v. 47% ($p = 0.007$). There was no difference in either OS or PFS compared to those who did not receive BV before AHSCT (5-year OS (89% v 83% $p = 0.466$) and 5-year PFS (72% v 64% $p = 0.408$). We compared BV treatments based on their indication (Figure 1. Group A: BV only after AHSCT as maintenance therapy, Group B: BV before and after AHSCT as maintenance treatment, Group C: BV only before AHSCT or after AHSCT due to relapse, Group D: no BV treatment), there was no difference in the 5-year OS (89% v. 93% v. 76 %, 92% $p = 0.654$), but there was statistically significant difference in the 5-year PFS (69 % v. 72 % v. 54 % v. 100 % $p = 0.014$). The 18 patients, who did not receive BV treatment at all, were at low risk based on the modified AETHERA criteria, among them no relapse occurred and only one patient died due to alcoholic cardiomyopathy. Patients who received BV before and after transplantation (as maintanence treatment) had better PFS than those who did not continue BV treatment after AHSCT or received it only for relapse.

Conclusions: The remission before AHSCT affects the success of the transplantation and the patients' chances of recovery. AHSCT can provide prolonged disease control and this can improve with BV treatment, which widely used in everyday practice (either as firstline or salvage or maintenance treatment).

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P449

FAVORABLE OUTCOME OF PATIENTS WITH HL AND NHL UNDERGOING ALLOGENEIC HCT: A SINGLE CENTER EXPERIENCE FROM SAUDI ARABIA

Mohsen Alzahrani[1,2,3], Ahmed Alaskar[1,2,3], Ayman Hejazi[1,2,3], Gemal Gmati[1,2,3], Hend Salama[1,2,3], Abdulrahman Al Raiza[1,2,3], AS Al Saleh[1,2,3], Ayman Ibrahim[1,2], Mohammed Bakkar[1,2], Abdul Rauf Ghouri[1,2], Zied Aljubour[1,2], Mazin Ahmed[1,2], Inaam Shehabeddine[1,2], Suha Alkhraisat[1,2], Amani Alharbi[1,2], Isam Mahasneh[1,2], Maybele Ballili[1,2], Husam Alsadi[1,2], Bader Alahmari[1,2,3]

[1]King Abdulaziz Medical City, Riyadh, Saudi Arabia, [2]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, [3]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Background: Allogeneic hematopoietic cell transplantation (AlloHCT) used to play a defined role in the treatment of lymphoma. With the advent of modern targeted molecular therapies and immunotherapies, treatment standards at least for lymphoma have undergone significant changes, thereby questioning the traditional role of AlloHCT in these diseases. We aim from this study to describe the trend of AlloHCT for lymphoma patients in our center and the treatment outcome.

Methods: After due IRB approval, patients with Hodgkin and Non-Hodgkin lymphoma who underwent AlloHCT from 2010 until 2022 were identified, and all records were retrieved retrospectively. All patients with age above 14 years were included in this study. Progression free survival (PFS) and Overall survival (OS) were computed using Kaplan-Meir method. PFS defined as disease relapse or progression or death from any cause.

Results: A total of 25 patients were identified and included for further analysis. Median age was 25 years and 68% were male patients. Of the 25 patients 15 (60%) had classical Hodgkin lymphoma and 10 as NHL. Of the NHL group 5 had High B grade lymphoma, 5 with T cell lymphoma and there was no low-grade lymphoma in our cohort. Nineteen (76%) of patients had previous Autologous HCT and median previous lines if therapy was 5 with range from 2 to 8 previous lines. Majority of patients proceeded to allogeneic HCT with either CR 48% or PR 48% and 4% underwent transplant with refractory disease.

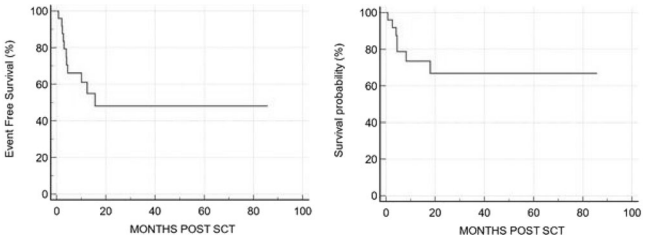
Regarding donor type, 16 patients had MRD, 2 MUD and 7 with haploidentical donor. All patients had PBSC as a source for stem cells except one with haploidentical donor the source was Bone marrow harvest. Myeloablative conditioning (MAC) was used in 14 patients and 11with reduced intensity conditioning (RIC). 10 patients underwent further therapies post AlloHCT as maintenance or treatment of residual disease or disease relapse.

Response post AlloHCT was complete response in 12 (48%) for all the group (46% in HL and 50% in NHL). Eleven patients had PR or disease relapse post AlloHCT requiring further therapies. Two patients did not undergo the response assessment (one for early TRM and 2nd patient not due). After a median follow up of 18 months (4 – 58 months) the median PFS was 18 months and median OS not reached. The median PFS for HL was not reached and for NHL was 10 months. GVHD developed in 64% of patients and in 75% of patients who are still in remission.

Table 1: Patients, disease and treatment characteristics

	Number (%/range)	Comments
Total	25	
Gender M/F	17/8 (68%/ 32%)	
Age (median)	25 (15-52)	
Diagnosis: HL	15 (60%)	All classical HL
NHL	10 (40%)	5 High grade B cell NHL, 5 T cell NHL
No. of previous lines of therapy (median)	5 (2 – 8)	
Previous ASCT	19 (76%)	
Disease status pre AlloSCT		
CR	12 (48%)	
PR	12 (48%)	
Refractory disease	1 (4%)	
ECOG 0-1 (median)	23 (92%)	
HCT-CI 0-2 (median)	23 (92%)	
>2	2 (8%)	
Donor type: MRD	16	
MUD	2	
HAPLO	7	(2 NHL, 5 HL)
Stem Cell Source: PBSC	24	
BMH	1	(Haploidentical donor for HL)
Conditioning intensity		
MA	14 (56%)	FluMel or FluBu3 or CyTBI 1200
RIC	11 (44%)	FluBu2 or FluCyTBI 200
Additional therapies post AlloHCT	10	7 CPI, 2 Bv, 1 DLI, 3 IFRT
Disease response		
CR	12 (48%)	CR in HL 7/15 (46%) and NHL 5/10 (50%)
PR	1	
Relapse/DP	10 (40%)	
Not evaluated	2	1 early TRM, 1 not due
Mortality	7 (28%)	
Relapse	4 (16%)	
TRM	3 (12%)	

Figure 1: Overall and Event Free Survival



Conclusions: In this small cohort we observed an OS and PFS benefit in high-risk HL and NHL patients compared to previous literatures. This could be related to multiple factors including higher rate of MAC regimens used, higher rate of GVHD, subtypes of lymphoma underwent transplant, recent transplant cohort with better transplant supportive therapies and finally additional therapies post-transplant. AlloHCT should remain as an important therapeutic option in the treatment algorithm of some types of lymphoma. Longer follow up and further validation of these observations are warranted.

Disclosure: None

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P450

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH ANAPLASTIC LARGE CELL LYMPHOMA (ALK +)

Alexander Galimov[1], Elena Lepik[1], Andrey Kozlov[1], Ilya Kazantsev[1], Tatiana Yuhta[1], Polina Tolkunova[1], Natalia Mihailova[1], Yury Punanov[1], Vadim Baykov[1], Ivan Moiseev[1], Alexander Kulagin[1], Ludmila Zubarovskaya[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation

Background: Anaplastic large cell lymphoma, anaplastic lymphoma kinase positive (ALK + ALCL) is a rare type of NHL. Relapsed and refractory (R/R) ALK + ALCL is an even rarer phenomenon (25-40% of cases). There are no standards for the treatment of R/R ALK + ALCL. AlloHSCT can be an effective method according to limited data.

Methods: Nine patients (F3, M6) with R/R ALK + ALCL received alloHSCT at the Pavlov University, St. Petersburg. There were four children (< 18 years) and five adults. The median age was 24 years (11 months- 37 years). Common type histology was diagnosed in all but one. Two patients had a refractory disease and seven had a relapsed disease. Early relapse (< 12 months after remission) was observed in 4 cases, late relapse - in 3 cases; local relapse - in 3 cases. Median number of therapy lines prior to alloHSCT was 3 (3-4). Second-line treatment included NHL-BFM (n = 4), GDP (n = 2), DHAP (n = 1), methotrexate+vinblastine (n = 1), bendamustine (n = 1). Third line therapy consisted of various protocols (brentuximab vedotin (BV) – 3, ICE + BV-1, bendamustine+crizotinib -1, COP-1, CC+crizotinib-1, DHAP-1, GIFOX-1). There were five patients with a history of autoHSCT. Prior to alloHSCT six patients were in complete remission (CR), two – in partial remission and one in progression. Matched unrelated (n = 6), matched sibling (n = 2) and haploidentical (n = 1) donors were used. The majority (n = 8) received non-myeloablative conditioning regimen Flu-Benda (fludarabine - 90 - 150 mg/m2, bendamustine - 390 mg/m2) with post-transplant cyclophosphamide and calcineurin inhibitors for GVHD prophylaxis. See Table 1 for detailed description.

Results:

Eight of nine patients were alive at a median follow-up of 59 months (3-108). Three of nine patients experienced relapse after alloHSCT with a median of 8 months (6-17). Two relapsed patients responded to ALK-inhibitors, and one died of disease progression. Five-year OS and PFS after alloHSCT was 85% (CI 95%, 33-98%) and 60% (CI 95%619-85%), respectively. There was no clinically significant GVHD.

Conclusions: Single-center experience in a rare indication shows encouraging results of alloHSCT in heavily pretreated patients with R/R ALK + ALCL. Further multicenter studies are required.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P451

EFFICACY AND SAFETY OF BRENTUXIMAB VEDOTINE AS A SALVAGE TREATMENT BEFORE AUTOLOGOUS SCT IN PATIENTS WITH RELAPSED AND REFRACTORY HODGKIN LYMPHOMA- UKRAINIAN EXPERIENCE

Kateryna Filonenko[1], Yana Stepanishyna[2], Yevhen Kushchevyi[2], Arina Martynchyk[3,3]

[1]University Clinical Center, Gdańsk, Poland, [2]National Cancer Institute, Kyiv, Ukraine, [3]Epworth, Melbourne, Australia

Background: Brentuximab vedotine (BV) is administered as a consolidative treatment after autologous stem cell transplantation (auto-SCT) to patients with high-risk relapsed/refractory (R/R) Hodgkin's lymphoma (HL) after auto-SCT or as a salvage regimen after at least two treatment lines. It is unknown, however, if patients receiving BV before auto-SCT and who continue BV as maintenance have a similar outcome to those receiving BV only after auto-SCT.

Methods: The abstract represents the data from a retrospective analysis of the treatment results of the R/R HL patients from the National Cancer Institute (Kyiv, Ukraine), who received salvage therapy with BV vs. standard chemotherapy (sCT) regimens (DHAP, ICE, IGEV) before auto-SCT.

Results: The retrospective cohort included 42 patients with R/R HL treated between 2017-2022, 18 males and 24 females with a median age of 30(20-57) years. Eleven(26%) patients were treated with BV before auto-SCT, 31(74%) received the sCT. The Median follow-up was 26 months. Primary refractory HL was documented in 14 patients and relapse – in 28 patients. There were no significant differences in the demographic data, results of the stem cell collection, clinical characteristics of the disease, response to the last treatment line before auto-SCT, or toxicity between both groups (table 1). The refractory disease was observed in 3 patients (27.3%) in the BV group and in 11 patients (36.7%) in the sCT group, p = 0.57. All patients in the BV group were at high-risk of relapse compared to 17 patients (56.7%) in the sCT group, p = 0.082. The median number of stem cells collected was 6.14 and 8.68 10^6/kg body weight CD34+ cells in the BV and sCT groups, respectively, p = 0.95. Patients from the BV group received a higher number of treatment lines before auto-SCT: 4 vs. 2 in the sCT group, p = 0.011. There were no differences in the CR rate before auto-SCT: 7(63.6%) in the BV group and 18(60%) in the sCT group, p = 0.35. The CR rate assessed on the day +100 was 60.0% and 63.64%, respectively, p = 0.56. The consolidative treatment with BV received 8/11 high-risk patients in the BV group (72.7%) and 13/17 (76.5%) in the sCT group (p = 0.77). The 2-year progression-free survival rate was 81,8% in the BV group and 70.3% in the sCT group, p = 0.615. 2-year overall survival rate was 92.2% and 72.7%, respectively, p = 0.15. The median time of ANC and PLT recovery was significantly longer in the BV group (table 1). Nevertheless, it did not influence the frequency of infections and the need for platelet transfusions. The frequency of neuropathy during the whole treatment period was similar in both groups (table 1).

Table 1. Patients'characteristics and outcome

Patient	Age, years	Prior therapy	Disease status at alloHSCT	Donor	Source of HSCT	Conditioning regimen	GVHD prophylaxis	Follow-up, months	Status
1	11 months	NHL-BFM-90, NHL-BFM-90, COP, autoHSCT, BV	CR	MUD	PB	FluBenda	PTCy+Tx +MMF	78	alive, remission
2	8	NHL-BFM, ALCL-Rez-2016+crizotinib, CC+crizotinib	PR	MSD	BM	FluBenda	PTCy	18	alive, progression
3	11	NHL-BFM-95, NHL-BFM 95 + ICE, autoHSCT, BV	CR	MUD	PB	FluBenda	PTCy+Tx +MMF	59	alive, remission
4	12	NHL-BFM-2012, MTX + V, ICE + BV, autoHSCT+crizotinib, ViGePP+BV +crizotinib	CR	Haplo	BM	FluBenda	PTCy+Tx +Sir	11	alive, remission
5	24	CHOEP, GDP, bendamustine +crizotinib	CR	MUD	PB	FluBenda	PTCy+Tx +MMF	3	alive, remission
6	28	NHL-BFM-90, GDP, GIFOX	progression	MSD	PB	FluMel	PTCY+Mtx +CsA	108	alive, progression
7	36	NHL-BFM-90, TL-REZ-2008 + ALL-2009, BV, BV+bendamustine	PR	MUD	PB	FluBenda	PTCy+Tx +MMF	17	dead, progression
8	36	HyperCVAD, Be, GVP, BV	CR	MUD	PB	FluBenda	PTCy+Tx +MMF	89	alive, remission
9	37	NHL-BFM-90, autoHSCT, DHAP, ICE	CR	MUD	PB	FluBenda	PTCy+Tx +MMF	75	alive, remission

Characteristic	BV salvage group	Standard CT group	p
Age (years), median(range)	31(26-57)	29(20-45)	0.24
Gender:			0.9
Male, number(%)	5(45.5)	13(43.3)	
Female, number(%)	6(55.5)	17(56.7)	
ANC recovery (days), median	13	11	0.03
PLT recovery (days), median	20	15	0.009
Febrile neutropenia, number(%)	10(90.9)	26(89.7)	0.9
PLT transfusions, median number	4	2	0.29
Neuropathy, number(%)	5(45.5)	10(34.5)	0.079

Conclusions: About 25% of patients were successfully transplanted after achieving an appropriate response to BV treatment. Despite a longer recovery in the BV group, there were no other significant differences in the outcomes of the auto-SCT with respect to the salvage regimen (BV vs. sCT) used before auto. Our results suggest that BV before auto-SCT in patients refractory to standard 2nd line equalizes their prognosis to the patient sensitive to CT with the same tolerance and toxicity.

Disclosure: No CI to disclose.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P452

SUCCESSFUL TREATMENT OF CNS LYMPHOMA WITH HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION: A SINGLE CENTER EXPERIENCE

Tulin Tuglular[1], Fatma Arıkan[1], Ahmet Mert Yanık[1], Derya Demirtas[1], Ozen Oruc[2], Tarik Ercan[3], Asu Fergun Yilmaz[1], Isik Kaygusuz Atagündüz[1], Tayfur Toptas[1]

[1]Marmara University, Istanbul, Turkey, [2]Balıkesir Ataturk City Hospital, Balıkesir, Turkey, [3]Haydarpasa State Hospital, Istanbul, Turkey

Background: Primary and secondary central nervous system lymphoma (CNSL) represents a rare and aggressive subset of extranodal non-Hodgkin lymphoma (NHL). PCNSL is an accounts for 2% of all brain tumors and up to 4 to 6% of NHL. Secondary CNSL (SCNSL) occurs in 2 to 10% of patients with aggressive subtypes NHL. The Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score is a predictor of patient outcomes in both PCNSL and SCNSL. PCNSL carries very poor prognosis with an overall survival 1.5 months in untreated patients. On the other hand, 5- year survival rate is about 30% with high-dose methotrexate-based regimens. Autologous stem-cell transplant (ASCT) is increasingly used as a consolidative treatment. In a phase 2 study, complete response rate was found to be 77.2% in patients who were treated with high dose MTX regimen and ASCT in newly diagnosed PCNSL. In this case series, we report outcomes of our CNSL patients who were treated with ASCT treatment.

Methods: This was a single-center retrospective study which included 14 patients with PCNSL (n = 12) and SCNSL (n = 2). All patients were at least 18 years old. The patients received an intensive induction chemotherapy including high-dose MTX one patient received R DEVIC because of methotrexate toxicity, followed by consolidative ASCT. Response assessment was done with cranial MR and cranial PET-CT.

Results: The baseline characteristics of the patients are summarized in Table 1. Diagnosis was made by stereotaxic tissue biopsy expect one patient with SCNSL. Nine patients had multifocal lesions. Most common pathologic subtypes were nongerminal center diffuse large cell lymphoma (DLBCL) (n = 13). EBV was not detected in any of the patients, while one patient was HIV positive. Median follow-up time was 40.5 (17-89) months. The majority of patients (n = 10, 71.4%) had class I MSKCC prognostic score (Table 1). Overall response rate was 92.8% with induction chemotherapy before ASCT (Table 1). All patients were in CR at 3 months after ASCT. Overall survival rates

were 92% and 83.9% at 18 and 24 months, respectively. Three patients (two with MSKCC class II, one with MSKCC class III) died at 14, 18 and 24 months. Two patients died because of relapsing disease after 4 and 5 months of ASCT. None of the patients who had MSKCC class I died.

Table 1. Demographic and clinical findings of the patients (n:14)

Variables	
Age, n (%)	
≤60 y	12 (85.7)
>60 y	2 (14.3)
Sex, n (%)	
Male	8 (57.1)
Female	6 (42.9)
Involvement, n (%)	
PCNSL	11 (78.6)
SCNSL	3 (21.4)
Pathology, n (%)	
DLBCL	13 (92.8)
High grade lymphoma	1 (7.2)
Prognostic score, n (%)	
MSKCC Class	
Class 1	10 (71.4%)
Class 2	3 (21.4%)
Class 3	1 (7.2%)
IELSG score	
0/1	9 (64.3%)
2/3	5 (35.7%)
4/5	0
PreASCT reponse rate, n(%)	
CR	7 (50%)
CRu	3 (21.4%)
PR	3 (21.4%)
SD	1 (7.2%)
Induction Regimen, n (%)	
Freiburg regimen	6 (42.9%)
R-MPV	7 (50%)
R-DEVIC	1 (7.2%)
Conditioning regimen, n (%)	
BCNU/Thiotepa	7(50%)
TBC	7 (50%)
Complications, n (%)	
Diarrhea	5 (35.7%)
Grade1-2	2 (14.2%)
Grade3	3 (21.4%)
Febril neutropenia fever	4 (28.5%)
Increased liver function enzyme	3 (21.4)
Grade 1	2 (14.2)
Grade 2	1 (7.2)
Cathater thrombosis -HITT	1 (7.2)

Conclusions: In this study, overall survival rates were 92% and 83.9% at 18 and 24 months, respectively which is compatible with the literature. High response rates and prolonged PFS were demonstrated in Freiburg (0RR:91.1%, median PFS 74 months, median OS was not reached) and R-MPV (ORR:82%; median PFS and OS; 9.5 and 31 months, respectively) protocols, both of which underwent ASCT with a thiotepa conditioning regimen. MSKCC prognostic scoring was a good predicted of patient survival in our patients.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P453

A COMPREHENSIVE ANALYSIS OF RELAPSE PATTERN IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA AFTER CHEMOIMMUNOTHERAPY USING NATIONAL HEALTH INSURANCE DATABASE OF SOUTH KOREA

Hyun Jung Lee[1], Myung Hee Chang[2], Dong Wook Kim[3], Jae Joon Han[1]

[1]Kyung Hee University Medical Center, Seoul, Korea, Republic of, [2]National Health Insurance Service Ilsan Hospital, Goyang, Korea, Republic of, [3]Gyeongsang National University, Jinju, Korea, Republic of

Background: Diffuse large B cell lymphoma (DLBCL) is the most common lymphoma in South Korea and rituximab (R) based chemoimmunotherapy (CIT) has been the standard of treatment since 2004 when rituximab was started to be reimbursed in National Health Insurance. We analyzed the real-world relapse pattern of DLBCL in the era of R-based CIT.

Methods: From 2005 to 2021, cases of newly diagnosed DLBCL patients who were treated with R-based CIT as an induction therapy were extracted from National Health Insurance Database of South Korea. Patients with prior history of other malignancies were excluded. Time to next treatment was used as a surrogate marker of relapse and was defined from the first day of R-based CIT to the first day of next salvage treatment for relapsed DLBCL.

Results: From 2005 to 2021, 26,265 patients were diagnosed as de novo DLBCL and the annual trend of DLBCL cases showed gradual increase. Among the newly diagnosed DLBCL, 17,743 (67.6%) patients were treated with R-based CIT and the proportion of patients who were treated with R-based CIT was not changed during every study year. Among the patients who had got R-based CIT, 3,275 patients (18.5%) relapsed after induction therapy. Most of the relapses were occurred within 2 years (71.5%) and the relapse rate decreased after 2 years. Late relapse beyond 5 years was reported in 216 patients (6.6%) and late relapse after 10 years was found in 29 patients (0.88%). A total of 2,176 (66.4%) of patients died after relapse and the median time from relapse to death was 252 days (IQR 125.5- 504.5 days). Mortality cases from recurrence accounted for the most of the deaths before the age of 40's, and deaths from other causes were more common after the age of 50's. Patient group with age > 80 years showed relatively low relapse risk (HR 0.7, 95% confidence interval (CI) 0.57-0.85), but higher mortality rate (HR 7.563, 95% CI 2.829 – 10.217) when compared with the patient group with age 40-49 years. Hematopoietic stem cell transplantation (HSCT) was performed in 1,445 relapsed patients (8.1%) and 834 of 1,445 patients (57.7%) survived after HSCT despite recurrence.

Conclusions: Annual incidences of DLBCL increased during study period and the most of the patients were treated with R-based CIT. Although treatment outcome was improved with the R-based CIT, early relapse within 2 years after induction treatment still remained as a huge obstacle for improving DLBCL survival. Still HSCT is meaningful as a salvage treatment option in relapsed disease. Late relapse after 5 years and non-relapse related mortality in the old aged group cannot be ignored future DLBCL management.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P454

DO GWAS-IDENTIFIED RISK VARIANTS FOR CHRONIC LYMPHOCYTIC INFLUENCE OVERALL PATIENT SURVIVAL?

Antonio José Cabrera-Serrano[1,2,3], José Manuel Sánchez-Maldonado[1,2,3], Rob ter Horst[4], Angelica Macauda[5], Paloma García-Martín[6], Yolanda Benavente[7], Stefano Landi[8], Alyssa Clay-Gilmour[9], Yasmeen Niazi[5], Blanca Espinet[10], Juan José Rodríguez-Sevilla[10], Eva Pérez[6], Rossana Maffei[11], Gonzalo Blanco[12], Matteo Giaccherini[8], James R. Cerhan[13], Roberto Marasca[11], Miguel Ángel López-Nevot[14], Tzu Chen-Liang[15], Hauke Thomsen[16], Irene Gámez[15], Daniele Campa[17], Víctor Moreno[18,19], Silvia de Sanjosé[6,18], Rafael Marcos-Gragera[20,21,22,23], María García-Álvarez[24], Trinidad Dierssen-Sotos[18,25], Andrés Jerez[15], Aleksandra Butrym[26], Aaron Norman[27], Mario Luppi[28], Susan L. Slager[29,30], Kari Hemminki[31,32], Yang Li[33,34], Sonja Berndt[35], Delphine Casabonne[6,18], Miguel Alcoceba[24], Anna Puiggros[36,12], Mihai G. Netea[33,37], Asta Försti[38,39], Federico Canzian[40], Juan Sainz[1,2,3,41]

[1]Genomic Oncology Area, GENYO, Centre for Genomics and Oncological Research, Pfizer / University of Granada / Andalusian Regional Government, PTS, Granada, Spain, Virgen de las Nieves University Hospital, Granada, Spain, [3]Instituto de Investigación Biosanataria IBs., Granada, Spain, [4]Radboud University Medical Center, Rabboud, Netherlands, [5]German Cancer Research Center, Heidelberg, Germany, [6]Hospital Campus de la Salud, PTS Granada, Granada, Spain, [7]Institut Català d'Oncologia, L'Hospitalet de Llobregat, Spain, [8]University of Pisa, Pisa, Italy, [9]University of South Carolina, Greenville, United States, [10]Hospital del Mar, Barcelona, Spain, [11]University of Modena and Regio Emilia, Modena, Italy, [12]Translational Research on Hematological Neoplasms Group, Cancer Research Program, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain, [13]Mayo Clinic College of Medicine and Science, Rochester, United States, Virgen de las Nieves University Hospital, Granada, Spain, Morales Meseguer University Hospital, Murcia, Spain, [16]ProtaGene CGT GmbH, Heidelberg, Germany,, University of Pisa, Pisa, Italy, [18]Catalan Institute of Oncology, Bellvitge Biomedical Research Institute (IDIBELL), Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP) and University of Barcelona, Barcelona, Spain, [19]Unit of Biomarkers and Susceptibility, Cancer Prevention and Control Program, IDIBELL, Catalan Institute of Oncology, University of Barcelona, Barcelona, Spain, [20]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain, University of Girona, Girona, Spain, [22]Institute of Biomedical Research of Girona Dr. Josep Trueta (IDIBGI), Girona, Spain, [23]Josep Carreras Leukemia Research Institute, Girona, Spain, University Hospital of Salamanca (HUS/IBSAL), CIBERONC and Cancer Research Institute of Salamanca-IBMCC (USAL-CSIC), Salamanca, Spain, [25]University of Cantabria, Santander, Spain, [26]Medical University of Wrocław, Wrocław, Poland, [27]Division of Epidemiology, Mayo Clinic, Rochester, United States, University of Modena and Reggio Emilia, AOU Policlinico, Modena, Italy, [29]Division of Computational Genomics, Mayo Clinic, Rochester, United States, [30]Division of Hematology, Mayo Clinic Rochester Mayo Clinic, Rochester, United States, [31]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany, Biomedical Center in Pilsen, Charles University in Prague, Prague, Czech Republic, Radboud University Medical Center, Nijmegen, Netherlands, [34]Centre for Individualised Infection Medicine (CiiM) & TWINCORE, joint ventures between the Helmholtz-Centre for Infection Research (HZI) and the Hannover Medical School (MHH), Hannover, Germany, [35]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, United States, [36]Molecular Cytogenetics Laboratory, Hospital del Mar, Barcelona, Spain, Life and Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany, [38]Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Heidelberg, Germany, [39]Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany, [40]Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany, University of Granada (UGR), Granada, Spain

Background: Although genome-wide association studies (GWAS) have uncovered the germline genetic component underlying chronic lymphocytic leukaemia (CLL) susceptibility, the potential use of GWAS-identified risk variants to predict disease prognosis remains unmet.

Methods: We evaluated whether 41 GWAS-identified risk variants for CLL could influence the overall survival (OS) in a European cohort of 1039 CLL cases ascertained through the CRuCIAL consortium.

Forty-one single nucleotide polymorphisms (SNPs) were selected from results of published GWASs for CLL risk. The genotyping of the SNPs was carried out using KASPar® assays. The primary outcome was OS and the endpoint was defined as death from any cause. Survival time was calculated as the time from CLL diagnosis until the occurrence of the study endpoint, censoring at the date of death or the last observed follow-up time.

Association estimates were calculated using cox regression analyses and a polygenic risk score (PRS) was also computed to determine the utility of susceptibility markers associated with OS at a $p < 0.05$ to predict patient survival, considering either subjects with a call rate of 100% (n = 891) or 80% (n = 1003).

Considering the number of SNPs and the number of inheritance models tested (log-additive, dominant and recessive), we set a significance threshold to 0.00041. Finally, we also tested if any of the genetic markers correlated with cytokine expression quantitative trait loci (cQTL) data from in vitro stimulation experiments, but also absolute numbers of 91 blood-derived cell populations and 103 serum or plasmatic inflammatory proteins quantified in the 500 Functional Genomics cohort from the Human Functional Genomics Project (HFGP). Association analyses were performed using the STATA (v12.1) and power calculations were estimated using the survSNP package in R (v4.1.1).

Results: Cox regression analyses showed that 10 genetic variants (*CAMK2D*$_{rs1476569}$, *CASP8*$_{rs3769825}$, *CFLAR*$_{rs7558911}$, *CXXC1*$_{rs1036935}$, *GPR37*$_{rs2267708}$, *IRF8*$_{rs391855}$, *LEF1*$_{rs898518}$, *MYNN*$_{rs10936599}$, *PRKD2*$_{rs11083846}$, and *TERC*$_{rs12638862}$) were associated with OS at $p < 0.05$ level. Although none of these SNPs remained significant after correction for multiple testing, 9 of them (with the exception of the *CAMK2D*$_{rs1476569}$ variant) were found significantly associated with CLL at GWAS level in the CRuCIAL cohort ($< 5\times10^{-8}$), with might suggest common mechanisms for susceptibility and OS. We also found that none of these SNPs correlated with functional data, with the exception of the *CXXC1*$_{rs1036935}$ and *IRF8*$_{rs391855}$ SNPs that we have previously reported to be involved in modulating absolute numbers of specific subsets of B and T cells. As expected, and in agreement with a previous study that, using a similar approach, demonstrated that susceptibility variants do not influence the OS of patients diagnosed with multiple myeloma, another B-cell malignancy, the association between the weighted PRS and OS of CLL patients was modest (HR = 1.22, $p = 1.80\times10^{-05}$ and $HR_{Scaled\_80\%} = 1.19$, $p = 7.61\times10^{-05}$) and it did not substantially increase the capacity to predictive OS, only by 7% (AUROC = 0.57).

Conclusions: This study suggests that susceptibility variants for CLL do not largely influence the OS of CLL patients. Due to is the first study to investigate the association between CLL PRS on patient survival additional studies are warranted to confirm these results.

Disclosure: Authors declare that no conflict of interest exists in relation to the work described.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P455

AUTOLOGOUS STEM CELL TRANSPLANTATION IN RELAPSED OR REFRACTORY B-NON-HODGKIN LYMPHOMA - A

RETROSPECTIVE SINGLE-CENTER EXPERIENCE OF LONG TERM OUTCOME AND DEVELOPMENT OVER TWO DECADES

Judith Rexer[1], Knut Wendelin[2], Stefan Knop[2]

[1]Paracelsus Medical University, Nuremberg, Germany, Nuremberg, Germany

Background: B-Non-Hodgkin lymphoma (B-NHL) is the most common NHL and has relapse and refractory (r/r) rates up to 50% with consecutive autologous stem cell transplantation (ASCT). As new therapeutic approaches to these lymphoma entities are being explored, it was essential to perform a status quo analysis of ASCT as established relapse therapy recording survival rates and evaluate the role of distinct therapeutic regimens as well as patient and lymphoma characteristics with regard to survival times.

Methods: We retrospectively analyzed ASCTs in B-NHL over the last 20 years at the stem cell unit of Klinikum Nuremberg with targeted follow-up periods of > 36 months. There were 97 patients from 2001 and 2020 undergoing ASCT for r/r B-NHL. The estimated event-free survival (EFS) and overall survival (OS) were being computed via Kaplan-Meier. An event was defined as relapse, disease-related event or death of any cause. The survival rates with regard to dinstinct patient or therapeutic characteristics were compared via log-rank test, the hazards were calculated via cox-regression.

Results: We recorded estimated 1, 3 and 5-year EFS rates of 59%, 49%, 37% and OS rates of 72%, 59%, 44% respectively. ORR (overall response rates) after ASCT were 91%, from which 64% showed CR (complete response) and 27% showed PR (partial response). Patients in the first decade (n = 47) had longer EFS than patients in the second decade (n = 50) with 1-year EFS 71% vs. 44%, $p = .018$.

As statistically significant variables for survival time we identified age ($p = .005$), IPI ($p = .008$) and LDH measured two months after ASCT ($p < .001$)

We observed a tendency of (R)-DexaBEAM (n = 16) as salvage regimen resulting in better OS than (R)-DHAP (n = 46), though this was not statistically significant ($p = .167$).

Kaplan-Meier curve shows differences in overall survival in groups of low and high LDH level measured two months after ASCT with 250 U/l as cut-off point ($p < .001$).

Conclusions: The results of our analysis of survival outcome in r/r B-NHL can be used as a reference in other analyses and for comparing new innovative treatment options with established therapy.

The LDH level at time of re-staging could be shown to have prognostic value for further disease progression and can be used as prognostic marker that can be incorporated in planning of follow-up frequency.

(R)-DexaBEAM as salvage therapy has not been used in a high frequency in the last years. We could show the tendency of better outcomes compared to (R-)DHAP. This regimen should be reconsidered as a valuable treatment option and be analyzed in further investigations.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

P456

COMPLETE REMISSION AFTER RELAPSE FOLLOWING ALLOGENIC STEM CELL TRANSPLANTATION IN A PATIENT WITH PERIPHERAL T NON-HODGKIN LYMPHOMA UNDERGOING EXTRACORPOREAL PHOTOPHERESIS

Igor Age Kos[1], Onur Cetin[1], Jörg Bittenbring[1], Moritz Bewarder[1], Konstantinos Christofyllakis[1], Zanir Abdi[1], Lorenz Thurner[1]

[1]University of Saarland, Homburg, Germany

Background: Angioimmunoblastic T-cell lymphoma (AITL) is a subtype of mature peripheral T-cell lymphoma (PTCL) (WHO Classification of Tumours), which represents 1-2% of non-Hodgkin lymphomas. Many patients present with a refractory disease and may undergo allogenic stem cell transplant (alloSTC) as an individual curative attempt. Since many patients are poor responders to chemotherapy, graft versus lymphoma effect (GvL) plays an important role. Extracorporeal Photopheresis (ECP) is an efficient therapy for cutaneous lymphomas and GvHD, nevertheless it has no proven efficacy for AITL. Here we report the case of a patient who presented a complete disease remission after relapse following alloSTC without lymphoma-specific therapies while undergoing ECP due to severe GvHD.

Methods: Case report of single patient.

Results: 71-year-old patient who presented with new onset lymphadenopathy in January of 2020. A biopsy of an inguinal lymph node showed a T-cell lymphoma of angioimmunoblastic type (AITL). Ann Arbor Stage was IIIB. The patient received 4 cycles of chemotherapy with cyclophosphamide, doxorubicine, vincristine and prednisone (CHOP) achieving a partial remission. For consolidation, the patient underwent a high dosage (HD) chemotherapy with BEAM (Carmustine, Etoposide, Cytarabine and Melphalan) with autologous stem cell support. Three months after HD chemotherapy, he showed once more disease progress. As salvage therapy with ICE (Ifosfamide, Carboplatin and Etoposide) was performed, nevertheless, re-staging showed new signs of progressive disease. Due to unresponsiveness to chemotherapy, we opted for an allogenic stem cell transplantation, since one matched unrelated donor with DPB1 mismatch was available. As conditioning therapy, he received a non-myeloablative regimen with cyclophosphamide and fludarabine. For GvHD prophylaxis, we opted for ATG at a 20mg/kg dose over three days before transplant and Tacrolimus starting on day -1. Two months later, in December of 2020, a re-staging with FDG-PET/CT showed a complete remission of the lymphoma. In January 2021 he developed skin GvHD grade III. Tacrolimus' targets were lower due to frequent infections. As steroid treatment did not result in clinical improvement, we began a therapy with ruxolitinib. In February 2021 a new PET-CT was performed in February of 2021, which showed multi nodal involvement. An excisional biopsy confirmed relapse of the AITL. At the same time, he presented worsening of the skin GvHD(g rade IV). Considering his reduced performance status (ECOG III) we began a therapy with extracorporeal photopheresis (ECP) as an attempt to improve quality of life. Immunosuppression with tacrolimus was later stopped. After 6 cycles of ECP (at two weekly intervals) the patient showed improvement of the skin (grade II). Re-staging showed a surprisingly complete remission of the AITL. ECP was continued every four weeks. In August of 2021 the patient presented a flare of the ECP, which could be managed with steroids. The patient is still in complete remission.

Conclusions: The exact trigger trough which GvL was stimulated remains unclear, however there is a temporal correlation between the start of ECP and achivevement disease control. Even though it remains speculative, the immunomodulatory effect of ECP may have induced GvL, through reversion of T-cell exhaustion or even inducing anti-tumor activity.

Disclosure: IK, OC and ZA declare no conflicts of interest. L.T. received travel support from EUSA Pharma, Janssen and Abbvie, and received honoraria for advisory boards from Takeda, AstraZeneca, Merck and EUSA Pharma. J.T.B. received travel support from Gilead and received honoraria as an advisory board member from Roche and Novartis. M.B. received travel support from Abbvie and

grants from the non-profit Deutsche José-Carreras Leukaemie Stiftung. All authors declare no competing interests.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P457

SEQUENTIAL QUANTIFICATION OF T-CELL RECEPTOR EXCISION CIRCLES (TREC) PREDICTS LONG-TERM OUTCOMES OF EARLY SURVIVORS AFTER ALLOGENEIC HSCT

Carlos De Miguel Jimenez[1], Ferran Briansó[2], Rosalia Alonso[1], Maria Esther Martinez-Muñoz[1], Guiomar Bautista[1], Carlos Manchado-Perdiguero[2], Jose Antonio Garcia-Marco[1], Ali Sanchez-Peral[2], Rafael Duarte[1]

[1]Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain, Roche, Barcelona, Spain

Background: The analysis of TREC to assess immune recovery and predict patient outcomes after allogeneic HSCT has been traditionally limited by technical and methodological heterogeneity that prevented comparison and validation of results among centres.

Methods: We performed absolute TREC quantification using a standardized platform with LightCycler 480 and TREC-KREC-ACTB primers (Roche Diagnostics, Barcelona, ES) on sequential PBMC samples collected prospectively (pre-transplant, 1, 3, 6 and 12-months post-transplant) in alloHSCT recipients for hematological malignancies between 1999 and 2017. Funded by the Spanish CDTI (IDI-20180259).

Results: Three-hundred and seventy-four allogeneic HSCT in 350 patients are included: 59.6% men; median age 45 (16-68); ALL/AML/MDS 69.8%, lymphoma 22.2%, myeloma 8%; 52.9% matched related, 30.5% cord blood, 13.1% matched unrelated, 3.5% haploidentical. We have previously communicated (EBMT 2021 abstract 550 OS6-3) that pre-transplant TREC values associate with patient age ($p < 0.001$) and underlying malignancy ($p = 0.001$), as well as with non-relapse mortality (NRM) and overall survival (OS). Patients with higher pretransplant TREC values had a reduced NRM ($p = 0.044$; 17% vs 35% at 1 year) and an increased OS ($p < 0.001$; 78% vs 65% at 1 year), independently from clinical factors such as age and type of HSCT in multivariate analyses. Now, here we have carried out landmark analyses at 6 and 12 months that further confirm that higher TREC recovery at those same timepoints strongly and independently associate with improved long-term outcomes after transplant. Our data show that early survivors at 6 months after HSCT with TREC levels >=0.1 U/R have a significantly superior OS 5 years later (72% vs 39%; $p < 0.001$), and that early survivors at 12 months after HSCT with TREC levels >=0.4 U/R also have a significantly superior OS 5 years later (83% vs 47%; $p < 0.001$). Furthermore, in the multivariate analyses, these associations are independent from other patient and transplant factors, including GVHD, both at 6 months (HR 0.33 [0.13-0.81], $p = 0.016$) and 12 months (HR 0.13 [0.04-0.42], $p < 0.001$).

Conclusions: Sequential quantification of TRECs in alloHSCT recipients using a standardized commercial platform provides novel biomarker measurable data that associate with patient and transplant characteristics and outcomes. Pre-transplant TREC levels have an independent association with patient NRM and OS that may help decision-making that is currently based only on clinical factors. Now, these data suggest that the recovery of TREC levels at 6 and 12 months after transplant strongly associate with better long-term survival, providing a novel objective tool to predict long-term outcomes of early survivors after alloHSCT. External, multicenter, prospective validation of these results through the standardized LightCycler 480/TREC-KREC-ACTB platform is warranted.

Disclosure: No conflict of interest. Funded by the Spanish CDTI (IDI-20180259).

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P458

GRADE I-II ACUTE GVHD PROTECTS FROM RELAPSE IN CHILDREN WITH ALL CONDITIONED WITH TBI AND VP-16 DESPITE MRD POSITIVITY PRE-HSCT

Adriana Balduzzi[1], Peter Bader[2], Jean-Hugues Dalle[3], Franco Locatelli[4], Raquel Staciuk[5], Jacek Wachowiak[6], Petr Sedlacek[7], Jochen Büchner[8], Tayfun Güngör[9], Luisa Sisinni[10], Marc Bierings[11], Peter Svec[12], Evgenia Glogova[13], Ulrike Poetschger[13], Christina Peters[14], Marianne Ifversen[15]

[1]Università degli Studi di Milano-Fondazione MBBM, Monza, Italy, [2]Goethe University Hospital, Frankfurt, Germany, [3]Robert Debré Hospital, Paris, France, [4]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [5]Hospital de Pediatría, Buenos Aires, Argentina, [6]Poznań University of Medical Sciences, Poznan, Poland, [7]Motol University Hospital, Prague, Czech Republic, [8]Oslo University Hospital, Oslo, Norway, [9]Universitäts-Kinderspital, Zürich, Switzerland, [10]Hospital Santa Creu, Barcelona, Spain, [11]Princess Maxima Hospital, Utrecht, Netherlands, [12]Comenius University, Bratislava, Slovakia, [13]Children's Cancer Research Institute, Vienna, Austria, [14]St. Anna Children's Hospital, Vienna, Austria, [15]Copenhagen University Hosptial, Copenhagen, Denmark

Background: Pre-transplant MRD is known to impact the outcome of patients with ALL. We aimed to assess the impact of MRD at HSCT within the expanded FORUM trial, enrolling patients with ALL in CR, diagnosed at <18 years.

Methods: All FORUM patients 4 years or older transplanted from a matched donor and conditioned with TBI were eligible for the study, as long as their MRD at HSCT (within 45 days), detected either by PCR or FCM, was available. MRD was classified as negative (undetectable or < 0.01%) or positive (≥ 0.01%) and will be labelled as MRD- and MRD+ henceforth.

Results: 485 patients ≥4 years (32% female, median age 10 years), transplanted after TBI from an HLA-identical sibling (147) or a matched unrelated donor (338) of the 728 (62%) eligible patients who had MRD upon HSCT available were included in the study. 48% were transplanted in CR1, 44% in CR2 and 8% in >CR2.

Upon HSCT 390 patients (80%) were MRD- and 95 patients (20%) MRD + .

At 3 years after HSCT, overall survival (OS) was 83% (±3%) and 69% (±6%) (p-value 0.003), event-free survival (EFS) 77% (±3%) and 60% (±6%) (p-value 0.003), cumulative incidence of relapse (CIR) 15% (±2%) and 31% (±6%) (p-value 0.006), transplant-related mortality (TRM) 6% (±1%) and 8% (±3%) (p-value 0.350) in patients with MRD- and MRD+ upon HSCT, respectively.

For patients surviving in CR at 100 days, GVHD was absent, grade I-II or III-IV in 38%, 53% and 9% of the patients, respectively. 3-year EFS was 86% (±3%) in MRD- patients who experienced grade I-II acute graft-versus-host disease (aGVHD), 78% (±5%) in MRD- patients who experienced no aGVHD, 69% (±9%) in MRD+ patients who experienced grade I-II aGVHD and 65% (±10%) in MRD+ patients who experienced no aGVHD (p-value 0.008). Three-year CIR was 10% (±3%) in MRD- patients who experienced grade I-II aGVHD, 17% (±4%) in MRD- patients who experienced no aGVHD, 26% (±9%) in MRD+ patients who experienced grade

I-II aGVHD and 32% (±9%) in MRD+ patients who experienced no aGVHD (p-value 0.034).

In multivariate analysis, the HR of relapse of being MRD+ versus MRD- was 2.31-fold higher (p-value 0.003), the HR of any treatment failure (1y-EFS) 2.12-fold higher (p-value 0.001), the HR of death (1y-OS) 2.31 (p-value 0.001). The HR of treatment-related mortality (TRM) was not significantly different. Having experienced grade I-II aGVHD was protective for relapse (HR 0.55, p-value 0.0028) and associated with better EFS (HR 053, p-value 0.007). The model was adjusted for age, remission phase, which significantly affected outcome, and for immunophenotype and type of donor, which did not significantly affect outcome.

Conclusions: MRD level at HSCT was confirmed as one of the strongest factors affecting outcome, by doubling the risk of relapse or death. Low grade aGVHD was protective against relapse, even in case of MRD positivity at HSCT.

Disclosure: Christina, Peters: Grants from Amgen, Neovii, Jazz.and payment/honoraria from Riemser, medac.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P459

COMPARISON OF IMMUNE RECONSTITUTION BETWEEN MATCHED UNRELATED AND HAPLOIDENTICAL DONOR FOR ALLOGENEIC STEM-CELL TRANSPLANTATION IN PATIENTS WITH ACUTE LEUKEMIA WITH IDENTICAL CONDITIONING AND PTCY GVHD-PROPHYLAXIS

Radwan Massoud[1], Evgeny Klyuchnikov[1], Nico Gagelmann[1], Ameya Kunte[1], Ulrike Fritzsche-Friedland[1], Marion Heinzelmann[1], Gaby Zeck[1], Dietlinde Janson[1], Francis Ayuk[1], Christine Wolschke[1], Nicolaus Kröger[1]

University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Studies investigating the influence of donor type on immune reconstitution are confounded by different GVHD-prophylaxis regimens, heterogeneity of diseases, stem cell sources and conditioning protocols. The homogeneity of the patient's population and GVHD-Prophylaxis limits confounding factors when investigating the influence of donor type on IR. In this study we aim to investigate the influence of donor type (Haplo vs MUD) on immune reconstitution using identical conditioning regimen and identical post-transplant Cyclophosphamide based GvHD prophylaxis.

Methods: This study was conducted at University-Medical-Center-Hamburg-Eppendorf between the years 2019-2022 and included 27 consecutive acute Leukemia patients who underwent allo-SCT from MUD (n = 13) or Haplo (n = 14). All Patients were transplanted in CR (CR1 n = 22, CR2 n = 5) received MAC (TBI-Flu n = 10, BuFlu n = 17), PBSC as stem cell source and 50mg/kg/day PTCY on days+3 + 4 combined with Tacrolimus from day+5 to day+120 and mycophenolate mofetil from day +5 to +35. Immunophenotypes were assessed at day +30 and +100 using four color cytometry using mouse anti-human antibodies for the following cells: T-lymphocytes (CD3 +), activated-T-lymphocytes (CD3 + HLADR +), T-helper (CD3 + /CD4 +), T-cytotoxic (CD3 + / CD8 +), B-lymphocytes (CD19 +), B-lymphocytes subpopulations (CD19 + CD5 + CD1d +)(CD19 + CD27 +), naïve-B-cells (CD19 + CD27-CD10 +), NK-cells (CD56 + CD3-), NKT-cells (CD56 + CD3 +), naïve-T-helper (CD4 + CD45RA +), memory-T-helper (CD4 + CD45R0 +), naïve-T-cytotoxic (CD8 + CD45RA +), memory-T-cytotoxic (CD8 + CD45R0 +), γδT-cells (γδTCR + ,CD3 +), regulatory-T-cells (CD4 + CD25+CD127low-neg).

Results: Patients' donor and transplant characteristics were comparable in both groups. (Table1). The median time to leucocytes engraftment was 16 days (range, 14-34) in the MUD group vs 16 days (range, 13-20) in the Haplo group. The median time to platelets engraftment was higher in the Haplo group however the difference was not statistically significant (MUD median 14days (range, 8-34) vs Haplo 18 days (5-38), p = 0.8). There were no differences in IR regarding T, B and NK cell compartment early after SCT on day 30 or later on day 180 between Haplo and MUD.

	MUD N (%)	Haplo N (%)	P
Disease			
AML	9 (69)	8 (57)	NS
ALL	4 (31)	6 (43)	NS
Disease Status at SCT CR1/CR2	12 (92) / 1 (8)	10 (71)/ 4 (29)	NS
Disease Risk			
ELN high-Risk	4(31)	5 (36)	NS
ELN intermediate risk	5 (39)	3 (21)	NS
ESMO high-Risk	3 (23)	3 (21)	NS
Patient age median (range)	53 (19-68)	51 (25-70)	NS
Patient Sex			NS
Male/Female	8 (67) / 4 (33)	8 (57) / 6 (43)	
Patient CMV serology			NS
negative	5 (39)	6 (46)	
Positive	8 (62)	7 (54)	
Donor age median (range)	29 (20-49)	37 (20-44)	NS
Donor gender			NS
Male / Female	11 (85) / 2 (15)	9 (69) / 4 (31)	
Donor CMV serology			NS
negative	6 (46)	6 (46)	NS
positive	7 (54)	7 (54)	NS

Conclusions: This preliminary data showed that IR between MUD and Haplo is comparable if same conditioning and same GvHD prophylaxis is used and the in literature described delayed IR after Haplo is most likely due to difference in GvHD prophylaxis rather than due to donor source.

Disclosure: nothing to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P460

ROLE OF HLA EVOLUTIONARY DIVERGENCE IN SINGLE HLA-MISMATCHED UNRELATED DONOR HCT FOR MALIGNANT HEMATOLOGICAL DISORDERS: A REPORT ON BEHALF OF THE CTIWP OF THE EBMT

Simona Pagliuca[1], Jarl E. Mooyaart[2], Nicolaus Kröger[3], Jürgen Finke[4], Victoria Potter[5], Peter Dreger[6], Inken Hilgendorf[7], Wolfgang Bethge[8], Régis Peffault de Latour[9], Alessandro Rambaldi[10], Henrik Sengeloev[11], Jakob Passweg[12], Tobias Gedde-Dahl[13], David Burns[14], Kim Orchard[15], Stephan Mielke[16], Matthias Edinger[17], Marco Andreani[18], Pietro Crivello[19], Pietro Merli[18], Jorinde D. Hoogenboom[20], Liesbeth C. de Wreede[21], Christian Chabannon[22], Jurgen Kuball[23], Carmelo Gurnari[24], Katharina Fleischhauer[19], Annalisa Ruggeri[25], Tobias L. Lenz[26]

[1]CHRU de Nancy, Vandœuvre-lès-Nancy, France, [2]EBMT Statistical Unit, Leiden, Netherlands, [3]University Hospital Eppendorf, Hamburg,

Germany, [4]University of Freiburg, Freiburg, Germany, [5]Kings College Hospital, London, United Kingdom, [6]University of Heidelberg, Heidelberg, Germany, [7]Universitaetsklinikum Jena, Jena, Germany, [8]Universitaet Tuebingen, Tuebingen, Germany, [9]Saint-Louis Hospital, BMT Unit, Paris, France, [10]ASST Papa Giovanni XXIII, Bergamo, Italy, [11]Bone Marrow Transplant Unit L 4043, Copenhagen, Denmark, [12]University Hospital Basel, Basel, Switzerland, [13]Oslo University Hospital Rikshospitalet, Oslo, Norway, [14]University Hospital Birmingham NHSTrust, Stoke, United Kingdom, [15]Southampton General Hospital, Southampton, United Kingdom, [16]Karolinska University Hospital, Stockholm, Sweden, [17]University Regensburg, Regensburg, Germany, [18]IRRCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [19]Institute for Experimental Cellular Therapy, University Hospital Essen,, Essen, Germany, [20]EBMT Leiden Study Unit, Leiden, Netherlands, LUMC, Leiden, Netherlands, [22]Institut Paoli-Calmettes, Comprehensive Cancer Center & Aix-Marseille Université - Inserm CBT-1409, Marseille, France, [23]University Medical Centre, Utrecht, Netherlands, University of Rome Tor Vergata, Rome, Italy, [25]San Raffaele Scientific Institute, Hematology and Bone Marrow Transplantation Unit, Milan, Italy, [26]Evolutionary Immunogenomics, University of Hamburg, Hamburg, Germany

Background: In allogeneic hematopoietic cell transplantation (allo-HCT), alloreactive T-cell responses (graft versus leukemia - GvL and graft versus host disease - GvHD) are mediated by the interaction between recipient antigens and donor lymphocytes via human leukocyte antigen (HLA) molecules. HLA evolutionary divergence (HED) is an emerging metric that characterizes functional differences between the peptide binding sites of two homologous HLA alleles and is correlated with the breadth of pathogen and cancer-specific immune peptidomes (**A**). Here, we hypothesize that differences in donor and recipient HED may modulate alloreactivity possibly informing on post-transplant outcomes. We tested this hypothesis in onco-hematologic patients undergoing allo-HCT from a single HLA-A, -B, -C, -DRB1, or –DB1 (9/10) mismatched unrelated donor (MMUD) at EBMT centers.

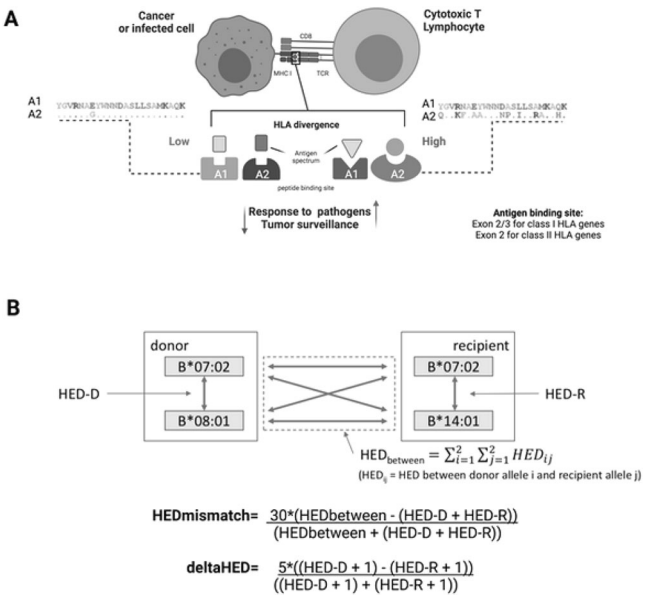
Methods: We included patients with selected hematological malignancies for whom complete clinical and HLA information was available in the EBMT database. Individual locus-specific recipient/donor HED (HED-R, HED-D) and inter-individual mismatch HED scores were computed as previously described[1]. The latter were considered as: DeltaHED (score range -5 to 5), i.e. the relative directional difference between HED-D and HED-R, or as HEDmismatch (score range 0 to 10), i.e. HED of the mismatched locus between donor and recipient (**B**). Using multivariable cox-regression (cause-specific) models, we investigated the associations of HED-R, HEDmismatch and DeltaHED with relapse-free survival (RFS), overall survival (OS), non-relapse mortality (NRM), incidence of relapse and of grade II-IV acute and chronic GvHD. For each outcome and in each mismatched subgroup, we built separate models for DeltaHED and HEDmismatch, including locus-specific HED-R and relevant clinical variables (**Table 1**). To account for multiple comparisons, a p-value < 0.01 was considered significant.

Results: Overall, 4639 adult patients received a 9/10 MMUD allo-HCT between 2010 and 2019 for acute leukemia (N = 3853, 83%), myelodysplastic syndrome or myeloproliferative neoplasms (N = 786, 17%). Median recipient age was 53.54 (40.28-61.96), median donor age was 33.07 (24.95-40) and male/female ratio was 1.28. Majority of patients (90%) received peripheral blood stem cells and were mismatched for locus A (33%), followed by C (21%), B (15%), DQB1 (14%) and DRB1 (6%). We observed that most interactions occurred with class II-related metrics. In particular, increasing HEDmismatch scores at DQB1 locus were associated with improved OS in the overall cohort [HR:0.97 (95%CI 0.95-0.99), p = 0.009], whereas higher HED-R DRB1 negatively influenced survival outcomes of the HLA-B [HR: 1.03 (95%CI 1.01-1.06), p = 0.008] and DRB1 mismatched subgroups [HR:1.02 (95%CI 1.02-1.12), p = 0.009]. In the latter, patients with higher HED-R DRB1 also showed significantly worse RFS [HR:1.07 (95%CI 1.02-1.12), p = 0.003] and NRM [HR:1.11 (95%CI 1.03-1.2), p = 0.006]. Finally, ascending DeltaHED scores at HLA-A were found to be associated with lower risk of chronic GvHD in the HLA-DRB1 mismatched subgroup [HR:0.93 (95%CI 0.89-0.98), p = 0.008]. No significant associations with post-transplant outcomes were found with any of the other metrics.

Conclusions: Here, we assessed the prognostic significance of donor-recipient immunogenetic configurations in MMUD allo-HCT, creating a statistical framework predicting outcomes, regardless of any other transplant-related factor. These results inform on how the spectrum of donor-recipient HLA divergences may influence alloreactive responses, with a potential impact on future donor selection strategies.

Table 1: Clinical variables integrated into each HED model

Stem-cell source
Patient age (in decades)
Donor age (in decades)
Diagnosis at transplant
T-cell depletion
Donor sex match
Karnofsky score
CMV -/- vs. other
Disease stage at transplant
Year of transplant
Total body irradiation
Conditioning intensity
GVHD prophylaxis



Disclosure: TLL is co-inventor on a patent application for using HED as a prognostic marker for immunotherapy success. The other authors declare the absence of any commercial or financial conflict of interest.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P461

NPM1(+) AML PATIENTS UNDERGOING ALLOGENEIC TRANSPLANTATION IN FIRST OR SECOND REMISSION: MEASURABLE RESIDUAL DISEASE PREDICTS OUTCOME

Apostolia Papalexandri[1], Sotiria Dimou-Besikli[1], Christos Demosthenous[1], Eleni Paphianou[1], Fotini Kika[1], Kira Panteliadou[1], Nikos Spyridis[1], Zoe Boussiou[1], Giannis Kyriakou[1], Anna Vardi[1], Tasoula Touloumenidou[1], Panagiota Zerva[1], Maria Georgia Koutra[1], Angeliki Paleta[1], Georgia Konstantinidou[1], Lamprini Vachtsetzi[1], Chrisavgi Lalayanni[1], Eleni Gavriilaki[1,2], Maria Papathanasiou[1], Anastasia Marvaki[1], Antonia Syrigou[1], Georgios Karavalakis[1], Vasiliki Douka[1], Stefanos Finitsis[3], Anastasia Athanasiadou[1], Ioanna Sakellari[1]

[1]G. Papanikolaou Hospital, Thessaloniki, Greece, Aristotle University of Thessaloniki, Thessaloniki, Greece, [3]Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) offers the best chance for relapse-free survival (RFS) to most patients with acute myeloid leukemia (AML) but is accompanied by treatment-related mortality. The choice to offer allo-HSCT between patients in first (CR1) or second (CR2) complete remission is usually guided by the expected genetic risk, as defined by the 2022 ELN criteria. AML with mutated NPM1(NPM1 +), when not accompanied by FLT3-ITD is considered low risk and not consolidated with allo-HSCT in CR1. Relapse occurs, however, in a considerable proportion and allo-HSCT in CR2 the only curative option. Concurrent FLT3-ITD indicates intermediate risk and allo-HSCT in CR1 is reasonable. MRD guided decisions on whether to perform allo-HSCT in CR1 or CR2 gain ground.

The main objective of this study was to study the effect of MRD status in AML NPM1+ patients transplanted in first or second remission.

Methods: We retrospectively analysed AML NPM1+ patients who underwent allo-HSCT in CR1 or CR2 between 2012 and 2022. Overal survival (OS) and Relapse Free Survival (RFS) were calculated from HSCT until death from any cause and relapse, respectively. MRD was measured by Q-PCR for NPM1 mutation during treatment, pre-HSCT and post-HSCT. NPM1mutated copies/ABL copies > = 10-3 was considered as MRD positive and low level MRD(< 10-3) or non-detectable disease as MRD negative.

Results: Among 39 patients (10 female, 29 male) with NPM1 + AML, n1 = 18 were transplanted in CR1 and n2 = 21 in CR2. Median follow-up after HSCT for living patients was 26 months (3-71). The majority of the patients (24/39, 62%) received graft from a Volunteer Unrelated Donor (VUD), 9/39 from identical sibling and 6/39 from haplo-identical relatives. Conditioning was myeloablative (19/39), non-myeloablative(17/39) or reduced intensity(3/39). There was no statistical difference in donor selection between patients receiving transplant in CR1 vs CR2. Median age at HSCT was 49 (range, 22-65) years. As expected, patients transplanted in CR1 were more likely to have FLT3-ITD (14/18, 78%, vs 2/21, 9%, $p < 0.05$). 50% OS was 31 months (95%CI: 17.8-48) and was not related to FLT3-ITD, conditioning, CR status in allo-HCT and MRD pre-HSCT or MRD at +3 months post-HSCT. MRD status, however, was relevant to relapse: Patients with negative MRD pre-HSCT were less likely to relapse: HR:0,21, (95%CI:0.04-1.07, $p = 0.06$) either in CR1 or in CR2. Moreover, patients with positive MRD + 3 months post HSCT were more likely to relapse: HR:5.1, (95%CI:1.04-25.6, $p = 0.01$), regardless the remission status at transplantation. RFS was not related to FLT3-ITD, conditioning and was similar in CR1 or CR2 patients.

Conclusions: Patients with AML NPM1+ who are transplanted in CR2 benefit similar to those transplanted in CR1, regarding OS. MRD status provides high prognostic value with dismal outcomes for patients who were MRD^+ before and early after transplantation. Negativity of MRD should be a goal in order to best benefit from allo-HSCT.

Disclosure: No conflict of interest to disclose.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P462

HUMAN HERPESVIRUS 6 SPECIFIC T-CELL IMMUNITY IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Maddalena Noviello[1], Francesca Lorentino[1], Elisabetta Xue[1], Sara Racca[1], Giulia Furnari[2], Veronica Valtolina[1], Edoardo Campodonico[1], Roee Dvir[1], Maria Teresa Lupo-Stanghellini[1], Fabio Giglio[1], Simona Piemontese[1], Daniela Clerici[1], Chiara Oltolini[1], Elena Tassi[1], Valeria Beretta[1], Francesca Farina[1], Daniele Mannina[1], Anna Ardemagni[1], Luca Vago[1], Massimo Bernardi[1], Consuelo Corti[1], Jacopo Peccatori[1], Massimo Clementi[1], Fabio Ciceri[2], Chiara Bonini[2], Raffaella Greco[1]

[1]IRCCS Ospedale San Raffaele, Milan, Italy, [2]Università Vita-Salute San Raffaele, Milan, Italy

Background: Human herpesvirus-6 (HHV-6) can reactivate after allogeneic hematopoietic stem cell transplantation (allo-HSCT), and may lead to severe clinical manifestations. HHV-6 specific immune responses after HSCT are largely unexplored.

Methods: Herein, we conducted a prospective observational study on a cohort of 208 consecutive adult patients who received allo-HSCT, in order to investigate HHV-6 reactivation and specific immune responses. Numbers of IFN-γ-producing HHV-6 T-cells were determined by enzyme-linked immunospot assay (ELISpot).

Results: HHV-6 reactivation occurred in 63% of patients. Median time from allogeneic HSCT to first HHV-6 reactivation was 25 days. Only 40% of reactivating patients presented a clinically relevant infection, considered as the presence of HHV-6 end organ diseases (EOD) according to ECIL consensus, including encephalitis and delayed engraftment. Moreover, while aware of the weak association between HHV6 and others EOD, and prospectively ruling out other concomitant causes, we considered as possible HHV6-related EOD also pneumonitis, hepatitis and gastrointestinal infection. All patients with clinically relevant HHV-6 infection received antiviral treatment according to center guidelines.

Through multivariate analysis, we identified the following risk factors for HHV-6 reactivation: previous allo-HSCT (Hazard Ratio, HR 2.89; p-value < 0.01), post-transplant cyclophosphamide (PT-Cy; HR 2.59; p-value < 0.01), time-dependent introduction of steroids (HR 3.64; p-value < 0.01). The use of PT-Cy (HR 3.77; p-value < 0.01) and steroids (HR 2.74; p-value < 0.01) were significantly associated to clinically relevant infections, whereas higher $CD3^+$ cell counts (> 100/μl; HR 0.23; p-value = 0.02) seemed to be protective.

Interestingly, the number of circulating IFN-γ-producing HHV-6 specific T-cells was significantly higher in reactivating patients. Moreover, we found that IFN-γ ELISpot assay for HHV-6-specific T-cell quantification, performed at ≥4 days after the first positive HHV-6 DNAemia predicts clinically relevant HHV-6 infections (p-value < 0.0001). The ROC analysis identified a threshold of ≥18 HHV6-specific spot forming cells (sfc)/10^5 PBMC, found to be highly significant in distinguishing patients at risk to develop

clinically relevant infections, with higher specificity (93%) and sensitivity (79%) than polyclonal $CD3^+$ cell counts (< 100/µl; specificity=59%; sensitivity=36%).

The hazards of overall survival (OS) and transplant-related mortality (TRM) were not affected by time-dependent HHV-6 reactivation, while a significant association was observed between a clinically relevant infection and acute graft-versus-host disease.

Conclusions: These results shed light on the role of HHV-6 in allo-HSCT recipients and may impact on HHV-6 monitoring and treatment.

Disclosure: Nothing to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P463

THE OCCURRENCE AND PROGNOSIS OF MIXED CHIMERISM POST HSCT: A MULTISTATE ANALYSIS

Erik G J von Asmuth[1], Hein Putter[1], Dagmar Berghuis[1], Joëll E Bense[1], Anne P J de Pagter[1], Emmeline P Buddingh[1], Robbert G M Bredius[1], Frans J Smiers[1], Alexander B Mohseny[1], Arjan C Lankester[1]

[1]Leiden University Medical Centre, Leiden, Netherlands

Background: Mixed chimerism (MC), the persistence of autologous haematopoietic cells after allogeneic HSCT, is associated with complications including recurrence of disease and graft loss. Existing literature often either assumes mixed chimerism is permanent, or only analyses a single timepoint.

Methods: We included patients transplanted for inborn errors of immunity (IEI) and hemoglobinopathies (HBP) between 2008 and September 2022 and used multistate models to analyse MC in the context of death and subsequent transplants, while allowing MC to convert to full donor chimerism (FDC) or regress to loss of chimerism (LOC).

Chimerism was defined based on circulating granulocytes analysed by VNTR to directly reflect HSC progeny, with FDC defined as >95% donor cells, LOC as ≤ 5% donor cells, and MC in between.

Results: 230 patients were included, with 120 receiving a HSCT for a HBP, and 110 for an IEI. Unrelated donor (UD) transplants were most common (61%), with 27% having a matched sibling (MSD) and 11% a haploidentical donor. Graft source was bone marrow in the majority of transplants. On average, patients had 7 chimerism measurements during the first year after SCT.

At day 100, 69.1% of patients achieved FDC, 17.4% had MC, 1.7% had LOC, 6.1% died, and 5.7% received a second transplant. At 1 year, 57.5% had FDC, while 20.2% had MC and 1.5% had LOC, 12.4% received a retransplant, and 8.3% died. FDC was similar between UD and MSD (59.4 vs 61.7% at 1 year), however, there was less MC (19.2 vs 27.2%) and more mortality (11.4 vs 3.2%) in the UD group. This trend held when analysing IEI and HBP separately. In a 100-days landmark analysis, both the occurrence of acute Graft vs Host disease and CMV reactivations did not influence MC.

Analysing the clinical course starting at +1 year, patients with MC then still had MC at +2 years in 89.1% of cases, with 2.4% converting to FDC, 2.3% to LOC, and 6.2% needing a subsequent transplant. At 5 years, 5.4% had FDC, 8.7% LOC, and 14.2% underwent retransplant. When being in FDC at 1 year, 5.1% had MC at 2 years, which increased to 6.3% at 5 years. The cumulative rate of death or second transplant was 4.7% at 5 years. Patients that experienced MC after being FDC at 1 year had not had MC at any time in the first year in 7 of 10 cases.

Conclusions: By analysing chimerism continuously from the start of SCT with multistate models, we can accurately analyse the occurrence of MC and its clinical course. Myeloid mixed chimerism at 1 year strongly influences prognosis, with over 3 times as many patients either dying or needing a second transplant than those in FDC.

We demonstrated that transitions from FDC to MC can occur beyond 1 year after SCT, often in patients that had not had myeloid MC previously, and sometimes with chimerism being entirely undetectable in the first year. To further elucidate this phenomenon, more research is needed, especially from a stem cell biology perspective.

Disclosure: Nothing to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P464

STABLE MIXED T-CELL CHIMERISM AFTER HCT FOR SEVERE APLASTIC ANAEMIA DOES NOT PREDICT GRAFT LOSS AND DOES NOT MANDATE IMMUNOMODULATION

Rubiya Nadaf[1], Ramya Nataraj[1], Denise Bonney[1], Madeleine Powys[1], Srividhya Senthil[1], Omima Mustafa[1], Kay Poulton[2], Helena Lee[2], Robert Wynn[1]

[1]Royal Manchester Childrens Hospital, Manchester, United Kingdom, [2]Manchester Royal Infirmary, Manchester, United Kingdom

Background: The occurrence of mixed chimerism (MC) is influenced by the intensity of immune-ablative therapies before and preparative regimens during the hematopoietic stem cell transplant (HCT) and the incidence is particularly high in severe aplastic anemias (SAA) due to the use of reduced-intensity conditioning (RIC) regimens. The literature demonstrates declining donor chimerism levels are associated with graft loss and rejection warranting interventions including escalation of immunosuppression, or donor lymphocyte infusion.

Methods: We reviewed 41 patients aged 1-16 years, treated with allogeneic HCT using bone marrow or PBSC for non-constitutional severe aplastic anemias at Royal Manchester Children's Hospital. All patients with SAA received RIC regimen with Fludarabine combined with cyclophosphamide. All patients received serotherapy, usually with Alemtuzumab. Patients were categorized into mixed chimerism (MC) and complete chimerism (CC) groups. Complete chimerism was defined as greater than 98% of the donor whole blood (WB). We assessed the disease response to the transplant in both groups using disease-specific measures.

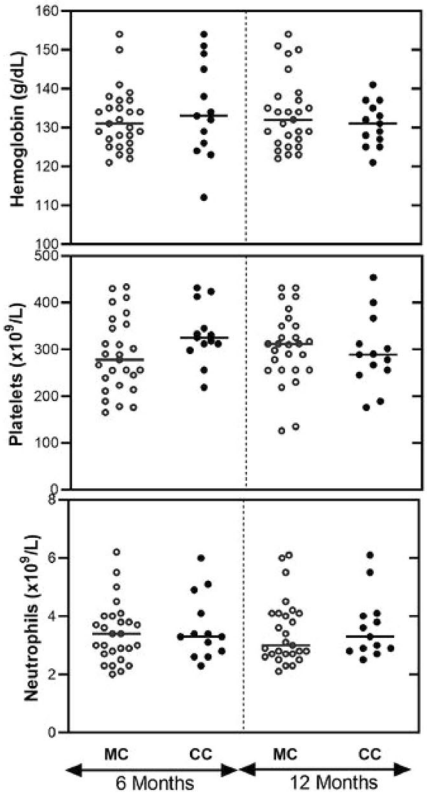
Results: **Transplant outcomes:** Thirteen (31.7%) patients were always fully donor-engrafted after transplant using WB chimerism, and 28 (68.2%) had mixed stable chimerism, always with mixed T-cell chimerism but fully donor myeloid chimerism but did not experience late graft failure or require a second transplant. There was only one patient who experienced primary graft failure and was successfully salvaged with a re-transplant immediately. There was no relationship between mixed chimerism and graft loss, and immune suppression was withdrawn in all patients at 6 months, regardless of chimerism.

The median post-transplant follow-up was 2.8 years. No grade III-IV acute GvHD was seen and no chronic GVHD requiring continuing immune suppression was seen. The overall survival (OS) and engrafted, GVHD-free, event-free survival (EFS) at 6 years post-transplant were 100% and 98% respectively. Survival statistics were not affected by chimerism status.

No difference in mean blood counts between MC and CC groups

In all the patients with stable mixed chimerism, no disease manifestation in form of blood product support or cytopenia was seen. At 6 months post-HCT mean hemoglobin levels and mean platelets values were 132g/dL vs 134g/dL and 287 x 10^9/L vs 332 x 10^9/L in MC and CC groups respectively and the means at 12 months also showed no statistical difference of 133g/dL vs 130g/dL and 305 x 10^9/L vs 294 x 10^9/L. Similarly, mean neutrophil counts showed no statistical difference between MC and CC groups both at 6 and 12 months. (3.4 x 10^9/L vs 3.6 x 10^9/L at 6 months, 2.8 x 10^9/L vs 3.6 x 10^9/L at 12 months).

Figure 1:Hemoglobin, platelets and neutrophil distribution between Mixed and complete chimerism groups at -6 and -12 months post HSCT



Conclusions: These data demonstrate excellent GVHD-free, disease-free survival with very low transplant-related morbidity. Mixed chimerism is common in our patient cohort, reflecting low-intensity conditioning. We demonstrate that there is no relationship between this mixed chimerism and subsequent graft loss.

In conclusion, these data illustrate modulation of immune suppression in response to mixed T-cell chimerism after transplant for aplastic anemia is not required. Donor and recipient hematopoiesis co-exist which eventually converts into full donor hematopoiesis, and clinical parameters for disease recurrence like cytopenia's should be monitored instead.

Disclosure: Nothing to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P465

THE COMPOSITE IMMUNE RISK SCORE PREDICTS OVERALL SURVIVAL AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A RETROSPECTIVE ANALYSIS OF 1838 CASES

Yigeng Cao[1], Xiaowen Gong[1], Yahui Feng[1], Mingyang Wang[1], Yu Hu[1], Huilan Liu[2], Xueou Liu[1], Saibing Qi[1], Yanping Ji[3], Fang Liu[1], Ye Guo[1], Zimin Sun[2], Erlie Jiang[1], Junren Chen[1]

[1]Institute of Hematology & Blood Diseases Hospital, Tianjin, China, [2]The First Affiliated Hospital of University of Science and Technology of China, Hefei, China, [3]Anhui Medical University, Hefei, China

Background: Immune reconstitution after hematopoietic stem cell transplantation (HSCT) is complicated and of vital importance for survival. There has been, however, little consensus on how to quantitatively assess immune reconstitution in real time as part of standard of care. We aimed to identify the trajectory of immune reconstitution and identify an immune signature for prognosis.

Methods: We retrospectively analyzed 11150 post-transplant immune profiles of 1945 patients who underwent HSCT between 2012 and 2020 at two medical centers in China. 1838 (94.5%) of the cases were allogeneic HSCT. We utilized manifold learning to visualize the temporal profiles of immune cell repopulation (integrating neutrophil, total lymphocyte, natural killer (NK), total T, $CD4^+$ T, and B cell counts in the peripheral blood), used grid-search optimization to identify a composite immune signature that was associated with mortality, and then verified the high-risk signature in two independent subsets of the patients.

Results: On average, recovery of absolute cell counts was concentrated on the repopulation of $CD8^+$ T cells during the initial two months after transplant. Inter-patient variance of immune status peaked at around day 60 post-transplant, and broad-ranged recovery in NK, $CD8^+$ T, $CD4^+$ T, and B cells initiated afterwards. Using the training set of patients ($n = 729$), we identified a composite immune signature during days 91 – 180 after allogeneic HSCT that was predictive of early mortality and moreover simplified it into a formula for a Composite Immune Risk Score. When we verified the Composite Immune Risk Score in the validation ($n = 284$) and test ($n = 391$) sets of patients, a high score value was found to be associated with hazard ratios of 3.64 (95% C.I. 1.55 – 8.51; $P = 0.0014$) and 2.44 (95% C.I., 1.22 – 4.87; $P = 0.0087$), respectively, for early mortality. The high-risk patients were significantly more likely to suffer from non-relapse mortality (hazard ratio (HR), 3.28; 95% C.I., 2.28 – 4.73; $P < 0.0001$), including infection-related mortality (HR, 3.12; 95% C.I., 1.97 – 4.96; $P < 0.0001$). A high Composite Immune Risk Score during days 91 – 180 remained an independent risk factor for early mortality after allogeneic HSCT (HR, 1.80; 95% C.I., 1.28 – 2.55; $P = 0.00085$) in multivariate analysis.

Conclusions: In conclusion, the Composite Immune Risk Score is easy to compute and could identify the high-risk patients of allogeneic HSCT who require targeted effort for prevention and control of infection.

Disclosure: The authors declare no conflict of interest.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P466

B-CELL RECONSTITUTION IN THE BONE MARROW FOLLOWING PEDIATRIC HSCT: HIGHER LEVELS OF B-CELL PRECURSORS AND PLASMABLASTS IN CHILDREN NOT RESPONDING TO RE-VACCINATION POST-HSCT

Elisa Christine Peen[1], Hanne Vibeke Marquart[1], Klaus Müller[1], Katrine Kielsen[1]

[1]Rigshospitalet, Copenhagen, Denmark

Background: Vaccination against vaccine-preventable diseases (VPDs) is used to reinstate protection after allogeneic HSCT but response rates may be limited due to insufficient reconstitution and functional maturation of B cells as well as insufficient T cell help leading to a need for immunoglobulin substitution post-transplant. In this study, we investigated associations between B-cell reconstitution in the bone marrow and vaccination responses after pediatric HSCT.

Methods: We included 33 children undergoing HSCT for ALL (n = 20) or AML (n = 13) from 2015-2020 with median age of 8.9 years (range: 3.1-17.3). All received myeloablative conditioning based on TBI (n = 13) or chemotherapy alone (n = 20). All patients underwent vaccination against pneumococcus, measles, mumps, rubella, diphtheriae, tetanus, polio, and haemophilus influenzae type B (Hib) post-HSCT. Vaccination responses were measured within three years post-HSCT. Data for all vaccination responses were available for 27 patients (82%), partially available for 3 patients (9%), and unavailable for 3 (9%).

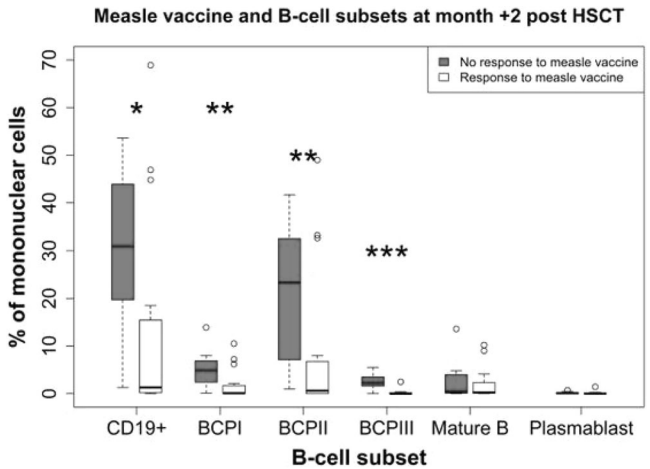
Fresh bone marrow samples were analyzed for specific B-cell subsets using flow cytometry at month +1, +2, +3, +6, +9, +12, +15 and +18 post-HSCT.

Results: The highest percentages of seroprotectivity after vaccination was seen against polio (93% of children), rubella (82%) and diphtheria (82%), while responses were moderate for tetanus (71%) and measles (64%), and lowest rates of seroprotectivity with Hib (57%), pneumococcal polysaccharide (52%) and mumps (50%).

We found significantly lower levels of B-cell precursors stage I (BCPI) at +3 months in patients with insufficient response to diphtheria ($p = 0.007$), lower level of BCPI at +6 months in patients seronegative for tetanus ($p < 0.05$), lower levels of BCPII at month +6) in patients seronegative to rubella ($p < 0.05$), and lower levels of plasmablasts at month +6 and +9 in polio non-responders ($p < 0.05$).

In contrast, we found a significantly higher level of CD19+ cells, BCPI, BCPII and BCPIII at month +2 in patients seronegative to measles (figure), as well as increased levels of BCPIII, mature B cells and plasmablasts at month +3 ($p < 0.05$), increased levels of BCPI and plasmablasts at month +6 ($p < 0.05$), and higher levels of plasmablasts at month +12($p < 0.01$).

Similarly, we found significantly higher levels of CD19+ cells, BCPI, BCPII and BCPIII at month +2 (all $p < 0.05$) in seronegative patients not responding to mumps compared to the seropositive group. Furthermore, we found lower levels of BCPI, BCPIII and plasmablasts at month +3 ($p < 0.05$), lower levels of CD19 B-cells, BCPI, BCPII and plasmablasts at month +6 ($p < 0.05$), and lower levels of plasmablasts at month +9($p = 0.01$) in the seropositive group.



Conclusions: By exploring vaccines responses in children after allogeneic HSCT, we found complex relations between B-cell subpopulations in the bone marrow and vaccination responses, dependent upon the specific vaccines. These findings indicate that fully mature B-cell responses, based on B-cell repopulation of the peripheral lymphoid tissues may be partly dependent upon the specificities, vaccination status prior to HSCT and type of vaccination. Further studies are warranted to explore how the immune reconstitution in bone marrow and peripheral blood may influence the success of vaccination against VPDs after pediatric HSCT.

Disclosure: None to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P467

IMMUNE RECONSTITUTION KINETICS AFTER POST-TRANSPLANT CYCLOPHOSPHAMIDE BASED HLA-MATCHED SIBLING STEM CELL TRANSPLANTATION

Pilar Lancho[1], Gillen Oarbeascoa[1,2], Ana Pérez-Corral[1,2], Rebeca Bailén[1,2], Paula Fernández-Caldas[1,2], Ignacio Gómez-Centurión[1,2], Eva Catalá[1,2], Ana Alarcón[1,2], Diego Conde[1,2], Jorge Gayoso[1,2], Javier Anguita[1,2], Jose Luis Díez-Martín[1,2,3], Mi Kwon[1,2,3]

Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]Gregorio Marañón Health Research Institute, Madrid, Spain, Universidad Complutense de Madrid, Madrid, Spain

Background: Post-transplant cyclophosphamide (PTCy) is increasingly being used as graft-versus-host disease (GvHD) prophylaxis in HLA-matched stem cell transplantation (SCT) with promising outcomes. Nevertheless, data regarding immune recovery in this setting is scarce. The aim of this study was to describe the immune reconstitution kinetics and outcomes of a PTCy based HLA-identical sibling SCT series in a third level center.

Methods: Data from consecutive patients who underwent an HLA-identical sibling SCT with PTCy based prophylaxis from 2017-2022 in a single center were retrospectively analyzed. Lymphocyte subsets were measured by flow cytometry (CD4+, CD8+, CD56+ and CD19+) and immunoglobulin levels were collected on 1, 3, 6, 12, 18 and 24 months after transplantation.

CMV was monitored by RT-PCR in whole blood twice weekly until day +30, weekly until day +100 and every two weeks until day +180 except patients with steroid therapy or active GVHD.

Results: 57 patients were included with a median age of 49 years. Acute myeloid leukemia was the most frequent transplant indication (52,6%) but there was a significant amount of patients diagnosed with high risk diseases such as lymphoma, chronic lymphocytic leukemia or myeloproliferative neoplasms. Baseline characteristics are summarized in Table 1. All patients received high-dose PTCy on days +3 and +4 in combination with a calcineurin inhibitor and mycophenolate mofetil (MMF) from day +5. Median time to neutrophil (>500/mm3) and platelet (>20.000/mm3) engraftment was 14 days and 17 days respectively.

With a median follow-up of 2,64 years the 3-year OS and EFS were 64,8% (CI95%, 52,1-80,6) and 53,6% (CI95% 40,7-70,5) respectively. Cumulative incidence of G2-4 and G3-4 acute GvHD was 23% and 5% respectively at day +180. Cumulative incidence

of moderate and severe forms of chronic GVHD at one year was 17,5%. Cumulative incidence of non-relapse mortality was 18,9%. Among the causes of death, only 7% of the patients died due to infection, and none due to severe GVHD. Relapse rate at 3 years was 27,5%.

Median count of CD56+ cells recovered on day +30. Median counts of CD8+ and CD19+ lymphocytes and immunoglobulins (IgG, IgA, IgM) showed recovery after day +90. Normal ranges of CD3+ cell counts were not reached until day +180, and CD4+ cell counts were under the lower normal values until the 2nd year post-transplant, although >200/mm3 cell counts were reached since day +180.

26 patients (45,6%) experienced at least one CMV reactivation. Median time to first reactivation since transplant was 20 days (11,5-33). Patients experiencing CMV reactivation showed lower NK cell counts on day +30 ($p = 0.01$).

Table 1: Baseline characteristics of the patients and transplant

Age, years, median (range)	49 (20-70)	Disease Risk Index, n (%)	
Sex, male, n (%)	36 (63,2%)	Intermediate	28 (49,1%)
Diagnosis, n (%)		High and very high	20 (35,1%)
AML	30 (52,6%)	Low	8 (14%)
Non-HL and CLL	9 (15,8%)	Conditioning	
ALL	5 (8,8%)	Mieloablative, n (%)	33 (57,9%)
MPN	5 (8,8%)	Reduced intensity, n (%)	24 (42,1%)
MDS	4 (7%)	Stem cell source, peripheral blood, n (%)	57 (100%)
Others	4 (7%)	Donor sex (male), n (%)	34 (63,3%)
Pre-transplant status, n (%)		Donor age, median (range)	49 (34-56)
Complete Remission, Negative MRD	24 (42,1%)	Recipient CMV serostatus	
Complete Remission, Positive MRD	17 (29,8%)	Positive	46 (80,7%)
SD / PD / QT-induced aplasia	12 (21,1%)	Donor CMV serostatus	
PR or VGPR	4 (7%)	Positive	40 (70%)

AML acute myeloid leukemia; *ALL* acute lymphoid leukemia; *HL* Hodgkin lymphoma; *MDS* myelodysplastic syndrome; *MPN* myeloproliferative neoplasms; *CLL* chronic lymphocytic leukemia; *SD* stable disease; *PD* progressive disease; *PR* partial response; *VGPR* very good partial response.

Conclusions: Patients undergoing matched sibling SCT with PtCy based GVHD prophylaxis showed an early and robust NK, CD8 and humoral reconstitution, while CD4 count normalization was frequently delayed. Mortality due to infections was low. However, CMV reactivations are frequent in our series. Comparative studies with classic prophylaxis strategies are granted in order to evaluate the best anti-infectious prophylaxis strategy in these patients.

Disclosure: Nothing to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P468

AGE-RELATED DYNAMICS OF IMMUNE CELL RECONSTITUTION INFLUENCE OUTCOMES AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Alizée Jandin[1], Cécile Pochon[1], Arnaud Campidelli[1], Anne-Béatrice Notarantonio[1], Maud D'Aveni[1], Céline Kicki[1], Gabrielle Roth-Guepin[1], Tshinguta Anita Mbuyi[1], Marcelo De Carvalho Bittencourt[1], Cyril Schweitzer[1], Pierre Feugier[1], Pascal Chastagner[1], Marie-Thérèse Rubio[1], Simona Pagliuca[1]

[1]CHRU de Nancy, Vandœuvre-lès-Nancy, France

Background: Allogeneic hematopoietic cell transplantation (HCT) holds a pivotal place in the setting of therapeutic algorithm for hematological disorders. Factors influencing recipient immune recovery have been investigated across multiple cohorts issuing heterogenous results. Differences in outcomes in adult and pediatric populations suggest an age-related contribution to post-transplant immune recovery, however it is unclear how recipient and donor age may affect the dynamics of single immune cells.

Methods: Here we conducted a monocentric retrospective study questioning on the modifications of immune cell recovery in a cohort of 174 patients (57 children and 117 adults) with hematological disorders receiving a HCT between 2015 and 2020. Complete flow-based immune reconstitution data on T-CD4, T-CD8, NK and B cell populations were collected at defined time-points (+1, 3, 6 and 12 months).

After ascertaining the dynamics in adult and pediatric populations of each cell component, the effect of a set of baseline clinico-biological variables on late (>6 months) reconstitution for each cell population was tested through univariable and multivariable linear or logistic regression models.

Results: While donor age did not impact on any of the parameters in study, CD4-T (Adj R^2 0.4, $p = 5.7x\ 10^{-15}$) and, in minor part, B cell post-transplant increments (Adj R^2 0.05, $p = 0.004$) were inversely correlated with recipient age, which instead did not influence CD8-T nor NK cell reconstitution. This correlation between CD4-T cells and recipient age was confirmed in multivariable analysis ($p = 0.0148$). Results of stepwise multivariable analyses showed that CD8-T cell reconstitution was positively impacted by recipient-positive CMV serostatus ($p = 0.00009$) while donor CMV serostatus positively influenced CD4-T cell recovery ($p = 0.017$). Donor EBV positive serostatus resulted instead to be a negative predictor of B cell recovery ($p = 0.0442$). The impact on age mirrored a different kinetics of immune reconstitution in adult and pediatric patients. Therefore, while early after HCT immune cell composition was similar in the two groups, with NK cells representing the largest component, followed by CD8-T and CD4-T, and minimal B cell contribution, in later phases we assisted to a faster expansion of CD4-T arm in children whereas CD8-T remained the major contributor of the immune recovery processes in adults still one year after transplant. B cell reconstitution was also faster in children, with better immunoglobulin levels recuperation despite no differences in post-transplant pre-emptive rituximab utilization. Overall and event-free survivals were significantly higher in children ($p = 0.00062$ and $p = 0.0062$). While no difference in acute grade III-IV GvHD, adults experienced a significantly higher cumulative incidence (CI) of chronic GvHD ($p = 0.0258$) and of specific infections, including EBV ($p = 0.031$) and fungi ($p = 0.007$). Although CI of relapse was not different, children experienced later relapses as compared to adults (median of

294 vs. 139 days, p = 0.039), indicating better disease control at least at early post-transplant stages.

Conclusions: Here, starting from immune reconstitution data prospectively collected for patients transplanted at our institution, we dissected the effect of age on post-transplant immune cells. A faster CD4-T and B cell recovery in children may be the driver of a better immune competence underpinning superior outcomes in pediatric populations.

Disclosure: No conflict of interest to disclose.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P469

THE EFFICACY AND SAFETY OF MODERATE-DOSE AZACYTIDINE FOR MAINTENANCE THERAPY FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION IN MYELOID MALIGNANCY

Xinhui Zheng[1], Yigeng Cao[1], Erlie Jiang[1]

[1]Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

Background: Recurrence after allo-HSCT is the primary cause of treatment failure for patients with myeloid malignancy. AZA maintenance has been considered a promising therapy to prevent relapse and improve survival, nevertheless, the efficacy still remains controversial.

Methods: We conducted the prospective clinical trial and patients 15 to 65 years of age who had AML, MDS, or CMML and underwent allo-HSCT were screened. Patients with AML were eligible if they had adverse risk according to ELN 2017, relapsed/refractory disease, detected MRD before transplantation, or MDS or CMML transformation to AML. Patients with MDS were eligible if they had the diagnosis of MDS-EB2, poor karyotype, very high-risk disease by the IPSS-R, or TP53 mutation. In the trial, 78 patients were enrolled in the AZA group between September 2019 and April 2022. AZA was applied 50 mg/m2 subcutaneously or intravenously daily for 5 days from day +60 post-SCT in a 28-day period. The control group was comprised of 108 patients who met the inclusion criteria, didn't receive maintenance therapy post-SCT, and had no death, relapse, delayed platelet or neutrophil engraftment or Grade III-IV acute GVHD for 60 days post-SCT between January 2015 and April 2020. The primary endpoint of this trial was relapse-free survival (RFS), plotted according to the Kaplan–Meier method with P-value calculated by log-rank test. Univariate and multivariate analyses were performed with cox-regression analysis. Statistical analyses were performed using R version 4.1.3.

Results: The median time to AZA starting was 94 (28-210) days and 62 patients (79%) received the first dose within 120 days after transplantation. The median number of AZA cycles administered was 5 (1-12). The median follow-up time was 19.6 (2.1–91.7) months for the entire cohort. AZA maintenance was related to significantly improved RFS (log-rank test, p = 0.01). The 1-year RFS was 87.7% (95% CI, 0.80-0.96) and 70.1% (95%CI, 0.62-0.79) for AZA and control cohort, respectively. OS in the AZA group was improved compared with the control group, but the difference was not statistically significant (log-rank test, p = 0.19). In a multivariable Cox regression analysis (Figure 1), the HR of AZA maintenance for RFS in this study was 0.19 (95% CI 0.07-0.52, p < 0.001). The cGVHD remained the independent protective factor for OS (HR = 0.38, 95% CI: 0.20-0.72, p = 0.003) and RFS (HR = 0.27, 95% CI: 0.13-0.59, p < 0.001). While the status of no remission (NR) prior to HCT was an independent risk factor for OS (HR = 4.39 (95% CI: 1.86-10.34, p < 0.001) and RFS (HR = 3.39 (95% CI: 1.63-7.08, p = 0.001). According to CTCAE 5.0 grading, hematological adverse effects were the most common (79%, n = 62), including neutropenia (64%, n = 50), and thrombocytopenia (64%, n = 50). Grade 1-2 adverse events were reported at a rate of 54% (n = 42), and 28% (n = 22) for Grade 3. No grade 4 adverse effects or death related to AZA occurred.

	OS		RFS	
	HR	p	HR	p
AZA maintenance	0.61(0.26-1.46)	0.27	0.20(0.09-0.49)	<0.01
cGVHD	0.24(0.10-0.61)	<0.01	0.32(0.15-0.67)	<0.01
aGVHD	2.43(1.06-5.58)	0.04	1.1 (0.52-2.36)	0.80
ELN for AML, n (%)				
Favorable	Ref		Ref	
Intermediate	0.85(0.27-2.7)	0.78	0.85(0.3-2.43)	0.77
Adverse	0.58(0.2-1.70)	0.32	0.75(0.29-1.97)	0.56
Disease status at HCT, n (%)				
CR1	Ref		Ref	
≥CR2	0.56(0.07-4.57)	0.59	0.74 (0.17-3.33)	0.70
NR	6.74(2.48-18.34)	<0.01	4.75(2.07 -10.92)	<0.01
MRD status at HCT, n (%)				
MRD (-)	Ref		Ref	
MRD (+)	0.9(0.34-2.41)	0.84	1.85(0.81-4.22)	0.14

Table 1: Multivariable analysis of covariate using Cox proportional hazard regression model.

Abbreviations: AZA: azacytidine, ELN: European Leukemia Net (ELN) Guidelines 2017, HCT: hematopoietic stem cell transplantation, CR: Complete remission, MRD: measurable residual disease, MNC: mononuclear cells.

Conclusions: In summary, our study concluded that moderate-dose AZA maintenance following allo-SCT had a positive impact on RFS for patients with a high risk of recurrence. Additional investigations in larger randomized controlled trials are warranted.

Clinical Trial Registry: NCT 04645199

Disclosure: The authors declared that they have no conflicts of interest in this work.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P470

ROLE OF MEASURABLE RESIDUAL DISEA SE QUANTIFIED BY MULTIPARAMETRIC FLOW CYTOMETRY BEFORE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR HIGH-RISK PHILADELPHIA-NEGATIVE ACUTE LYMPHOBLASTIC LEUKEMIA

Rimmel Yosra Kanoun[1], Sabrine Mekni[1], Nour Ben Abdeljelil[1], Rihab Ouerghi[1], Insaf Ben Yaiche[1], Ines Turki[1], Saloua Ladeb[1], Lamia Torjmane[1], Dorra Belloumi[1], Ines Safra[2], Tarek Ben Othman[1]

[1]National Bone Marrow Transplant Center, Tunis, Tunisia, [2]Pasteur Institute of Tunis, Tunis, Tunisia

Background: Measurable residual disease (MRD) status is commonly associated with high-risk of relapse. It is still uncertain whether allogeneic hematopoietic stem cell transplantation (AHSCT) can overcome the negative impact of MRD positivity.

Methods: Observational study conducted on patients with Philadelphia-negative acute lymphoblastic leukemia (Ph-negative ALL) who underwent AHSCT between January 2003 and June 2022. Patients selected were in complete remission: CR1, n = 69 (80%), ≥CR2, n = 17 (20%). Graft sources were bone marrow (BM) in 71% of patients and peripheral blood stem cell in 29% of patients. Myeloablative conditioning was TBI or chemotherapy-based (CT) regimen. BM MRD level was quantified using four or six color multiparametric flow cytometry (MFC). Threshold for MRD positivity (MRD +) was ≥ 0.1%.

Results: Eighty-six patients (45 B-ALL and 41 T-ALL) were included with median age of 18 years (range, 4–55). MRD pre-AHSCT was positive in 42 patients (49%) with median of 0.4 $*10^{-3}$ (range, 0.01-75.6 $*10^{-3}$).

After a median follow-up of 25 months (range 1-205), the cumulative incidence of relapse (CIR) was significantly higher in MRD+ group (39% vs 20%, respectively, p = 0.048). Median time of relapse post-AHSCT was 14 months (range, 1-203) in MRD+ group and 32 months (range, 4-209) in MRD– group. Non-relapse mortality (NRM) was 15% in both groups (p = 0.972).

The 2-years estimated overall survival (OS) and event-free survival (EFS) were 43% vs 64% (p = 0.021) and 43% vs 57% (p = 0.09) in MRD+ and MRD- groups, respectively.

In univariate analysis, pre-AHSCT MRD+ patients receiving TBI regimen had lower CIR (22% vs 60% respectively, p = 0.043) and better OS (57% vs 26% respectively, p = 0.039) compared to CT regimen.

In multivariate analysis, pre-AHSCT negative MRD status and TBI-based conditioning were significantly associated with better OS.

Conclusions: Pretransplant positive MRD status in Ph-negative ALL is associated to higher CIR and lower OS, rational for including immunotherapies and TBI based conditioning regimen before AHSCT.

Disclosure: Nothing to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P471

GENE EXPRESSION PROFILING AND SIGNALING PATHWAY ANALYSIS OF TOLERANT T CELLS CIRCULATING IN ADULT PATIENTS AFTER PTCY HAPLOTRANSPLANTATION

Paul Szabolcs[1], Taylor Nee[1], Dhivyaa Rajasundaram[1], Rafic Farah[2], Xiaohua Chen[1]

[1]UPMC Children's Hospital of Pittsburgh, Pittsburgh, United States, [2]UPMC Hillman Cancer Center, Pittsburgh, United States

Background: The mechanisms for the signaling pathways of T cell-dependent tolerance after haploidentical hematopoietic stem cell transplantation (haplo-HSCT), are incompletely understood.

Methods: We tested 8 patients with leukemia (5) or myelodysplastic syndromes (MDS, 3) (median age: 51-years-old) following IRB-approved consenting. All received Flu+TBI (+/- Cy) preconditioning and haplo-HSCT with post-transplant Cytoxan (PTCy) and FK506 as GvHD prophylaxis. At the time of the in vitro tolerance study, chimerism was donor dominant (mean: 99% for both CD33+cells and CD3 + T cells) and immunosuppression drug (ISD) was withdrawn ~6 months after haplo-HSCT.

We described previously that purified T cell responses to recipient dendritic cells (DC) were measured in mixed lymphocyte reaction (MLR) assay and cytokine profiling. To test for clonal deletion, alloreactive T-cell clones with frequency >0.1% identified in vitro from the graft pre-infusion were tracked by ImmunoSEQ™ assay. Gene expression profiling and signaling pathway analysis on alloreactive or tolerant T-cells were performed by collecting T cells from in vitro MLR reactions, purifying total RNAs from these cells, running RNA-sequencing, and analyzing with the software of CLC Genomic Workbench® v21, GSEA® v4.1.0, and IPA®.

Results: We have previously shown that circulating T cells were hyporeactive to recipient DC in patients at 1yr (or 2yrs in 1 patient) post-haplo-HSCT [6 months, (or 2-5 months in 3 patients) post-ISD withdrawal], while these T cells responded vigorously to 3rd party APC. As positive control, host DC triggered robust 3rd party T-cell response. Neither depletion of Tregs, nor blockade of IL10R or PD1 could reverse T-cell hyporeactivity. Low-dose IL2 triggered mild anti-host proliferation responses. Similar scenarios were detected in graft T cells against self-DC, (negative control in autologous setup), while vigorous responses were shown in the graft T cells against host-DC pre-haplo-HSCT. Cytokine profiling further confirmed the MLR responses. ImmunoSEQ™ revealed the disappearance of alloreactive T-cell clones from peripheral blood with time. Low-dose IL2 had minimal impact on reversing hyporeactivity. While most alloreactive T clones were undetectable, a few remained in the peripheral pool in tolerant patients tested.

Unlike graft T-cell responses against host DC, tolerant T-cells in circulation (including remaining alloreactive T cells) against hDC showed distinct patterns of gene expressions, with relative downregulation of allograft rejection and T-helper response, co-stimulation, cell proliferation pathway, that was paired with upregulation of co-inhibition, PD1-PDL1, Ferroptosis, PTEN and CREB pathways. The profiles suggested systemic alterations in the signaling pathways on tolerant T cells post-haplo-HSCT.

Conclusions: Hypo-reactivity of donor-derived circulating T cells to recipient DC and graft T cells to graft DC (negative control) were evident. We found Treg, Tr1 activity, or T-cell exhaustion insignificant as their blockade or removal did not lead to a 'flare' in circulating tolerant T-cell reactivity against patient DC. T-cell clonal deletion appears to be the dominant mechanism explaining the in vitro hyporeactive proliferation, cytokine secretion, and alloreactive TCR clonotype attrition, along with systemically altered signaling pathways in tolerant T-cells including the alloreactive T cells remaining. Anergy may play a minor supportive role.

Disclosure: Nothing to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P472

CHANGES IN NATURAL KILLER IMMUNE RECONSTITUTION FOLLOWING POST-TRANSPLANT CYCLOPHOSPHAMIDE

Alejandro Luna de Abia[1,1], Gemma Moreno JImínez[1], Fernando Martín-Moro[1], Carlos Jiménez-Chillón[1], Beatriz Astibia-Mahillo[1], Lucía Pérez-Lamas[1], Rubén Ballester Rodríguez[1], Cristina Sun[2], Anabelle Chinea Rodríguez[1], Valentín García-Gutiérrez[1], Pilar Herrera Puente[1], Eulalia Rodríguez Martín[1], Ernesto Roldán Santiago[1], Javier López-Jiménez[1]

[1]Hospital Ramón y Cajal, Madrid, Spain, [2]Universidad de Alcalá de Henares, Alcalá de Henares, Spain

Background: Post-transplant cyclophosphamide (PT-Cy) has revolutionized hematopoietic stem cell transplantation (HSCT), optimizing GVHD risks. Immune reconstitution may be impaired in this context, affecting Natural Killer (NK) cells development. Our objectives: were: to describe NK cells reconstitution in HSCT with PT-Cy, from donor to recipient, by means of a simple and affordable cytometry protocol.

Methods: 53 samples were analyzed at different points of 17 HSCT with PT-: donor without G-CSF, donor with G-CSF, HSCT recipient on: day+1, month+1, month+3 and month+6. Flow cytometry was performed by BD FACSCanto II with the following antibodies: CD16-FITC, CD57-PE, CD3-PerCP, CD56-PE-Cy7, NKG2D-APC, CD25-APC-H7, NKG2C-BV421, CD45-V500, KIR2DL1-FITC, KIR2DL2/2DL3/2DS2-PE, KIR3DL1-APC, CD8-APC-H7, NKG2A-BV421. PT-Cy was administered on days+3 and +4, at 50mg/kg per day, cyclosporine and mycophenolate after day+5.

Results: Fifteen donor samples (9 donors in total) and 38 samples from patients with PT-Cy HSCT were processed at different points (17 recipients in total: 3 MRD, 3 MUD, 1 MMUD

and 10 haploidentical). Lymphocyte subpopulations (Table 1) at the 4 reconstitution points was: T lymphocytes accounted for a median of: 56% (day+1) → 74% (month+1) → 46% (month +3) → 64% (month+6), of total lymphocytes, respectively. NK cells evolved: 3% → 5% → 32% → 18%, with NK/T varying by 3.5% → 1.1% → 0.8% → 0.9%. For NK cells, the $CD56^{dim}$ subset decreased in month+1 and month+3 in favour of $CD56^{bright}$: 73% vs. 27% in month+1 and 73 vs. 27% in month+3, respectively. Regarding NK maturation, CD16 decreased markedly from day+1 to month+1 (51% to 25%) with subsequent recovery to 75% at month+6. CD57 showed a more pronounced decline from day+1 (7%) with respect to baseline donor (43%), and a slower recovery to 29% at month+6. NKG2 markers underwent known maturational changes, such as an early increase of NKG2A as an immature phenotype being progressively replaced by NKG2C/D at month +6. In KIR markers, stability was observed except for CD158b (KIR2DL2/2DL3/3DS2) doubling baseline values on day+1 to 57%. As for the CD25 marker, it remained at much lower levels in all samples except in 4 recipients (24%), who also had CMV reactivation in peripheral blood at that time; the remaining patient with active CMV showed no changes in CD25. Before and after PT-Cy (samples day+1 and month+1), the most characteristic changes were the decrease in CD16 and increase in NKG2A. Considering donors, most parameters remained unchanged after G-CSF excluding CD16 and NKG2D, which decreased a -15% and a -34%, respectively.

% Expression	T cells	NK cells	NK/T cells
Basal donor	67%	10%	4%
Donor with G-CSF	70%	6%	5%
Day+1	56%	3%	4%
Month+1	74%	5%	1%
Month+3	46%	32%	0.8%
Month+6	64%	18%	0.9%

Conclusions: A simple 2-tube flow cytometry protocol can assess NK reconstitution along with T and NK/T evolution. The initial NK phenotype shows markers of immaturity such as NKG2A, with cytotoxic subpopulations such as $CD56^{dim}$ carrying CD16 and CD57 developing later. At month+3 an immunological switch occurs in the T and NK populations, with an increase of the latter to their highest values before T cells prevail. Disclosures: nothing to declare. G-CSF may impair NK cytotoxicity, while markers such as CD25 appear as highly specific in CMV reactivation, with little increase in other situations.

Disclosure: Nothing to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P473

DEFINITIONS, INCIDENCE AND OUTCOME OF POOR GRAFT FUNCTION AFTER HEMATOPOIETIC CELL TRANSPLANTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Konradin F. Müskens[1], Caroline A. Lindemans[1,2], Rana Dandis[1], Stefan Nierkens[1,3], Mirjam E. Belderbos[1]

[1]Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands, [2]Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands, [3]Center for Translational Immunology, Utrecht University, University Medical Center Utrecht, Utrecht, Netherlands

Background: Poor graft function (PGF) is an important complication after allogeneic hematopoietic cell transplantation (HCT), predisposing for infections, bleeding complications and increased mortality. The reported incidence of PGF, its risk factors and clinical outcome vary substantially between studies. This variability may be explained by clinical differences in the patient cohorts and HCT strategies assessed, as well as by differences in the criteria used to define PGF. In this systematic review and meta-analysis, we aimed to provide a pooled estimate of the incidence, risk factors and outcome of PGF, and to determine how these are impacted by the different definitions used.

Methods: We performed systematic searches in MEDLINE, EMBASE and Web of Science, from database inception to June 2022. We included any study reporting on PGF in human allogeneic HCT recipients. Outcome parameters included the definition, incidence, survival and risk factors of PGF. We utilized random-effect models to derive pooled estimates on the incidence and outcome of PGF, and performed subgroup analyses to dissect the impact of the different criteria used to define PGF.

Results: Of 797 retrieved citations, 69 unique studies (N = 14020 HCT recipients) met our inclusion criteria. Most of these studies were performed in unselected cohorts (24 studies), in patients with hemato-oncological diseases (30 studies) or in patients with bone marrow failure (10 studies). Overall, 22 studies reported estimates of the incidence, and 18 of the outcome of PGF. Overall, thee pooled incidence of PGF was 7% (IQR: 5-11%, 22 studies), with substantial heterogeneity between studies. For survival, the pooled estimate was 53% (95% CI: 45-61%, 18 studies). The most commonly reported risk factors associated with PGF were history of cytomegalovirus infection (5 studies) and history of graft-versus-host disease (5 studies). Notably, the included studies varied substantially in the criteria used to define PGF and in the time after HCT at which these criteria were assessed. Studies using stricter thresholds for cytopenia and studies that used 8 or more criteria to define PGF generally reported a lower incidence of PGF compared to studies using more lenient criteria.

Conclusions: Our systematic review demonstrates that PGF is a common and severe complication after allo-HCT. A more standardized, quantitative and evidence-based definition is required to advance our understanding of the pathophysiology of PGF, to identify PGF patients at risk for poor outcome and to facilitate therapeutic intervention.

Disclosure: None of the authors has any conflicts of interest to report.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P474

VACCINATION WITH AN ADJUVANTED RECOMBINANT ZOSTER VACCINE (ARZV) IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS. A SINGLE CENTRE EXPERIENCE

Ana Belén Bocanegra[1], Carlos De Miguel[1], Guiomar Bautista[1], Maria Esther Martínez-Muñoz[1], Angel Asensio[1], Mireia Cantero[1], Maria Francisca Portero[1], Rafael Francisco Duarte[1]

[1]Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Spain

Background: Hematopoietic stem cell transplant (HSCT) recipients are at high risk for varicella-zoster virus (VZV) infection and reactivation. The adjuvanted recombinant zoster vaccine aRZV has been shown effective to prevent VZV infection in older adults, autologous HSCT recipients and patients with hematological

malignancies receiving immunosuppressive treatments. However, its role in allogeneic HSCT is unclear, and several studies suggest that it might be safe but not immunogenic, specially early after transplant.

Methods: We have retrospectively analyzed our initial experience with aRZV vaccination in allogeneic HSCT recipients, from the beginning of the program in our center in January 2022.

Results: Seventeen allogeneic HSCT recipients underwent aRZV vaccination in the initial months of the program: 9 men and 8 women, median age at vaccination 49 years (range, 19-71), at a median month +30 (range, 3-236) after transplant. Thirteen patients (76%) had completed a full vaccination schedule with two doses. The median time between doses was 90 days (range, 41-150). Approximately half of the patients (8; 47%) were receiving acyclovir prophylaxis at the time of vaccination, either for early vaccination within the first year posttransplant or for concurrent immunosuppressive therapy for transplant complications. The rest had acyclovir discontinued at a median of 15 months post-transplant (range, 11-32) and were vaccinated at a median of 10 months later (range, -6-32). Following vaccination, eight cases either seroconverted or experienced an increase in their pre-vaccine anti-VZV titers of 579.7 mUI/ml (2.11-3645.9). In four cases, the antibody levels decreased despite two doses of aRZV in the context of concurrent immunosuppressive treatment. Somewhat unexpectedly, three cases out of this rather small group of allogeneic HSCT recipients (18%) presented with a zoster infection after receiving aRZV vaccination at a median of 8 months after transplant (range, 3-21), and all three after discontinuing acyclovir prophylaxis: two cases of monometameric zoster in the limbs and one case of multimetameric zoster in the cervical region after two doses of aRZV and having suspended prophylaxis with acyclovir one month earlier. One of them despite having had a marked increase of antibody titers, and two of them in the context of ongoing intestinal and skin GVHD. Patients were successfully treated with acyclovir with no further complications from the VZV episode.

Conclusions: Despite the efficacy of aRZV in autologous HSCT and other immunosuppressed hematological patients, a few studies suggest that it may not be immunogenic in allogeneic HSCT, specially early after transplant. Evidence in this setting is still overall very limited. Nevertheless, our real-life experience with an 18% of VZV infections in vaccinated patients, in about a third of cases without acyclovir prophylaxis, is a matter of concern. Beyond the intrinsic limitations of any retrospective analysis in a small number of cases in real life, this experience in the context of the broader evidence available does not support the use of the vaccine in these patients. Antiviral prophylaxis should remain the key component of VZV prevention in allogeneic transplant recipients at high risk.

Disclosure: No conflict interest to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P475

POST DLI NPM-1 MINIMAL RESIDUAL DISEASE NEGATIVITY PREDICTS OVERALL SURVIVAL IN AML PATIENTS UNDERGOING REDUCED INTENSITY CONDITIONING TRANSPLANT

Maria Fyrilla[1], Marianna Michalettou[1], Theodore Lytras[1], Aris Angouridis[1], Alex Kanellopoulos[2], Emmanouil Nikolousis[2,1]

[1]European University of Cyprus, Nicosia, Cyprus, [2]Heart of England NHS Trust, Birmingham, United Kingdom

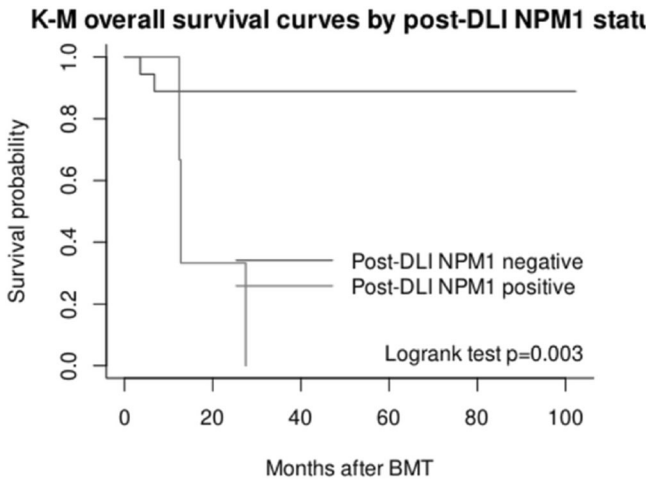
Background: AML patients positive for NPM-1 mutations but negative for other mutations such as FLT3 are considered to be a good risk group. It has been proven that AML NPM1 positive disease is highly chemosensitive and thus related to improved outcomes. Due to recent advances in minimal residual disease by measuring NPM-1 PCR copies we can determine the subset of patients who remain MRD positive after 2 courses of induction chemotherapy and based on the literature they will need to undergo stem cell transplantation. The presence of MRD positivity post stem cell transplantation leads to adverse outcomes and necessitates further management.

Methods: This retrospective study was conducted in 22 patients with AML who underwent a stem cell transplant in 3 transplant centres and positive NPM1 MRD positivity post BMT diagnosed between 2011 and 2019. The median age at diagnosis was 62.5 years(40-73) and median follow up 38 months (10 - 87). Post allogeneic stem cell transplant NPM1 MRD was measured at D + 30 and D + 90 days with a bone marrow test and all these patients were MRD positive and had mixed donor chimerism for which they received escalating doses of DLI as per SOP starting at 6 months post transplant. Post DLI MRD was reassessed with a bone marrow test 4 weeks after DLI administration. The cytogenetic analysis has shown that 16 (72.75%) patients had a normal karyotype, 3(13.63%) patients had an abnormality with 20q- and 1 (4.54%) patient had an abnormality at 11q- and 2 (9.09%) patients had trisomy 8.

The main transplant outcomes studied were overall survival, relapsed rates and progression free survival. Also, acute and chronic GvHD rates were assessed post DLI.

10 patients were male and 12 female. 6 patients (27.8%) received a fully matched sibling allogeneic transplant and the rest 16(72.2%) were fully matched unrelated donor transplants. Two conditioning regimens were used Fludarabine, Busalfan and Campath (Flu/bu2/campath) and Fludarabine, Melphalan and Campath (Flu/mel/campath). Campath dose was determined by the donor whether it was sibling (30mg on D-1) or unrelated donor (2 days of Campath 25mg on D-2 and D-1).

Results: A total of 5 patients died (4 female and 1 male). Post-DLI NPM1 positivity and was found in 4 individuals, of whom 3 died from disease progression. The 1 year transplant related mortality was 9% (2 out of 22 1 from infection and 1 from GvHD) Post DLI negativity was significant in predicting overall survival p:0.003.6 patients developed acute GvHD post DLI (27% in total 4 grade 1-2, 2 grade 3-4).



Conclusions: NPM-1 positive minimal residual disease could be managed by DLI cellular therapy and achieve molecular remission with escalated does of DLI. Further studies are needed to establish whether DLI or a combination pharmacological treatment with

hypomethylating agents and Venetoclax is the optimum management since there are patients who will be NPM1 MRD positive post DLI and will require further management.

Disclosure: no conflict of interest.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P476

PREVALENCE STUDY OF INFORMATIVE MARKERS FOR THE ANALYSIS OF CHIMERISM AMONG RECIPIENTS IN CAMPANIA REGION

Mafalda Caputo[1], Mariangela Pedata[1], Assunta Viola[2], Simona Maria Muggianu[1], Rosa Peluso[1], Manuela Pisa[1], Maria Celentano[1], Serena Marotta[1], Cira Riccardi[1], Lisa Mercante[1], Rossella Iula[1], Maria Salzano[1], Carmela Gallo[1], Claudio Falco[3], Maddalena Raia[4], Aldo Leone[1], Alessandra Picardi[1,5]

[1]Stem Cell Transplant Program, AORN A. Cardarelli, Naples, Italy, [2]Hematology Unit, AORN A. Cardarelli, Naples, Italy, [3]Transfusion Medicine Service, AORN A. Cardarelli, Naples, Italy, [4]CEINGE-Advanced Biotechnology, Naples, Italy, [5]Dep. Of Biomedicine and Prevention, Tor Vergata University, Rome, Italy

Background: Chimerism analysis is a test to assess the outcome of the Hematopoietic Stem Cell Transplantation (HSCT). To date, the chimerism test is mainly based on the differences in biallelic insertion/deletion (In/del) polymorphisms markers between patient and donor in order to identify the informative markers in the recipients. The aim of this study was to evaluate the prevalence of the informative markers in Campanian recipient/donor pairs.

Methods: Between July 2019 to date, 83 first allogeneic Hematopoietic Stem Cell transplant (HSCT) were performed at AORN Cardarelli Transplant Program in Naples. All but 3 patients were born in Campania, 52 males and 31 females with a median age of 48 years (range 20-69), 59 out of 83 (71%) affected by high risk Acute Leukemia. Most of them (65%) received PBSC, as stem cell source, from HLA-identical sibling, unrelated or haploidentical donor in 43, 32 and 25% of cases, respectively. Whole peripheral blood samples of 83 pairs were analyzed through the DNA isolation, using a commercial kit (QIAamp® Blood Mini kit Qiagen, Hilden, Germany), at baseline. All pairs were genotyped using KMRtype Extended Genotyping kit (GenDx, Utrecht, the Netherlands) which includes 39 In/del polymorphisms markers situated on all 46 chromosome. qPCR was carried out using Applied Biosystems® 7500 Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA, US). Analysis was performed using KMRengine® Chimerism Analysis Software (GenDx). Definition of informative marker consists of in/del polymorphic marker on patient DNA and its absent on donor DNA and vice versa. Moreover, we defined as prevalent Campanian informative markers those which occurred > 15% of recipients.

Results: In our Campanian population, the median of informative markers for every patient resulted 5 (range 2-10) and the prevalence of each informative marker of the pairs is detailed in table 1. According to diagnosis, we identified KMR041 and KMR042 as informative markers only in AML setting (9,5%) while KMR010 and KMR016 were more present respect to KMR041 and KMR042 (23% vs 9.5%) but not specific for AML. On the other hand, KMR038 and KMR052, KMR028 and KMR031, KMR048 and KMR050 were observed in 31% of ALL, in 50% of MDS, in 58% and 67% of HD, respectively.

MARKERS	LOCUS	%RECIPIENTS	%DONORS
KMR016	17q	23	11
KMR010	5q	22	18
KMR050	1p	22	17
KMR030	9p	20	8
KMR043	1p	20	22
KMR048	14q	20	14
KMR052	10q	19	5
KMR014	12q	18	11
KMR028	20q	18	18
KMR039	17p	18	11
KMR047	18q	17	22
KMR056	1p	17	7
KMR034	1p	16	13
KMR009	17p	10	18
KMR004	18q	11	17
KMR051	4q	14	16
KMR019	20q	12	16

Our preliminary data shows that KMR016 on CHR17q locus seem to represent the informative marker with higher prevalence (23%) in Campanian recipients setting. Moreover, KMR029, KMR035, KMR037, KMR055, KMR057 were never observed in female Campanian recipients while KMR041 and KMR049 were never observed in reletad donor. On the contrary, K0MR41and KMR049 were identified as informative markers in unrelated donors with non Campanian origin.

Conclusions: This prevalence analysis on Campanian pairs represents a useful tool for the laboratory management in terms of marker orders leading to the acquisition of single markers instead of kits (including multiple markers) for monitoring the chimerism outcome in allogeneic HSCT. Moreover, our preliminary data suggests a specific absence of KMR041 and KMR049, as informative markers, in Campanian donors but not in Campanian recipients and in unrelated donors. Further investigation is necessary to better understand this preliminary data.

Disclosure: Nothing to declare.

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

P477

IMMUNE MONITORING USING 13-COLOR FLOW CYTOMETRY: DURACLONE PANELS ENABLE ROBUSTNESS, PROLONGED STABILITY AND FLEXIBILITY

Sabine Huenecke[1], Claudia Cappel[1], Melanie Bremm[1], Yola Busekros[1], Theres Fingerhut[1], Stephanie Erben[1], Peter Bader[1]

[1]University Hospital Frankfurt, Frankfurt, Germany

Background: Flow cytometric phenotyping of patient blood is an established method in the diagnostic and treatment of various malignancies. Current flow cytometers are able to distinguish up to 13 different fluorochromes in combination with scatter properties, allowing a very comprehensive characterization of immune cells.

Methods: The DuraClone IM Phenotyping BASIC Tube is an 8-color antibody reagent that allows the identification of various immune cells via CD45, CD16, CD56, CD19, CD14, CD4, CD8 and CD3. Applying the Beckman Coulter DxFLEX 13-color flow cytometer we have completely utilized the remaining 5 colors by additionally adding CD45-RA, CD45RO, CD62L, CD69 and HLA-DR as drop-in liquid antibodies.

Results: By using the antibody panel described above, 13 different surface markers can be analyzed simultaneously in one tube, only. This reduces costs as no redundant use of antibodies is required as for example necessary on devices with fewer detectors where multiple tubes need to be applied. Furthermore, with eight antibodies already contained in the DuraClone tube, the probability of pipetting errors is reduced.

Leukocytes (CD45), monocytes (CD14) and eosinophil granulocytes (CD16) can be determined using the approach. Lymphocytes can be very comprehensively typed into T- (CD3), B- (CD19) and NK-cells (CD56). T-helper (CD4) and cytotoxic T cells (CD8) can be classified according to their maturation state into naive (CD45RA), effector and central-memory cells (CD45RO, CD62L). Furthermore, NK cells can be assigned to the immunoregulatory or cytotoxic phenotype (CD16). The activation state of the cells can also be analyzed (CD69, HLA-DR). In addition, CAR monitoring can also be integrated.

This format enables long term storage at room temperature and eliminates repeating and error-prone antibody handling steps. The flexibility to exchange five drop-in liquid antibodies gives the opportunity to adapt the panel to various questions such as immune regeneration after SCT, SCID diagnostics or therapy control after CAR-T cell application.

Conclusions: Multicolor fixed immunophenotyping panels can improve flow cytometric diagnostic while reducing the cost of antibodies and labor burden of laboratories. In combination with individual drop-in liquid antibodies the DuraClone IM Phenotyping BASIC Tube is an optimal solution for patient diagnostics and is particularly suitable for use in pediatrics, as very little patient blood is required for a comprehensive analysis of the immune status.

Disclosure: Peter Bader: Peter Bader declares research grants from Neovii, Riemser, Medac (to Institution); advisory board for Novartis, Cellgene, Amgen, Medac, Servier (personal and to Institution); Speakers Bureau of Miltenyi, Jazz, Riemser, Novartis, Amgen (to Institution), and patent and royalties from Medac.

27 - Multiple Myeloma

P478

LONG TERM OUTCOMES FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION FOR LIGHT CHAIN DEPOSITION DISEASE: A RETROSPECTIVE STUDY ON BEHALF OF THE CMWP OF THE EBMT

Laurent Garderet[1], Luuk Gras[2], Linda Koster[3], Rovira Montserrat[4], Laure Vincent[5], Guido Kobbe[6], Srinivas Pillai[7], Dries Deeren[8], Martin Kaufmann[9], Jurgen Kuball[10], Hakan Ozdogu[11], Maria Jesus Pascual Gascon[12], Jakob Passweg[13], Adam Rye[14], Urpu Salmenniemi[15], John Snowden[16], Thomas Stauffer Larsen[17], Xavier Leleu[18], Lauris Gastaud[19], Joanna Drozd Sokolowska[20], Kavita Raj[21], Meral Beksac[22], Stefan Schonland[23], Patrick Hayden[24], Donal Mclornan[25]

[1]Sorbonne University, Paris, France, [2]LUMC, Leiden, Netherlands, [3]EBMT Leiden Study Unit, Leiden, Netherlands, [4]Hospital Clinic Barcelona, Barcelona, Spain, [5]CHU Montpellier, Montpellier, France, [6]Heinrich Heine Universitaet, Dusseldorf, Germany, [7]University Hospital of North Staffordshire, Stoke, United Kingdom, [8]AZ Delta, Roeselare, Belgium, [9]Robert-Bosch-Krakenhaus, Stuttgart, Germany, [10]University Medical Center, Utrecht, Netherlands, [11]Baskent University Hospital, Adana, Turkey, [12]Hospital Regional de Malaga, Malaga, Spain, [13]Basel, Basel, Switzerland, [14]Glouscestershire, Cheltenham, United Kingdom, [15]HUCH, Helsinki, Finland, [16]Sheffield, Sheffield, United Kingdom, [17]Odense, Odense, Denmark, [18]Hopital la Miletrie, Poitiers, France, [19]Centre Antoine Laccasagne, Nice, France, [20]Warsaw, Warsaw, Poland, [21]University College London, London, United Kingdom, [22]Ankara, Ankara, Turkey, [23]Heidelberg, Heidelberg, Germany, [24]Trinity College, Dublin, Ireland, [25]London, London, United Kingdom

Background: There is a paucity of data concerning long-term outcomes following autologous stem cell transplantation (ASCT) for light chain deposition disease (LCDD).

Methods: Patient selection included adult patients who underwent first ASCT for renal biopsy proven LCDD (AL amyloidosis excluded) between the years 1995-2021.

Results: A total of 51 patients were evaluated from 24 EBMT registered centres. 63% were male, median year of diagnosis was 2011 (IQR: 2008-2015). The underlying plasma cell disorder was myeloma (50%) or monoclonal gammopathy of clinical significance (MGCS, 47%), with 3% missing. Median bone marrow aspirate plasmocytosis was 10% (IQR: 7.8-20) and Ig phenotype was IgG (24%), IgA (2%), light chain (69%, kappa=57%, lambda=11%), 2% IgD and 2% non-secretory, respectively. Among the 17 patients with cytogenetics available: 3 had a t(11-14) and 1 a del 17p. All 51 patients with data on disease involvement had renal involvement, and of these 3 had additional cardiac and 2 additional hepatic involvement. At diagnosis, median serum creatinine was 233 µmol/L (IQR:159-467), median proteinuria was 1813 mg/24h (IQR:445-5974) and 15% had evidence of bone lesions. All patients had received an induction regimen (93% bortezomib based) and the hematological response prior to transplant was: CR (12%), VGPR (29%), PR (31%), MR/SD (16%), relapse/progression (6%). A total of 59% were transplanted in/or after 2012. The median age at transplant was 55 years (IQR:49-61), median time from diagnosis to transplant was 7.4 months (IQR:5.5-13.0) and 42% were undergoing dialysis at the time of transplant. Karnofsky performance score (KPS) was >80 in 79%. Melphalan conditioning dose (mg/m^2) was 100 (23%), 140 (55%) and 200 (21%), respectively (missing: 1%). The median number of CD34+ cells x 10^6/kg infused was 3.4 (IQR:2.5-4.6) and 33% received GCSF post ASCT. All patients engrafted with a median time to neutrophils engraftment of 12 days (IQR:11-13) and platelets of 13 days (11-16). Best hematological response at day 100 post ASCT (21% missing) was: sCR 16%, CR 26%, VGPR 21% and PR 16%. A total of 13% had consolidation and 8% maintenance treatment post ASCT. Median follow-up time after ASCT was 84 months (IQR:46-122). OS at 6 years after ASCT was 88% (95% CI: 78-98%) and 6-year PFS was 44% (95% CI 28-60%). Median OS was not reached, median PFS was 65 months (95% CI: 45-103), 2-year cumulative RI was 17% (95% CI: 6-27%) and 2-year cumulative incidence of NRM was 2% (95% CI: 0-6%). In univariate analysis, transplant in/or after the year 2012 associated with a better OS (6-year OS 100 vs. 75%, log-rank $p = 0.05$), females tended towards a better OS (6-year OS 100 vs 82%, $p = 0.05$). KPS, age and status of disease at ASCT (VGPR or better vs. other) did not have a significant association with any outcomes in this small cohort evaluation.

Conclusions: ASCT is a feasible option for patients with LCDD even if 42% were on dialysis at the time of transplantation. Overall outcomes are favourable with a low NRM and improved long-term OS benefit.

Disclosure: nothing to disclose.

27 - Multiple Myeloma

P479

INTERNATIONAL DIFFERENCES IN BASELINE CHARACTERISTICS AND PRACTICE PATTERNS IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA UNDERGOING UPFRONT AUTOLOGOUS STEM CELL TRANSPLANTATION

Laurent Garderet[1], Luuk Gras[2], Linda Koster[2], Anita Dsouza[3], Noel Estrada Merly[4], Hari Parameswaran[3], Wael Saber[4], Andrew Cowan[5], Minako Iida[6], Shinichiro Okamoto[7], Hiroyuki Takamatsu[8], Shohei Mizuno[9], Koji Kawamura[9], Yoshihisa Kodera[6], Nada Hamad[10], Bor Sheng Ko[11], Christopher Liam[12], Kim Wah Ho[12], A. Sim Goh[13], S. Keat Tan[13], Alaa Elhaddad[14], Ali Bazarbachi[15], Qamar un Nisa Chaudhry[16], Rozan Alfar[17], Mohamed Amine Bekadja[18], Malek Benakli[19], Cristobal Augusto Frutos Ortiz[20], Eloisa Riva[21], Sebastian Galeano[22], Francisca Bass[23], Hira Mian[24], Arleigh McCurdy[25], Feng Rong Wang[26], Daniel Neumann[27], Mickey Koh[28], John Snowden[29], Stefan Schonland[30], Donal McLornan[31], Patrick Hayden[32], Anna Sureda[33], Hildegard Greinix[34], Mahmoud Aljurf[35], Yoshiko Atsuta[36], Dietger Niederwieser[27]

[1]Sorbonne University, Paris, France, [2]EBMT Leiden Study Unit, Leiden, Netherlands, [3]Medical College of Wisconsin, Milwaukee, United States, [4]CIBMTR, Milwaukee, United States, [5]Fred Hutchinson Cancer Center, Seattle, United States, [6]Aichi Medical School, Aichi, Japan, [7]Keio University School, Tokyo, Japan, [8]Kanazawa, Kanazawa, Japan, [9]Jichi Medical University, Saitama, Japan, [10]Saint Vincent Hospital, Sydney, Australia, [11]Taiwan University Hospital, Taipei, Taiwan, [12]Ampang Hospital, Ampang, Malaysia, [13]Penang General Hospital, Penang, Malaysia, [14]Cairo University, Cairo, Egypt, [15]American University of Beirut, Beirut, Lebanon, [16]AFBMTC/NIBMT, Rawalpindi, Pakistan, [17]King Hussein Cancer Center, Amman, Jordan, [18]University Ahmed Benbella, Oran, Algeria, [19]Centre Pierre et Marie Curie, Alger, Algeria, [20]Hospital Central, Asuncion, Paraguay, [21]Montevideo, Montevideo, Uruguay, [22]British Hospital Montevideo, Montevideo, Uruguay, [23]Hospital del Salvador, Santiago, Chile, [24]McMaster University, Hamilton, Canada, [25]Ottawa Hospital, Ottawa, Canada, [26]Peking University, Beijing, China, [27]University of Leipzig, Leipzig, Germany, [28]Saint George Hospital, London, United Kingdom, [29]Sheffield, Sheffield, United Kingdom, [30]Heidelberg, Heidelberg, Germany, [31]London, London, United Kingdom, [32]Trinity College, Dublin, Ireland, [33]Universitat de Barcelona, Barcelona, Spain, [34]University of Graz, Graz, Austria, [35]King Faysal Hospital, Riyadh, Saudi Arabia, [36]Japanese Data Center for Hematopoietic Cell Transplantation, Nagakute, Japan

Background: Worldwide, patients with newly diagnosed multiple myeloma (NDMM) undergoing upfront autologous stem cell transplantation (ASCT) have different characteristics and survival outcomes. The goal of this retrospective study was to analyze differences in regional outcomes.

Methods: Data on patient characteristics and transplant outcomes for patients with NDMM who received an upfront ASCT between 2013 and 2017 were provided to the WBMT by the EBMT (61%), the CIBMTR (26%), the APBMT (6%), the ANZTCT (5%), the EMBMT (1%), the LABMT (0.5%), and the Ottawa Canadian Registry (0.3%). The primary endpoints were OS and NRM and the secondary were PFS and RI.

Results: 61725 patients from 629 centers were included. Males comprised 58% and the median age at diagnosis was 59.9 years (IQR: 53.6-64.9). Race data was available in 45%: 73% White, 16% Asian and 11% African American. The predominant phenotypes were IgG (54%), light chain (24%) (lowest (4%) in Malaysia and highest (38%) in EMBMT), and IgA (19%) (lowest (13%) in EMBMT and highest (24%) in Ottawa). The ISS stage at diagnosis (54% available) was I in 38%, II 35% and III 27% (III lowest (24%) in ANZTCT and highest (45%) in LABMT). Cytogenetic risk (44% available) was standard in 70% and high in 30% (high risk was lowest (5%) in EMBMT, and highest (62%) in Ottawa). The median time from diagnosis to ASCT was 7 months (IQR:5.5-9.9) (shortest (6.4) in CIBMTR and Ottawa, and longest (13) in LABMT). The median age at ASCT was 60.8 years (IQR: 54.6-65.8) (lowest (53.6) in EMBMT, and highest (62) in Ottawa). Only 5% of patients were older than 70 years (lowest (3.5%) in EBMT, and highest (9.8%) in CIBMTR). HCT-CI at ASCT (28% missing) was reported as low risk (0) in 52%, intermediate (1-2) 25% and high risk (≥ 3) 23% (high risk was lowest (5.5%) in LABMT and highest (42%) in CIBMTR). The KPS at ASCT (2.2 % missing) was 100 in 40% and ≤90 in 60% (≤ 90 was lowest (44%) in LABMT and highest (92%) in Ottawa). Disease status (9.7% missing) was CR in 19%, VGPR 38%, PR 36%, MR/SD 5% and refractory 2%. A ≥ VGPR status at ASCT was 60% in EBMT, 55% CIBMTR, 39% ANZTCT, 51% Japan, 64% EMBMT, 71% Taiwan, 76% LABMT, 51% Ottawa and 54% Malaysia. The most frequent preparative regimen was melphalan 200 mg/m^2 (82 %) (lowest (60%) in Malaysia and highest (90%) in Ottawa), 140 mg/m^2 accounted for 14% and others for 4%. Tandem ASCT was reported in 6.7% (10% in EBMT, 1.3% in CIBMTR and 0.6% LABMT and Taiwan). Of the 11% reported with post-ASCT maintenance treatment, 51% received lenalidomide. The median follow-up was 41.1 months. NRM at 1 year was between 1-2% in each registry with differences between registries in RI, PFS and OS.

Conclusions: This large worldwide study of patients with NDMM treated with upfront ASCT revealed marked regional differences in transplant activity and patient characteristics. NRM was low worldwide but with differences in relapse incidence and survival.

Disclosure: nothing to disclose.

27 - Multiple Myeloma

P480

WORLDWIDE NETWORK FOR BLOOD AND MARROW TRANSPLANTATION GLOBAL STUDY ON BASELINE CHARACTERISTICS/CLINICAL OUTCOMES IN MULTIPLE MYELOMA PATIENTS UNDERGOING ASCT, A STUDY OFF 61,725 PATIENTS

Laurent Garderet[1], Luuk Gras[2], Linda Koster[2], Anita Dsouza[3], Hari Parameswaran[3], Noel Estrada Merly[4], Wael Saber[3], Andrew Cowan[5], Minako Iida[6], Shinichiro Okamoto[7], Hiroyuki Takamatsu[7], Shohei Mizuno[8], Koji Kawamura[8], Yoshihisa Kodera[6], Nada Hamad[9], Bor Sheng Ko[10], Christopher Liam[11], Kim Wah Ho[11], A. Sim Goh[12], S. Keat Tan[12], Alaa M. Elhaddad[13], Ali Bazarbachi[14], Qamar un Nisa Chaudhry[15], Rozan Alfar[16], Mohamed Amine Bekadja[17], Malek Benakli[18], Cristobal Augusto Frutos Ortiz[19], Eloisa Riva[20], Sebastian Galeano[21], Francisca Bass[22], Hira S. Mian[23], Arleigh McCurdy[24], Feng Rong Wang[25], Daniel Neumann[26], Mickey Koh[27], John Snowden[28], Stefan Schonland[29], Donal Mclornan[30], Patrick Hayden[31], Anna Sureda[32], Hildergard Greinix[33], Mahmoud Aljurf[34], Yoshiko Atsuta[35], Dietger Niederwieser[26]

[1]Sorbonne University, Paris, France, [2]EBMT Leiden Study Unit, Leiden, Netherlands, [3]Medical College of Wisconsin, Milwaukee, United States, [4]CIBMTR, Milwaukee, United States, [5]Fred Hutchinson Cancer Center, Seattle, United States, [6]Aichi Medical School, Aichi, Japan, [7]Kanazawa, Kanazawa, Japan, [8]Jichi Medical University, Saitama, Japan, [9]Saint Vincent Hospital, Sydney, Australia, [10]Taiwan University

Hospital, Taipei, Taiwan, [11]Ampang Hospital, Ampang, Malaysia, [12]Penang General Hospital, Penang, Malaysia, [13]Cairo University, Cairo, Egypt, [14]American University of Beirut, Beirut, Lebanon, [15]AFBMTC/NIBMT, Rawalpindi, Pakistan, [16]King Hussein Cancer Center, Amman, Jordan, [17]University Ahmed Benbella, Oran, Algeria, [18]Centre Pierre et Marie Curie, Alger, Algeria, [19]Hospital Central, Asuncion, Paraguay, [20]Montevideo, Montevideo, Uruguay, [21]British Hospital Montevideo, Montevideo, Uruguay, [22]Hospital del Salvador, Santiago, Chile, [23]McMaster University, Hamilton, Canada, [24]Ottawa Hospital, Ottawa, Canada, [25]Peking University, Beijing, China, [26]University of Leipzig, Leipzig, Germany, [27]Saint George Hospital, London, United Kingdom, [28]Sheffield, Sheffield, United Kingdom, [29]Heidelberg, Heidelberg, Germany, [30]London, London, United Kingdom, [31]Trinity College, Dublin, Ireland, [32]Universitat de Barcelona, Barcelona, Spain, [33]University of Graz, Graz, Austria, [34]King Faysal Hospital, Riyadh, Saudi Arabia, [35]Japanese Data Center for Hematopoietic Cell Transplantation, Nagakute, Japan

Background: Patients with newly diagnosed multiple myeloma (NDMM) undergoing upfront autologous stem cell transplantation (ASCT) have different characteristics worldwide. The first aim of this retrospective study was to analyze the global baseline patient characteristics and outcomes of upfront ASCT in NDMM.

Methods: Data on patient characteristics and transplant outcomes for patients with NDMM who received an upfront ASCT between 2013 and 2017 were provided to the WBMT by the EBMT (61%), the CIBMTR (26%), the APBMT (6%), the ANZTCT (5%), the EMBMT (1%), the LABMT (0.5%), and the Ottawa Canadian Registry (0.3%). The primary endpoints were OS and NRM and the secondary were PFS and RI. Multivariable (cause specific) models included a random effect for each country and were censored at 3 years for OS and PFS and at 1 year for RI and NRM.

Results: 61,725 patients from 629 centers (median patients/center = 67) were included: Males comprised 58% and the median age at diagnosis was 60 years. The predominant phenotypes were IgG (54%), light chain (24%) and IgA (19%). The ISS stage at diagnosis was I (38%), II (35%) or III (27%) and cytogenetic risk was standard in 70% and high in 30%. The median time from diagnosis to ASCT was 7.1 months. The year of ASCT was equally distributed between 2013 and 2017 (the annual percentage varied between 18% and 22%). The median age at ASCT was 60.8 years with 5.1% of patients older than 70 years. The HCT-CI risk at transplant was low in 52%, intermediate in 25% and high in 23%. The KPS at ASCT was 100 in 40% and ≤90 in 60%. Disease status was CR in 19%, VGPR in 38%, PR in 36%, MR/SD in 5% and refractory in 2%. The most frequent preparative regimen was melphalan 200 mg/m^2 (82 %) and 140 mg/m^2 comprised 14%. Tandem ASCT was reported in 6.7%. Of the 11% of patients with data on post-ASCT maintenance treatment, 51% received lenalidomide. The median follow-up was 41.1 months (95% CI: 40.5 to 41.6, IQR:19.2-60.4). Outcomes: NRM at 12 months was 1% (95% CI 1-2%); OS at 4 and 8 years was 76% (75-76%) and 45% (42-48%) respectively; PFS at 2 and 4 years was 65% (95% CI: 64-65%) and 40% (40-41%) respectively; RI at 6 and 12 months was 7% (7-7%) and 16% (15-16%) respectively. In the multivariate analysis, later calendar year of ASCT, a better disease response at time of ASCT, higher KPS, and an IgG phenotype were all associated with an improved OS. A lower ISS stage, a lower HCT-CI score and standard risk cytogenetics were also associated with better OS. Overall NRM was low. Younger age, higher KPS, higher melphalan dose, better disease response at ASCT, lower ISS stage at diagnosis and lower HCT-CI score were associated with a lower NRM.

Conclusions: This study represents the largest study to date characterizing the outcomes of upfront ASCT performed worldwide. ASCT remains an effective and safe procedure for patients with NDMM world-wide.

Disclosure: nothing to disclose.

27 - Multiple Myeloma

P481

POLYMORPHISMS WITHIN AUTOPHAGY-RELATED GENES AS SUSCEPTIBILITY BIOMARKERS FOR MULTIPLE MYELOMA: A META-ANALYSIS OF THREE LARGE COHORTS

Antonio José Cabrera-Serrano[1,2,3], José Manuel Sanchez-Maldonado[1,2,3], Esther Clavero[3], Angelica Macauda[4], Rob Ter Horst[5,6], Artur Jurczyszyn[7], Alyssa Clay-Gilmour[8,9], Angelika Stein[4], Michelle A. T. Hildebrandt[10], Niels Weinhold[11,12], Gabriele Buda[13], Ramón García-Sanz[14], Waldemar Tomczak[15], Ulla Vogel[16], Andrés Jerez[17], Daria Zawirska[18], Marzena Wątek[19,20], Jonathan N. Hofmann[21], Stefano Landi[22], John J. Spinelli[23,24], Aleksandra Butrym[25,26], Joaquín Martínez-López[27], Sara Galimberti[13], María Eugenia Sarasquete[14], Edyta Subocz[28], Elzbieta Iskierka-Jazdzewska[29], Graham G. Giles[30,31,32], Malwina Rybicka-Ramos[33], Marcin Kruszewski[34], Niels Abildgaard[35], Katalin Kadar[36], Małgorzata Razny[37], Wendy Cozen[38], Parveen Bhatti[39,40], Marek Dudzinski[41], Agnieszka Druzd-Sitek[42], Yang Li[5,43], Aaron D. Norman[9,44], Jan Maciej Zaucha[45], Rui Manuel Vieira Reis[46,47], Miroslaw Markiewicz[38], Daniele Campa[48], Charles Dumontet[49], Annette Juul Vangsted[50], Elizabeth E. Brown[51], Celine M. Vachon[52], Mihai G. Netea[53], Federico Canzian[54], Asta Försti[54], Juan Sainz[1,2,3,55]

[1]Genomic Oncology Area, GENYO, Centre for Genomics and Oncological Research, Pfizer / University of Granada / Andalusian Regional Government, PTS, Granada, Spain, [2]Instituto de Investigación Biosanataria IBs., Granada, Spain, Virgen de las Nieves University Hospital, Granada, Spain, [4]Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany, Radboud University Medical Center, Nijmegen, Netherlands, [6]CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria, [7]Jagiellonian University Medical College, Kraków, Poland, Arnold School of Public Health, University of South Carolina, Greenville, United States, [9]Division of Epidemiology, Mayo Clinic, Rochester, United States, The University of Texas MD Anderson Cancer Center, Houston, United States, [11]Myeloma Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States, University of Heidelberg, Heidelberg, Germany, University of Pisa/AOUP, Pisa, Italy, [14]Diagnostic Laboratory Unit in Hematology, University Hospital of Salamanca, IBSAL, CIBERONC, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain, Medical University of Lublin, Lublin, Poland, [16]National Research Centre for the Working Environment, Copenhagen, Denmark, University Hospital Morales Meseguer, IMIB, Murcia, Spain, [18]University Hospital, Kraków, Poland, [19]Holycross Medical Oncology Center, Kielce, Poland, [20]Institute of Hematology and Transfusion Medicine, Warsaw, Poland, [21]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, United States, Italy, [23]Division of Population Oncology, BC Cancer, British Columbia, Canada, [24]School od Population and Public Health, University of British Columbia, British Columbia, Canada, [25]Wroclaw Medical Universtiy, Wroclaw, Poland, [26]Alfred Sokolowski Specialist Hospital in Walbrzych Oncology Support Centre for Clinical Trials, Walbrzych, Poland, [27]Hospital 12 de Octubre, Compluntense University, CNIO, CIBERONC, Madrid, Spain, Military Institute of Medicine, Warsaw, Poland, Medical University of Lodz, Lodz, Poland, [30]Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Australia, [31]Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia, Melbourne, Australia, [32]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia, Clayton, Australia, Specialist Hospital No.1 in Bytom, Academy of Silesia, Katowice, Poland, University Hospital No.

2, Bydgoszcz, Poland, Odense University Hospital, Odense, Denmark, [36]St Johns Hospital, Budapest, Hungary, Rydygier Hospital, Cracow, Poland, [38]Silesian Medical University, Katowice, Poland, [39]Cancer Control Research, BC Cancer, Vancouver, Canada, [40]Program in Epidemiology, Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, United States, Institute of Medical Sciences, College of Medical Sciences, University of Rzeszow, Rzeszow, Poland, Maria Skłodowska Curie National Research Institute of Oncology, Warsaw, Poland, [43]Centre for Individualised Infection Medicine (CiiM) & TWINCORE, joint ventures between the Helmholtz-Centre for Infection Research (HZI) and the Hannover Medical School (MHH), Hannover, Germany, [44]Genetic Epidemiology and Risk Assessment Program, Mayo Clinic Comprehensive Cancer Center, and Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, United States, Medical University of Gdansk, Gdansk, Poland, [46]Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal and ICVS/3B's - PT Government Associate Laboratory, Braga, Portugal, [47]Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, Brazil, [48]University of Pisa, Heidelberg, Germany, [49]Cancer Research Center of Lyon / Hospices Civils de Lyon, Lyon, France, [50]Rigshospitalet, Copenhagen University, Copenhagen, Denmark, [51]The University of Alabama at Birmingham, Birmingham, United States, [52]Mayo Clinic, Rochester, United States, [53]Radboud University Medical Center, Radboud, Netherlands, [54]German Cancer Research Center, Heidelberg, Germany, University of Granada (UGR), Granada, Spain

Background: Multiple myeloma (MM) arises following malignant proliferation of plasma cells in the bone marrow, that secrete high amounts of specific monoclonal immunoglobulins or light chains, resulting in the massive production of unfolded or misfolded proteins. Autophagy can have a dual role in tumorigenesis, by eliminating these abnormal proteins to avoid cancer development, but also ensuring MM cell survival and promoting resistance to treatments. To date no studies have determined the impact of genetic variation in autophagy-related genes on MM risk.

Methods: We performed meta-analysis of germline genetic data on 234 autophagy-related genes from three independent study populations including 13387 subjects of European ancestry (6863 MM patients and 6524 controls) and examined correlations of statistically significant single nucleotide polymorphisms (SNPs; $p < 1\times10^{-9}$) with immune responses in whole blood, peripheral blood mononuclear cells (PBMCs) and monocyte-derived macrophages (MDM) from a large population of healthy donors from the Human Functional Genomic Project (HFGP).

Results: After meta-analysis of genetic data from three independent cohorts of European ancestry including 13387 subjects (6863 MM patients and 6524 controls), we identified six loci, *ULK4*, *IKBKE*, *ATG5*, *CD46*, *CDKN2A*, and *PARK2*, associated with MM risk ($p = 4.79\times10^{-4} \sim 5.82\times10^{-14}$). Mechanistically, we found that the $ULK4_{rs6599175}$ SNP correlated with circulating levels of vitamin D3 ($p = 4.0\times10^{-4}$), whereas the $IKBKE_{rs17433804}$ SNP correlated with levels of transitional $CD24^{+}CD38^{+}$ B cells ($p = 4.8\times10^{-4}$) and circulating serum levels of MCP-2 ($p = 3.6\cdot10^{-4}$). We also found that the $CD46_{rs1142469}$ SNP correlated with numbers of $CD19^{+}$ B cells, $CD19^{+}CD3^{-}$ B cells, $CD5^{+}IgD^{-}$ cells, IgM^{-} cells, $IgD^{-}IgM^{-}$ cells, and $CD4^{-}CD8^{-}$ PBMCs ($p = 4.9\times10^{-4}$-8.6×10^{-4}) and circulating levels of IL20 ($p = 0.00082$). Finally, we observed that the $CDKN2A_{rs2811710}$ SNP correlated with levels of $CD4^{+}EMCD45RO^{+}CD27^{-}$ cells ($p = 9.3\times10^{-4}$).

Conclusions: This study reports the consistent association of genetic polymorphisms within the *ULK4, ATG5, CDKN2A, IKBKE, CD46* and *PARK2* loci in modulating MM risk and provides new insights into the functional role of *ULK4, IKBKE, CD46*, and *CDKN2A* polymorphisms in disease pathogenesis. Additional studies are still necessary to confirm the functional impact of these SNPs on the risk of developing MM and to identify the biological mechanisms behind the *ATG5* association.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P482

IMPACT OF THE ADDITION OF DARATUMUMAB TO THE STANDARD VTD REGIMEN ON HEMATOPOIETIC STEM CELL MOBILIZATION AND COLLECTION, POST-TRANSPLANT ENGRAFTMENT AND INFECTIOUS COMPLICATIONS

Gianluca Cavallaro[1], Alessandra Pompa[2], Sara Pezzatti[3], Laura Paris[1], Paola Stefanoni[1], Chiara Pavoni[1], Edoardo Olivari[4], Giuliana Rizzuto[1], Pantaleo De Simone[4], Fabio Serpenti[4], Stefano Crippa[5], Alessandro Rambaldi[1,4], Monica Galli[1]

[1]ASST Papa Giovanni XXIII, Bergamo, Italy, [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, [3]Ospedale San Gerardo, Monza, Italy, [4]Università degli Studi di Milano, Milano, Italy, [5]Università degli Studi di Milano-Bicocca, Milano, Italy

Background: Previous reports showed that adding daratumumab in induction therapy in newly diagnosed transplant-eligible (NDTE) multiple myeloma (MM) patients yielded to a higher number of poor mobilizers, with a lower median number of collected hematopoietic stem cells (HSC). However, these reports included different types of induction therapies and real-life data focusing on Dara-VTD is lacking. We report our ongoing experience on the impact of Dara-VTD on HSC mobilization and collection, with a retrospective comparison with a cohort of patients treated with VTD.

Methods: From January 2022 to October 2022, 43 NDTE MM patients received Dara-VTD treatment induction according to the approved doses and schedule. The control group consisted of 34 age-matched patients treated with VTD in the years 2015-2016. Mobilizing therapy consisted of cyclophosphamide 2-3 gr/sqm followed by G-CSF 10 mg/kg starting the 5th day thereafter, with HSC harvest planned for the 11th day thereafter. Patients received only G-CSF 10 mg/kg if they were older than 70 years, experienced hematologic toxicity during the induction or had renal impairment (i.e., eGFR < 50 ml/min). Poor mobilizer was defined as having less than 20 CD34 + /μL in peripheral blood on the 11th day after cyclophosphamide or on the 4th day of G-CSF administration. In that case, plerixafor was added at the standard dose of 0.24 mg/kg.

Results: In the Dara-VTD group, 38/43 patients received cyclophosphamide; among them, 3 patients had failed a previous G-CSF mobilizing therapy, even with the addition of plerixafor. In the VTD group, all patients received cyclophosphamide. Pre-harvest median number of CD34 + /mL in the Dara-VTD group was 21 (range 0-157) vs 76 (range 20-294) in the VTD group and the incidence of poor mobilizing patients was 51.2% vs 5.9%, respectively (OR 0.06, 95% CI 0.01-0.23, P = 0.0004). Plerixafor was used in 27/43 patients in the Dara-VTD group (although not poor mobilizers *sensu strictu*, 5 patients received plerixafor because of a number of CD34 + /mL just above the cut off value of 20) and in 2/34 patients of the VTD group. Two patients failed HSC mobilization both with G-CSF and cyclophosphamide. All patients that received G-CSF only resulted in poor mobilizers and required plerixafor before HSC harvest. The median number of collected HSC was significantly lower in the Dara-VTD group vs VTD group: 4.3 x 10^6/Kg (range 2-13.4) vs 7.25 x 10^6/kg (range 2.0-15.9), respectively (p = 0.0002). 18.6% of patients (8/43) in Dara-VTD group collected at least 6 x 10^6 CD34 + /Kg). Median time to neutrophils and

platelets engraftment were not different between the two groups (12 and 14 days, respectively), as well as infection incidence. Although the second transplant was planned for 21 patients treated with Dara-VTD, it was performed in 3 patients only.

Table 1: Main mobilization and transplantation characteristics of patients treated with Dara-VTD at induction

Patients evaluated, n	**43**
Mobilization succesful, n	**41**
Cyclophosphamide + G-CSF, n (%)	38 (88.3)
G-CSF only, n (%)	5 (11.6)
Pre-harvest CD34 + /mmc, median (range)	**21 (0-157)**
Poor mobilizer, n (%)	
Yes	22 (51.2)
No	21 (48.8)
Use of plerixafor, n (%)	
Yes	27 (62.7)
No	16 (37.2)
Total CD34+ harvested x10^6/kg, median (range)	**4.3 (2-13.4)**
Patients harvesting [3] 6 x 10^6 CD34 + /Kg, n (%)	**8 (18.6)**
First autologous transplant at data cutoff, n	**33**
Neutrophil engraftment, days (range)	12 (11-16)
Platelets engraftment, days (range)	14 (10-28)
Viral reactivation (HHV6, CMV), n (%)	3 (9)
Documented infectious complications, n (%)	6 (18)
Planned second autologus transplant, n	**21**
Done, n (%)	**3 (14.3)**
Not done, n (%)	**18 (85.7)**
for insufficient HSC harvest	14
for disease progression	1
for failed mobilization	2
for medical choice	1

Conclusions: Our experience with Dara-VTD confirms an increased number of poor mobilizers, higher use of plerixafor and a lower number of collected HSC. We did not observe differences concerning engraftment and infectious complications. The lower number of collected HSC hampers the possibility of a double transplant.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P483

REVISITING THE UTILITY OF G-CSF POST-AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Andrew Portuguese[1], Geoffrey Hill[1], Leona Holmberg[1], Stephanie Lee[1], Damian Green[1], Marco Mielcarek[1], Albert Yeh[1]

[1]Fred Hutchinson Cancer Center, Seattle, United States

Background: Autologous hematopoietic stem cell transplantation (ASCT) following chemotherapy is used to treat multiple myeloma (MM) and non-Hodgkin lymphoma (NHL), but prolonged neutropenia contributes to morbidity. The use of granulocyte colony-stimulating factor (G-CSF) after ASCT has been shown to reduce time to neutrophil engraftment and duration of hospitalization, leading to its adoption in guidelines and routine use in transplant centers. Prior studies of G-CSF have been limited to electively admitted patients, where admission duration often depends on time to engraftment. Given advances in monitoring, infectious disease management, and an increasing number of ASCTs performed in the outpatient setting, we revisited the utility of post-ASCT G-CSF.

Methods: Starting September 2021, a revised standard operating procedure (SOP) went into effect at the Fred Hutchinson Cancer Center (FHCC) whereby post-ASCT G-CSF became a supportive care component for all patients undergoing ASCT, except for those with concurrent amyloid, POEMS syndrome, or history of autoimmune disease. G-CSF 5 mcg/kg SQ daily was given from day +5 through neutrophil recovery ($\geq 0.5 \times 10^9$/L x3 days). This intention-to-treat analysis evaluated MM and NHL patients transplanted at FHCC between 9/2018 and 8/2022 in the pre- (9/2018-8/2021) and post- (9/2021-8/2022) G-CSF SOP periods. The primary outcome was duration of post-ASCT hospitalization. Additional analyses are ongoing for secondary outcomes including infections, resource utilization and long-term survival.

Results: Among 556 patients identified for inclusion, 428 (77.0%) and 128 (23.0%) had MM and NHL, respectively. The median patient age was 61.6 (interquartile range [IQR] 54.9-66.9). There were 410 and 146 patients identified in the no G-CSF (9/2018-8/2021) and G-CSF (9/2021-8/2022) periods, respectively. All NHL patients and 45.8% (n = 196) of MM patients were electively hospitalized for ASCT.

Following implementation of the G-CSF SOP, the proportion who received G-CSF by day +5 was greater for patients with MM (73.9% vs 2.3%) and NHL (81.5% vs 14.9%). The time to achieve an absolute neutrophil count ≥0.5 x 10^9/L ("ANC 500") was reduced by 3 days in patients with MM (11.8 vs 14.8 days, p < 0.0001) and NHL (9.9 vs 12.9 days, p < 0.0001). The total number of inpatient days through day +30 ("Inpatient 30") was reduced for NHL patients (12.1 vs 14.7 days, p = 0.0148), but not for MM patients (10.2 days vs 10.4 days, p = 0.8660), even after adjusting for age, sex, conditioning intensity, and CD34 count. Among MM patients not electively admitted for ASCT, the proportion requiring admission was similar (70.0% [42/60] vs 75.0% [129/172], p = 0.4487), as was the Inpatient 30 (5.9 vs 6.9 days, p = 0.2248). The proportion of NHL patients requiring re-admission was numerically reduced (7.4% [2/27] vs 24.8% [25/101], p = 0.0628). The proportion who developed NF was similar for MM (46.2% [55/119] vs 56.0% [173/309], p = 0.0696) and NHL patients (88.9% [24/27] vs 89.1% [90/101]), p = 1.0). Survival to day 100 was excellent (97.2% vs 98.2%, p = 0.71).

Table. Patient characteristics before (9/18-9/21) and after (9/21-8/22) implementation of a G-CSF post-ASCT standard operating procedure.

Characteristic	G-CSF, N = 146	No G-CSF, N = 410	p-value[1]
Sex, n (%)			>0.9
Male	87 (60%)	243 (59%)	
Female	59 (40%)	167 (41%)	
Age, Median (IQR)	62 (56, 68)	61 (55, 66)	0.2
CD34 cells x 10^6/kg, Median (IQR)	5.20 (4.44, 6.29)	5.47 (4.47, 6.94)	0.072
Disease type, n (%)			0.13
MM	119 (82%)	309 (75%)	
NHL	27 (18%)	101 (25%)	
Conditioning, n (%)			0.6
L-PAM	118 (81%)	309 (75%)	
L-PAM,ARA-C,BCNU,VP-16	24 (16%)	77 (19%)	

Characteristic	G-CSF, N = 146	No G-CSF, N = 410	p-value[1]
BU,CY,TEPA	4 (2.7%)	20 (4.9%)	
BU,TEPA	0 (0%)	3 (0.7%)	
L-PAM,TEPA,ARA-C,VP-16	0 (0%)	1 (0.2%)	
Elective admission, n (%)			
MM	59 (50%)	137 (44%)	0.3
NHL	27 (100%)	101 (100%)	

[1] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Conclusions: Use of post-ASCT G-CSF resulted in a shorter time to neutrophil engraftment for patients with both MM and NHL, but did not reduce Inpatient 30 for patients with MM, most of which underwent part of ASCT in an outpatient setting.

Disclosure: Geoffrey Hill: consultant fees from Generon Corporation, NapaJen Pharma, iTeos Therapeutics, Neoleukin Therapeutics; research funding from Compass Therapeutics, Syndax Pharmaceuticals, Applied Molecular Transport, Serplus Technology, Heat Biologics, Laevoroc Oncology, iTeos Therapeutics and Genentech. Leona Holmberg: royalties from Up-To-Date; served on a Data and Safety Monitoring Board for Iteos and as a panelist for the National Comprehensive Cancer Network; research funding from Seattle Genetics, Sanofi, Millennium-Takeda, Bristol Myers Squibb, Merck, Janssen, and Iteos. Stephanie Lee: consultant fees from Mallinckrodt, Equillium, Kadmon; research funding from Amgen, AstraZeneca, Incyte, Kadmon, Pfizer, Syndax; provision of study medication from Janssen; steering committee for a clinical trial, Incyte. Damian Green: research funding from Bristol Myers Squibb, Cellectar Biosciences, Janssen Biotech, Juno Therapeutics, Seattle Genetics, SpringWorks Therapeutics; membership on a board or advisory committee for Bristol Myers Squibb, GSK, Janssen Biotech, Neoleukin Therapeutics, Seattle Genetics; patents & royalties from Bristol Myers Squibb, Juno Therapeutics; consultant fees from Legend Biotech.

27 - Multiple Myeloma

P484

IS THERE STILL A ROLE FOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN REFRACTORY MULTIPLE MYELOMA? A RETROSPECTIVE MULTICENTER ANALYSIS IN THE AGE OF MODERN THERAPIES

Tim Richardson[1], G. Kobbe[2], T. Schroeder[3], M. Crysandt[4], E. Jost[4], C. Neuerburg[5], T. Holderried[5], M. Hallek[1], C. Scheid[1], U. Holtick[1]

[1]University of Cologne, Cologne, Germany, [2]Klinik für Hämatologie, Onkologie und Klinische Immunologie, Düsseldorf, Germany, [3]Klinik für Hämatologie und Stammzelltransplantation, Essen, Germany, [4]Klinik für Hämatologie, Onkologie, Hämastaseologie und Stammzelltransplantation, Aachen, Germany, [5]Medizinische Klinik und Poliklinik III, Bonn, Germany

Background: A growing list of therapies for patients with multiple myeloma (MM) result in deep response rates, but eventually all patients relapse. Allogeneic hematopoietic cell transplantation (allo-HCST) is a potentially curative approach for MM providing a unique platform on which immune therapies and novel agents can be employed to improve clinical outcomes against the background of the donor immune system.

Methods: Our work describes characteristics and outcome of 129 patients who underwent allo-HSCT for refractory MM at 5 German centers between 2010 and 2021. Overall survival (OS) and progression-free survival (PFS) were calculated from time of allo-HSCT to death from any cause and first observation of relapse or death. Both were estimated using the Kaplan-Meier method. Our interest is focused on the treatment of relapse after allo-HSCT. This analysis is pending and will be presented at the meeting.

Results: Median age at allo-HSCT was 56 years (range: 30–70). Median therapies prior to transplant were 6.

Allo-HSCT was performed at a median of 30 months (range 5 – 238) after diagnosis.

Cytogenetic risk stratification was 74% standard risk and 26% high risk according to IMWG criteria.

Remission prior to transplant was CR, VGPR, PR and SD in 16%, 24%, 39% and 13% of patients.

Pretransplant conditioning was fludarabine based, in 59% reduced intensity and in 41% myeloablative conditioning.

As GvHD prophylaxis, ATG was administered in 44% of patients in addition to calcineurin inhibitors and MTX or MMF.

Peripheral blood stem cells were used in 94% of patients.

Donor source was matched unrelated and matched related in 57% and 27% of transplants.

Median duration from admission to discharge was 28 days (range 17-198).

30 days after transplantation 70% of patients showed a CR and 98% a complete chimerism.

With a median follow-up of 6,4 years the median PFS and OS was 7 and 19 months.

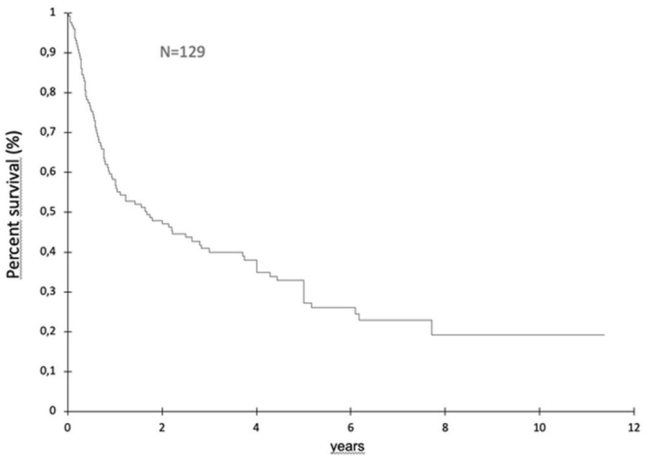
Non-relapse mortality was 24% overall (17% and 6% at 1 and 2 years).

25% of patients showed chronic graft-versus-host disease (cGvHD).

OS was 46% (N = 59) at 2 years, 31% (N = 40) at 4 years, and 22% (N = 29) at 6 years (Figure 1).

PFS was 28% (N = 36) at 2 years, 18% (N = 23) at 4 years, and 13% (N = 17) at 6 years.

No significant difference was detected with regard to age, number of previous therapies, or conditioning regimen. CGvHD was advantageous in terms of PFS and OS.



Conclusions: Allo-HSCT is considered a last-resort therapy for fit patients with refractory MM. But only 28% of patients are alive without progression at 2 years after transplant reflecting the limits of the concept. On the contrary, allo-HSCT resulted in long-term survival in a subgroup of patients with 13% being under immunological control and in remission at 6 years after transplant. There remains an unmet need for prospective studies investigating allo-HSCT as salvage therapy for refractory MM. Particularly against the background of novel treatment strategies, including

bispecifics, CAR-T cell treatment and other immunological approaches, which could benefit from the inplemented donor immunesystem. In our perspective, allo-HSCT remains an option for fit patients refractory to all other treatments available.

Disclosure: No potential conflict of interests to declare.

27 - Multiple Myeloma

P485

BUSULFAN PLUS CYCLOPHOSPHAMIDE AND ETOPOSIDE VERSUS HIGH-DOSE MELPHALAN AS CONDITIONING IN AUTOLOGOUS STEM CELL TRANSPLANTATION FOR NEWLY DIAGNOSED MULTIPLE MYELOMA

Seonyang Park[1], Youngjoon Lee[2], Sungnam Lim[2]

[1]Haeundae Paik Hospital, Busan, Korea, Republic of, [2]Inje University College of Medicine, Haeundae Paik Hospital, Busan, Korea, Republic of

Background: High-dose melphalan (HDMEL) represents the standard conditioning regimen before autologous stem cell transplant (ASCT) in multiple myeloma, but recent updates have suggested combination of busulfan with melphalan is also associated with favorable outcomes. In patients with hematologic malignancies, previous reports of etoposide, busulfan, and cyclophosphamide as a conditioning regimen have shown high efficacy with a wide maximal tolerated dose range. This retrospective study was performed to determine if the busulfan based conditioning without melphalan would be a tolerable and effective conditioning regimen. We report a single institution's experience with 35 multiple myeloma patients treated with high-dose busulfan, cyclophosphamide, and etoposide (BuCyE), followed by ASCT.

Methods: A total of 35 patients with multiple myeloma, enrolled between March 2016 and September 2021, patients aged 47-67 (median 57 years) with multiple myeloma were enrolled to receive bortezomib, thalidomide and dexamethasone (VTD) induction followed by ASCT. All patients received HDMEL or BuCyE as conditioning regimen. BuCyE conditioning regimen consisted of busulfan 3.2 mg/kg from days -7 to days -5, etoposide 200 mg/m^2 from days -5 to days -4, cyclophosphamide 50 mg/m^2 from days -3 to days -2. HDMEL conditioning regimen consisted of melphalan 200 mg/m^2.

Results: The median age of patients was 58 years old (range, 47-67 years old) in HD-MEL group and 57 years old (range, 48-63 years old) in BuCyE group, respectively. Revised international staging system (R-ISS) was showed as follows; stage I with 0 in BuCyE vs. 27.2% in HD-MEL, stage II with 84.6% in BuCyE vs. 68.1% in HD-MEL, and 15.4% in BuCyE vs. 4.5%, respectively.

The overall response rate before ASCT was 100% in both groups, including 76.9% in BuCyE and 63.6% in HDMEL with more than vary good partial response, and 30.8% in BuCyE versus 40.9% in HDMEL with complete response, respectively.

Median follow-up for the group was 33 months. The 3-year progression-free survival (PFS) was 57.7% for the HDMEL conditioning group versus 76.2% for the BuCyE conditioning group and median PFS was 37 months in HDMEL (range, 8.7 to 66.5 months) and 60 months in BuCyE (range, 16.9 to 77.8 months) ($P = 0.321$). Five-year overall survival rate was 73.1% in HDMEL versus 100% in BuCyE ($P = 0.059$). The average time from ASCT to leukocyte recovery ($\geq 1000/mm^3$ of absolute neutrophil count) and platelet recovery ($\geq 50000/mm^3$ of platelet count) is as follows: 11 days in HDMEL versus 12 days in BuCyE ($P = 0.101$) and 39 days in HDMEL versus 34 days in BuCyE ($P = 0.840$), respectively. Among the patients who did not achieve complete remission (CR) before ASCT, the proportion of patients who achieved CR after ASCT was 46% (6/13) in HDMEL versus 50% (4/8) in BuCyE.

Conclusions: Our study showed that BuCyE is an effective and well-tolerated alternative to HDMEL conditioning, with good PFS.

Disclosure: There is no conflict of interest.

27 - Multiple Myeloma

P486

DOES THE CONSOLIDATION TREATMENT EFFICIENT AFTER HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN MYELOMA PATIENTS? WHICH REGIMEN IS FEASIBLE?

Zübeyde Nur Özkurt[1], Şeyma Yildiz[1], Asil Demirezen[1], Zeynep Arzu Yeğin[1], Münci Yağci[1]

[1]Gazi University, Ankara, Turkey

Background: The approach in current myeloma treatments is to continue treatment until progression. Induction regimen, autologous stem cell transplantation, and maintenance treatment are the standard procedure in the patient candidate for ASCT. However, the efficiency of short-time consolidation after ASCT is not known certainly.

Methods: We screened our ASCT database and documented our patients' data including demographics, stage/risk, treatments, response to treatments, progression-free survival, and overall survival. Patients who had a response less than PR at +2 months of ASCT were excluded. One hundred seventeen patients [median age: 56 (30-74)years; 53 (45.3%) female, and 64 (54.7%) male] treated with proteasome inhibitory and/or immunomodulatory agents during the induction phase were enrolled in this study.

Results: Thirty patients didn't receive any consolidation, and 87 patients were treated with 2-4 cycles of VCD or VRD consolidation after ASCT. In all of the study population, PFS was found not different statistically between patients who received consolidation and did not (57 vs 44 months $p = 0.068$). When the PFS analysis was performed in two split files separately by response category (sCR/CR group and VGPR/PR group), among patients treated in the VGPR/PR group, the PFS was significantly longer among those treated with consolidation therapy (57 vs 12 months; $p = 0.04$); OS was not different ($p > 0.05$). Consolidation therapy had no effect on PFS in patients in the sCR/CR group (62 vs 56 months; $p = 0.599$). PFS was calculated median 61 months in VRD group and 50 months in VCD group ($p = 0.394$). Cytopenia requiring discontinuation of consolidation therapy was detected in 5 (0.8%) patients in the VRD group and 1 (3.7%) patient in the VCD group ($p = 0.144$).

Conclusions: Consolidation treatment aims to obtain a deeper response after ASCT and before maintenance therapy. Triplet regimens are chosen usually, but it's considered that some patients can't tolerate the phase of early post-ASCT because of frequent cytopenias. In our study, The favorable effects of consolidation treatment on PFS were more significant in patients who had VGPR and PR after post-ASCT + 2 months. Because the number of our analyses was limited, it might have not shown statistical significance in all patient population. We thought that consolidation therapy may be used based on the MRD status in CR patients.

The effect of short-term consolidation treatments, especially for OS, couldn't have been measured certainly in long-term myeloma therapy. Because of this reason consolidation therapy is not a

standard of care for myeloma patients after ASCT yet. Prospective studies involving more patients are needed to support the findings.

Disclosure: nothing to declare.

27 - Multiple Myeloma

P487

EMAGINE/CARTITUDE-6: RANDOMIZED PHASE 3 STUDY COMPARING DVRD FOLLOWED BY CILTACABTAGENE AUTOLEUCEL VERSUS DVRD FOLLOWED BY ASCT IN TRANSPLANT ELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

Salomon Manier[1], Mario Boccadoro[2], Jesús San-Miguel[3], Kenshi Suzuki[4], Amrita Krishnan[5], Niels van de Donk[6], Gordon Cook[7], Andrzej Jakubowiak[8], Deepu Madduri[9], Salma Afifi[9], An-Sofie Stevens[10], Jordan M Schecter[9], William Deraedt[10], Steven Kuppens[10], Pankaj Mistry[11], Lida Pacaud[12], Annemiek Broijl[13], Francesca Gay[2], Roberto Mina[2], Leo Rasche[14], Philippe Moreau[15], María-Victoria Mateos[16], Hermann Einsele[14], Pieter Sonneveld[13]

Lille University, CHU Lille, Lille, France, [2]University of Turin, Turin, Italy, [3]University of Navarra, Pamplona, Spain, [4]Japanese Red Cross Medical Center, Tokyo, Japan, [5]City of Hope Comprehensive Cancer Center, Duarte, United States, [6]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [7]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [8]University of Chicago, Chicago, United States, [9]Janssen Research & Development, Raritan, United States, [10]Janssen Research & Development, Beerse, Belgium, [11]Janssen Research & Development, High Wycombe, United Kingdom, [12]Legend Biotech USA, Piscataway, United States, [13]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [14]University Hospital of Würzburg, Würzburg, Germany, [15]Clinical Hematology, University Hospital Hotel-Dieu, Nantes, France, [16]University Hospital of Salamanca/IBSAL/CIC, Salamanca, Spain

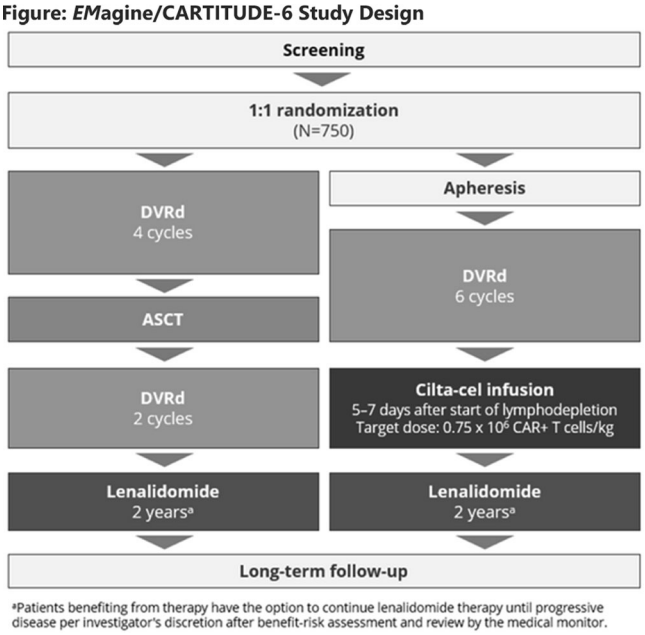
Background: For patients with newly diagnosed multiple myeloma (NDMM) who are eligible for transplant, the National Comprehensive Cancer Network guidelines recommend daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) as induction therapy followed by autologous stem cell transplant (ASCT), consolidation, and maintenance therapy. Ciltacabtagene autoleucel (cilta-cel) is a chimeric antigen receptor (CAR)-T cell therapy with two B-cell maturation antigen (BCMA)–targeting single-domain antibodies. A single infusion of cilta-cel resulted in deep and durable responses with a manageable safety profile in the phase 1b/2 CARTITUDE-1 study of heavily pretreated patients with relapsed/refractory multiple myeloma. At a median follow-up of 27.7 months, the overall response rate (ORR) was 98%, with 83% of patients achieving stringent complete response (CR); median duration of response was not reached. *EM*agine/CARTITUDE-6 (EMN28/68284528MMY3005; NCT05257083) is a randomized, open-label, global, multicenter, phase 3 study that aims to compare the efficacy of DVRd followed by cilta-cel and lenalidomide versus DVRd followed by ASCT, DVRd, and lenalidomide.

Methods: Patients aged ≥18 years with NDMM (based on International Myeloma Working Group criteria), measurable disease at screening, and high-dose therapy and ASCT as part of their intended initial treatment plan are eligible. Exclusion criteria include patients with any prior therapy for multiple myeloma or smoldering myeloma (except for a short course of corticosteroids). After providing informed consent, patients are randomized 1:1 into two treatment arms. Target recruitment is 750 patients. In the cilta-cel arm, patients will undergo apheresis prior to receiving 6 cycles of DVRd induction therapy. Patients will then receive lymphodepletion with intravenous cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2) daily for 3 days, followed by a single infusion of cilta-cel at a target dose of 0.75×10^6 CAR+ viable T cells/kg 5–7 days later. After cilta-cel infusion, patients will receive lenalidomide post CAR-T therapy for 2 years (or longer, per investigator discretion). Patients in the control arm will receive 4 cycles of DVRd induction therapy, followed by ASCT and 2 cycles of DVRd consolidation. After consolidation, patients will receive lenalidomide maintenance therapy for 2 years (or longer, per investigator discretion). The dual primary endpoints are progression-free survival (PFS) and minimal residual disease (MRD)-negative CR sustained for ≥12 months. MRD status is assessed by next-generation sequencing at a sensitivity of at least 10^{-5}. Secondary endpoints include the following: ORR, ≥CR rate, overall MRD-negative CR rate, time to subsequent therapy, PFS on next-line therapy, overall survival, adverse events, pharmacokinetic/pharmacodynamic markers, and changes in health-related quality of life. Exploratory correlative biomarker analyses will also be conducted.

Results: Patient enrollment opened in September 2022. The anticipated primary completion is in June 2026.

Conclusions: The *EM*agine/CARTITUDE-6 study will assess the efficacy and safety of a cellular therapy approach with cilta-cel versus standard of care ASCT in patients with NDMM who are eligible for transplant.

Figure: *EM*agine/CARTITUDE-6 Study Design



Clinical Trial Registry: NCT05257083

Disclosure: **Manier-**Consultancy: Abbvie, Adaptive Biotechnology, Amgen, Celgene/BMS, GlaxoSmithKline, Janssen, Novartis, Oncopeptide, Pfizer, Regeneron, Roche, Sanofi, Takeda; Honorarium: none.

Boccadoro-Honoraria/Research funding/Advisory: Amgen, Celgene, Sanofi, Novartis, Janssen, BMS, AbbVie, GlaxoSmithKline, Mundipharma.

San-Miguel-Consultancy/Advisory: Abbvie, Amgen, BMS, Celgene, GSK, Haemalogix, Janssen-Cilag, Karyopharm, MSD, Novartis, Takeda, Regeneron, Roche, Sanofi, SecuraBio.

Suzuki-Honoraria/Research funding/Consultancy: Amgen, Takeda, BMS, ONO, Novartis, Sanofi, AbbVie, Janssen.

Krishnan-Research funding/Consultancy/Speakers' Bureau/Equity Holder: Janssen, Adaptive Biotechnologies, Sanofi, Pfizer, Regeneron, Takeda, BMS, Sutco.

Donk-Research funding/Advisory: Amgen, Servier, Cellectis, Takeda, Adaptive Biotechnologies, Celgene, BMS, Novartis, Roche, Bayer, Janssen.

Cook-Consultancy/Research funding/Speakers Bureau: Takeda, BMS, Amgen, Roche, Janssen, Sanofi, Karyopharm, Pfizer.

Jakubowiak-Consultancy/Honoraria/Advisory: Janssen.

Madduri-Consultancy/Research funding/Employment: Janssen, BMS, Takeda, GSK, Kinevant, Legend, Sanofi, Celgene, Amgen, Allogene, Celgene.

Afifi, Stevens, Kuppens, Mistry-Employment: Janssen.

Schecter, Deraedt-Employment: Janssen and holder of stock options in a privately-held company.

Pacaud-Employment: Legend Biotech USA.

Broijl-Advisory/honoraria/Other: Janssen, Sanofi, Amgen, BMS.

Gay-Honoraria/Advisory: Amgen, Celgene, Janssen, Takeda, BMS, AbbVie, GlaxoSmithKline, Roche, Adaptive Biotechnologies, Oncopeptides, Bluebird bio, Pfizer.

Mina-Consultancy/Honoraria/Advisory: Janssen, Celgene, Takeda, Amgen, BMS, Sanofi.

Rasche-Honoraria/Advisory: GSK, Janssen, Pfizer, Amgen, BMS, Sanofi.

Moreau-Honoraria: AbbVie, Janssen, Celgene, Amgen, Sanofi.

Mateos-Advisory: Janssen, Celgene, Takeda, Amgen, GSK, AbbVie, Pfizer, Regeneron, Roche, Sanofi, Oncopeptides, Seagen.

Einsele-Consultancy/Honoraria/Advisory/Other: Travel Grants, Research-funding: BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, Novartis.

Sonneveld-Advisory/Research funding: Amgen, Janssen, Celgene, Pfizer, Karyopharm, BMS.

27 - Multiple Myeloma

P488

NATION-WIDE RETROSPECTIVE ANALYSIS OF ALLOGENEIC STEM CELL TRANSPLANTATION IN PATIENTS WITH MULTIPLE MYELOMA: A STUDY FROM KOREAN MULTIPLE MYELOMA WORKING PARTY (KMM1913)

Ho-Jin Shin[1], Do-Young Kim[1], Kihyun Kim[2], Chang-Ki Min[3], Je-Jung Lee[4], Yeung-Chul Mun[5], Won-Sik Lee[6], Sung-Nam Lim[7], Jin Seok Kim[8], Joon Ho Moon[9], Da Jung Kim[10], Soo-Mee Bang[11], Jong-Ho Won[12], Jae-Cheol Jo[13], Young Il Koh[14]

[1]Pusan National University Hospital, Busan, Korea, Republic of, [2]Samsung medical center, Seoul, Korea, Republic of, [3]Seoul St. Mary's Hospital, Seoul, Korea, Republic of, [4]Chonnam National University Hwasun Hospital, Hwasun, Korea, Republic of, [5]Ewha womans University, Seoul, Korea, Republic of, [6]Busan Paik Hospital, Busan, Korea, Republic of, [7]Haeundae Paik Hospital, Busan, Korea, Republic of, [8]Severance Hospital, Seoul, Korea, Republic of, [9]Kyungpook National University Hospital, Daegu, Korea, Republic of, [10]Kosin University, Busan, Korea, Republic of, [11]Seoul National University Bundang Hospital, Bundang, Korea, Republic of, [12]Soonchunhyang University Seoul Hospital, Seoul, Korea, Republic of, [13]Ulsan University Hospital, Ulsan, Korea, Republic of, [14]Seoul National University, Seoul, Korea, Republic of

Background: Despite a remarkable increase in effective treatment options, multiple myeloma (MM) still remains mostly incurable. Nevertheless, survival of patients diagnosed with MM has significantly improved over the last few years, although outcome may be poor with a median overall survival (OS) of only 2-3 years in subgroups of patients with higher stage and high-risk cytogenetics. Allogeneic stem cell transplantation (alloSCT) may help to achieve long-term progression-free survival (PFS) and offers a potentially curative option due to a graft-versus-myeloma effect. However, alloSCT remains controversial because of considerable toxicity, especially due to immunosuppression and subsequent infections, the risk of graft-versus-host disease (GVHD), and thus a potentially high non-relapse mortality.

Methods: This retrospective multicenter nation-wide study in Korea was evaluated the outcome of alloSCT in patients with MM. We analyzed 109 patients with MM who had received reduced-intensity conditioning or myeloablative conditioning alloSCT between 2003 and 2020.

Results: Although most patients were heavily pre-treated, the overall response rate was 66.9% (sCR plus CR rate, 46.8%; ≥ VGPR, 54.1%), the median OS 32.5 months, and the median PFS 10.0 months. Survival was significantly better in patients with response to previous therapies than in those with progressive disease (median OS 36.3 vs. 5.1 months, $P = 0.037$; median PFS 12.1 vs. 2.5 months, $P = 0.01$). Moreover, survival of patients achieving deep response after alloSCT was significantly prolonged compared to less obtaining of response (CR vs. no CR; median OS 89.8 vs. 15.2 months, $P < 0.0001$; median PFS 30.1 vs. 4.7 months, $P < 0.0001$). The transplant-related mortality was a 17.4% at one year. Acute GVHD was observed in 44.4%, and chronic GVHD in 38.8%.

Conclusions: This study suggests that alloSCT in the context of novel immunotherapeutic approaches may enable long-term survival in a carefully selected subgroup with acceptable toxicity and achievement of CR after alloSCT is an important predictor of prolonged survival.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P489

FEASIBILITY AND OUTCOME OF FIRST-LINE AUTOTRANSPLANT-BASED TREATMENT IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS AGED >65 YEARS: MONOCENTRIC RETROSPECTIVE EXPERIENCE

Paola Stefanoni[1], Laura Paris[1], Edoardo Olivari[2], Giuliana Rizzuto[1], Gianluca Cavallaro[1], Pantaleo De Simone[2], Nicola Pittalis[2], Chiara Pavoni[1], Alessandro Rambaldi[1,2], Monica Galli[1]

[1]ASST Papa Giovanni XXIII, Bergamo, Italy, [2]Università degli Studi di Milano, Milano, Italy

Background: Most clinical studies place at 65 years the age limit for patients with newly diagnosed multiple myeloma (NDMM) to receive autologous stem cell transplantation (ASCT)-based treatments. There is, however, a group of patients who, despite exceeding this age, have a degree of "fitness" adequate to receive these intensive treatments. Therefore, we evaluated the feasibility and the main results of an ASCT-based program in a cohort of patients with these characteristics.

Methods: Retrospective study on NDMM patients aged > 65 years, enrolled in ASCT-based programs at our Hematology Unit. Their degree of "fitness" was judged according to a simplified frailty score that takes age (≤75 years, score 0), Charlson Comorbidity Index (≤1, score 0; >1, score 1) and ECOG Performace Status (0, score 0; 1, score 1; ≥2, score 2) as variables to discriminate between nonfrail (score 0-1) and frail (score ≥2) patients (Facon T. et al. Leukemia 2020;34:224).

Results: From January 1st 2010 to December 31th 2021, 375 NDMM patients aged 66-75 years were treated in our Department.

Ninety of them (24%) were deemed eligible to an ASCT-based treatment. They had a median age of 67.9 years (range 65.2-72.9 years); according to the frailty score 79 patients (88%) were nonfrail and 11 (12%) were frail before starting the treatment. Because their frailty status was a direct consequence of MM-related disabilities (i.e., PS ≥2), these patients were also enrolled.

During the induction phase, the dose of one or more drugs was reduced in 82 patients (91%) and treatment was discontinued in 12 cases (13%). Seventy-eight patients (87%) underwent the peripheral blood autologous stem cell mobilization procedure, harvesting a median of $6.77x10^6$ CD34+ cells/kg body weight. No harvesting failure occurred. Sixty-two patients received one ASCT and other 14 patients received two ASCT. No ASCT-related mortality occurred. Eight of the 11 frail patients received one ASCT; none of them underwent the second procedure. Three months after the completion of the ASCT program, 80% of patients achieved ≥ very good partial remission, 11 improved and 7 worsened their PS. During a median follow-up of 38 months, median progression-free survival was estimated at 40 months and overall survival at 72 months.

Conclusions: The simplified frailty score is an easy tool to establish the fitness of NDMM patients aged > 65 years to be enrolled in an ASCT-based program. It also allows to dynamically follow-up their fitness during and after such program, which was, indeed, completed by most patients. The need to reduce and/or omit some drugs during each phase of treatment (due to side effects) did not compromise the results, which are very similar to those obtained in younger patients undergoing similar procedures. This suggests the possibility that the incorporation of monoclonal antibodies into ASCT-based treatments – which is possible in Italy since January 2022 - will further improve the results obtained in these patients.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P490

EFFECT OF MELPHALAN 140 MG/M^2 OR 200 MG/M^2 OUTCOMES IN MULTIPLE MYELOMA PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION A MULTIPLE CENTER EXPERIENCE IN SPAIN

Isabel Diez Campos[1], Beatriz Gómez Horsfield[1], Carolina Arevalo[2], Laura Abril[3], Shiomara Quiñones[2], Mireia Morgades[3], Carme Talarn[4], Anna Angona[1], Rosa Coll[1]

[1]Institut Català Oncologia, Hospital Josep Trueta, Girona, Spain, [2]Institut Català d'Oncologia, Hospital Bellvitge, Barcelona, Spain, [3]Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain, [4]Institut Català d'Oncologia, Hospital Joan XXIII, Tarragona, Spain

Background: Melphalan at a dose of 200 mg/m^2 is standard conditioning prior to autologous stem cell transplantation (ASCT) for multiple myeloma (MM), but a dose of 140 mg/m^2 (MEL140) is often used in clinical practice in patients perceived to be at risk of excess toxicity. Although melphalan at a dose of 140 mg/m^2 is an acceptable conditioning regimen, very few studies compared it to the most commonly used dose of 200 mg/m^2 (MEL200).

Methods: A retrospective review of record of MM patients (2018-2021) with single ASCT, identified 205 patient in three centers of Institut Català d'Oncologia (Spain) with same ASCT protocol, this 18 patients received MEL140 and 187 received MEL200.

Results: Patients in the MEL140 were older than MEL 200 at the time of ASCT, median 62 years [49-70] vs 58 years [29-71], with an ECOG > 2 in 55% in MEL140 vs 26% in MEL200. The MEL140 group presented glomerular filtration rate (GRF) < 50 ml/min 56% vs 2% MEL200 ($p < 0,05$). There were no differences statistically significant in high-risk cytogenetics, 28% MEL140 and 22% MEL200. Myeloma type more frequent both groups is common type (82% vs 65%), light chain (17% vs 33%) and non-secretory (1% vs 2%). Usage of post-ASCT maintenance was similar both groupsThe pre-transplant treatment is: proteasome inhibitor+Immunomodulatory drug was 67% and 87% respectively, in clinical trials 28% versus 12% and alkylating agents 5% versus 1% (MEL140 vs MEL200) respectively. Time from diagnosis to ASCT less 12 months 82% MEL140 vs 74% MEL200 and more 12 months 18% MEL140 vs 26% MEL 200. The differences in the Disease status at ASCT did not differ between both groups, presenting a complete response (CR) or very good partial response (VGPR) in MEL140 of 78% vs 70% MEL200, partial response (PR) 17% vs 26% (MEL140 vs. MEL200). At a median follow-up of 64 months from ASCT, there were no significant differences in relapse free survival (RFS) and overall survival (OS) between the two groups.

Conclusions: Our patient population is homogenous involving consecutive MM patients who received ASCT. The small size and the retrospective nature of our study are weaknesses

We feel MEL140 is a reasonable option in MM patients with comorbidities. Our results show that despite the lower melphalan dose of MEL140, patients with lower performance status, older age, renal failure experienced relatively few more toxicities.

Ther were no significant survival o relapse rate differences between melphalan 200 mg/m2 and melphalan 140 mg/m2 patients with hig-risk or standard-risck chromosomal abnormialities.

In conclusion, MM patients who received MEL140 had similar long-term outcomes to MEL200 patients despite their older age and co-morbidities.

Clinical Trial Registry: No Clinical Trial Registry

Disclosure: No disclosure.

27 - Multiple Myeloma

P491

ADEQUATE ENGRAFTMENT AND COST REDUCTION WITH NON-CRYOPRESERVED (NC) PERIPHERAL BLOOD STEM CELLS (PBSC) IN MULTIPLE MYELOMA PATIENTS UNDERGOING AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (APBSCT)

Ahmad Ibrahim[1], Ahmad Khalil[1], Abir Harmouch[1], Peter Noun[1], Kamal Zahran[1], Hawa Khodr[1], Charbel Khalil[1], Rima Moghnieh[1], Ali Youssef[1], Ahmad Hamandi[1], Tamima Jisr[1]

[1]Lebanese University, Middle East Institute of Health, Beirut Arab University, Makassed Hospital, Beirut, Lebanon

Background: In patients (pts) undergoing APBSCT, cryopreservation of PBSC using dimethyl sulfoxide (DMSO) can induce adverse reactions due to DMSO. The NC method is less expensive since stem cell collection can be performed before APBSCT in the same admission. An in vitro study showed that PBSC can be stored safely over 5 days at 4°C with preserved cell viability, proliferation, and differentiation capacity (Bittencourt et al. Bone Marrow Transplant, 2015). Previous data showed that the NC method led to adequate engraftment and cost reduction (Pessoa et al. Bone Marrow Transplant 2022).

Methods: This is a pilot study conducted between 5/2021 and 10/2022, involving 25 pts aged ≥18y with a newly diagnosed non high-risk MM who underwent APBSCT in first VGPR. Mobilization

of PBSC was performed with G-CSF (10 µg/kg/d for 5 d). PBSC were collected by apharesis if CD34+ cell count in blood was ≥ 20/µl after mobilization. If CD34+ cell count was ˂20/µl, Plerixafor was added. PBSC collected were stored at 4°C until d0 of APBSCT. High-dose chemotherapy was Melphalan (200mg/m^2). Transfusion of PBSC was planned 24 hours after administration of Melphalan. The minimal number of CD34+ cells required for APBSCT was 2.10^6/kg. After APBSCT, G-CSF (5 µg/kg/d) was started when ANC ≤ 0,5.10^9/L, and continued until neutrophil recovery. Non-hematological toxicities were evaluated according to WHO grading.

Results: Median age at APBSCT was 55y (30-71). There were 4 females and 21 males. First line therapy was VRD in 18 pts, Dara-VRD in 1 pt, VCD in 4 pts and Dara-VTD in 1 pt. After mobilization with G-CSF alone, 21 pts had CD34+ cell count in blood ≥ 20/µl and 4 needed the addition of Plerixafor. The median number of CD34+ cell count in blood before apharesis was 34/µl (20-93). The median number of CD34+ cells collected was 4.10^6/kg (2.2-9.5). The median viability of CD34+ transfused was 96% (91-99). G-CSF was started at a median of d4 (2-6) post APBSCT. G-CSF was given at a median of 10 d (8-12). ANC and platelets recovery occurred at a median of 11d (10-13) and 12d (9-17), respectively. Twenty one pts needed platelet transfusion with a median of 2 single donor platelet units (1-3), and 3 pts needed transfusion of PRBCs. Twenty pts developed febrile neutropenia with bacteremia due to Enterobacter Cloacae in 1 pt, a catheter-related blood stream infection in 2, a skin infection in 1, and COVID19 inducing death at d21 of APBSCT in 1 pt. Three pts developed stomatitis ≥grade 2 and 4 developed diarrhea ≥grade 2. The median duration of hospital stay was 13d (11-17). The cost of APBSCT varied from 10000 to 14000 USD (with reduction by 20% compared to cryopreserved PBSC).

Conclusions: NC PBSC led to adequate engraftment and cost reduction in MM pts undergoing APBSCT.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P492

LONG-TERM RESULTS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) IN 42 PATIENTS WITH MULTIPLE MYELOMA (MM)

Sabrina Akhrouf[1], Malek Benakli[1], Farih Mehdid[1], Nadia Rahmoune[1], Mounira Baazizi[1], Dina Ait Ouali[1], Hanane Bouarab[1], Rihab Benouattas[1], Nacera Ait Ameur[1], Farida Tensaout[1], Hanane Moussaoui[1], Naima Abdennebi[1], Fateh Boukhemia[1], Imane Abderrahim[1], Sara Zerkout[1], Fouzia Louar[1], Amina Talbi[1], Rachida Belhadj[1], Fatiha Belhadri[1], Farida Harieche[1], Rose-Marie Hamladji[1], Redhouane Ahmed Nacer[1]

[1]Pierre and Marie Curie Center, Algiers, Algeria

Background: Despite major therapeutic advances, MM remains an incurable pathology. Before new drugs and immunotherapy era allograft was recommended in young patients (pts), in relapse after autologous stem cell transplantation and was indicated for high-risk MM not eligible for intensification with an HLA-compatible donor. We report a retrospective, single-center study of 42 patients with MM who underwent geno-identical HSC allograft.

Methods: Between May 1999 to June 2016 (17 years period), 42 pts with MM underwent allogeneic HSCT with HLA -identical sibling donors. They are 20 myelomas with IgG (Kappa: 16, Lambda: 4), 6 with IgA (Kappa: 5, Lambda: 1), 9 with light chains (Kappa: 5, Lambda: 4), 6 non-secretory, 1 plasma cell leukemia; according to the Salmon and Durie classification: stage I: 1pt, stage II: 3pts and stage III: 38pts (90%). The allograft was proposed in 17 pts in post-intensification relapse, 4 pts due to failure to mobilize and 21 pts due to their very young age or chemoresistance. The median age of the pts is 48 years (28-60), the sex ratio is2 and the median time from diagnosis to transplant was 32 months (5-127). The pre-transplant disease status of pts is complete remission in 12 pts, refractory or in disease progression in 30 pts. Myeloablative conditioning (MAC) was used in 8pts and reduced intensity (RIC) in 34pts. Graft versus host disease (GVHD) prophylaxis consisted of Cyclosporin and Methotrexate (MAC) and Cyclosporin and Mycophenolate mofetil (RIC). A peripheral blood stem cell graft was used in all pts, with a median CD34+ cell count: 6.57. 10^6/kg (1.92-22). At 06/30/2022, a minimum follow-up is 75 months and a maximum follow-up is 278 months.

Results: The median duration of aplasia was 10 (5-21) days. Median time to achieve neutrophils count > 0,5. 10^9/l is 13 days (7-26). Nineteen (45%) pts required red blood cells transfusions, and 34 (81%) pts required platelet transfusions. One pt presented VOD, no rejection was observed. Acute GVHD was observed in 23 pts (57.5%) including 20 with grade II-IV, chronic GVHD in 13 pts (48%) of whom9 with an extensive form. Eleven pts (27.5%) showed CMV reactivation. Relapse was observed in 13pts (32.5%) within a median of 35 months (2-146). Thirteen pts (31%) are alive (10 in complete remission and 3 in partial response) with a median follow-up of 204 months (75-278), 29 pts (69%) died including 22 pts (52%) of TRM (early infection: 3, acute GVHD: 11, myocardial infarction: 2, late infection: 3, VOD: 1, cerebral hemorrhage: 1, Acute lung oedema: 1) and 7 deaths are unrelated to the procedure (disease relapse: 5, road traffic accident: 1, rectal neoplasia: 1). The median survival is 38 months, overall and event-free survival at 17 years are 29.2% and 25.4% respectively.

Conclusions: The HSC allograft seems to be an interesting therapeutic alternative in young subjects with refractory MM or in relapse after therapeutic intensification when new drugs and immunotherapy are not available. However, the TRM remains high and particularly the acute GVHD. Its indication is increasingly discussed in the era of innovative anti-myeloma molecules.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P493

AUTOLOGOUS STEM CELL TRANSPLANTATION IN AL AMYLOIDOSIS: A SINGLE-CENTER EXPERIENCE

Irene Romera Martínez[1], José Miguel Mateos Pérez[1], Rosalía Alonso Trillo[1], Guiomar Bautista Carrascosa[1], María Esther Martínez Muñoz[1], José Luis Bueno Cabrera[1], Ana Belén Bocanegra[1], Sara Lozano Jiménez[1], Pablo García Pavía[1], Manuel Gómez Bueno[1], Francisco Hernández Pérez[1], Cristina Mitroi[1], Merecedes Rivas[1], Javier Segovia[1], Isabel Krsnik[1], Rafael Ríos Tamayo[1], Rafael Duarte[1]

[1]Hospital Universitario Puerta de Hierro, Majadahonda, Spain

Background: The front-line treatment in AL amyloidosis includes autologous stem cell transplantation (ASCT) for selected patients. However, cardiac involvement determines the eligibility of patients and may delay or affect the results of ASCT.

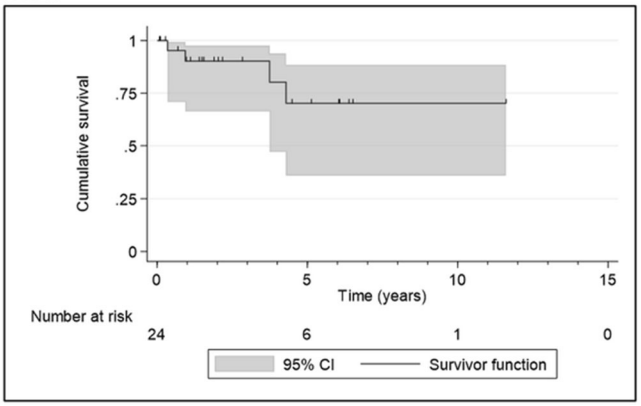
Methods: Retrospective study of patients with AL amyloidosis and ASCT performed in our hospital between 2008 and 2022 to assess security, efficacy and complications of ASCT.

Results: Twenty-four patients with AL amyloidosis, of whom 75%(18) were diagnosed in other hospitals and referred to us for assessment and treatment received an ASCT (**Table 1**). Most patients had achieved a complete hematologic response at ASCT after 1 (16, 66.7%) or 2 (8, 33.3%) prior lines of treatment. The commonest treatment employed was VCD (18, 75%), with which two patients also received daratumumab (D-VCD). Cardiac involvement was the most common vital organ affected (19, 79.2%) and led to a median delay in the time from diagnosis to transplantation of 52.4 months (IQR, 39.5-75.3), compared to 17.9 months (IQR, 13-18.9) in patients without cardiac involvement ($p = 0.003$). Nonetheless, 17 out of 18 patients with cardiac involvement (94.4%) reached transplantation in cardiac response, showing a marked lowering in NT-proBNP before transplant, that remains stable after ASCT ($p < 0.001$). Mobilization was performed only with G-CSF in 16 patients (66.7%), with chemotherapy plus G-CSF in 2 (8.3%), and adding plerixafor in 6 poor mobilizers (25%). All patients but one (96.5%) received Melphalan-200 as conditioning regimen. A median of $4.5x10^6$ CD34/kg were infused. The infusion of five patients with severe cardiac involvement was supervised by the cardiologists or took place in the Coronary Unit. The most common complications were mucositis (95.8%), infectious complications (70.8%) and congestive heart failure (41.7%). Seven patients (29.2%) received G-CSF from day +5 until granulocytic engraftment, with two cases of engraftment syndrome. Since G-CSF to accelerate the engraftment was withdrawn no more patients experienced this complication. Neutrophil and platelet engraftment were achieved at a median of 13 days (IQR, 12-13.5) and 12.5 days (IQR, 12-14), respectively. The median time of hospital admission was 22 days (IQR, 18-25.5). Only one patient has died, from a secondary myeloid neoplasm, at 9.6 years after transplant, and 95.8% of patients are alive with a median follow-up of 2.1 years after ASCT (CI95%, 1.4-5.1). The median progression-free survival (PFS) has not been reached yet and the 3-year PFS is 90.2% (CI95%, 66.2-97.5%) (**Image 1**). Following transplant, all patients with cardiac involvement continued outpatient cardiologic follow-up and only 3 patients (17.7%) needed new hospital admissions for cardiologic reasons: 4 admissions due to heart failure, 1 due to an auricular arrythmia and 1 due to pacemaker implantation.

Table 1: Characteristics of patients with AL amyloidosis and ASCT.

Variable	Result (n = 24)
Age (years)	56.1 (IQR 52.4-61.9)
Sex (male/female)	15 (62.5%) /9 (37.5%)
Light chain affected	20 (83.3%)
Lambda	4 (16.7%)
Kappa	
dCLL at diagnosis (mg/L; n = 21)	224,9 (IQR 100–490,4)
Multiple myeloma (≥10% of plasma cells in bone marrow)	15 (62.5%)
NT-proBNP (pg/ml) at diagnosis	2662.5 (IQR 565.5-6405.5)
FEVI at diagnosis	61.3% (IQR 51–65)
ECOG at diagnosis	
0	3 (4.2%)
1	8 (33.3%)
2	7 (29.2%)
3	8 (33.3%)
Revised Mayo 2012 Staging System	
1	3 (14.3%)
2	3 (14.3%)
3	9 (42.9%)
4	6 (33.4%)
Organs involved	
Heart	19 (79.2%)
Kidney	17 (70.8%)
Bone marrow	11 (45.8%)
Soft tissues	10 (45.8%)
Gastrointestinal	10 (41.7%)
Peripheral Nervous system	8 (33.3%)
Liver	4 (16.7%)
Number of involved organs	
1	5 (20.8%)
2	4 (16.7%)
3	7 (29.2%)
³4	8 (33.3%)
HCT-CI before ASCT	
1	11 (45.8%)
2	8 (33.3%)
³3	5 (20.8%)
Hematologic response at ASCT	
Partial response	4 (16.7%)
Very good partial response	4 (16.7%)
Complete response	16 (66.7%)

Image 1: Progression-free survival in patients with AL amyloidosis and ASCT.



Conclusions: ASCT in AL amyloidosis consolidates the hematologic and organic response. As ASCT is not free of risks, a multidisciplinary management is needed and it should be performed when the cardiac response is favourable. The experience of our centre, that receives patients from all over Spain, shows high rates of OS and PFS.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P494

ROLE OF DYNAMIC EASIX AS A FEASIBLE PREDICTIVE MARKER FOR EARLY RELAPSE AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION FOR MULTIPLE MYELOMA

Young Hoon Park[1], Sewon Lee[1], Yeung-Chul Mun[1]

[1]Ewha Womans University Mokdong Hospital, Seoul, Korea, Republic of

Background: Recent studies showed that pretransplant endothelial activation and stress index (EASIX) has predicted overall

survival (OS) or non-relapse mortality (NRM) in an allogeneic stem cell transplantation setting. We investigated the pattern and the role of the change in EASIX score after autologous stem cell transplantation (ASCT) for multiple myeloma (MM).

Methods: This retrospective study analyzed the records of 74 patients with MM who underwent ASCT between January 2016 and December 2021. EASIX scores were calculated continuously until 1-year after ASCT (prior to ASCT, day 0 to +30, from day +60 to one year every 3 months) using the formula-lactate dehydrogenase (U/L) × creatinine (mg/dL) / platelet (10^9/L) and were evaluated based on log2 transformed values. They received a combination regimen with bortezomib, thalidomide, and dexamethasone (VTD) as induction therapy and thalidomide as maintenance therapy after ASCT for one year.

Results: The median age of patients was 65 years (range, 57-67). EASIX scores increased rapidly in the early post-ASCT period and peaked at day +7 (median 2.87, range 1.12-7.43) followed by a sharp decline until day +30. Thereafter, EASIX scores declined gradually for the duration of the first year after ASCT. Lack of EASIX decline between day+7 and +10 was associated with a risk of occurrence of septic shock during the neutropenic period after ASCT. The optimal EASIX cutoff value for survival was determined at 2.0 based on receiver operating characteristic (ROC) curve analysis. The patients with high pre-transplant EASIX score (> 2.0) showed significantly inferior OS and progression-free survival (PFS) compared to those with low pre-transplant EASIX score (OS, 56.8 vs. 82.5 months, $p < 0.001$; PFS, 38.1 vs. 61.4 months, $p = 0.001$). During the follow-up, 10 patients experienced an early relapse after ASCT and the highest association between EASIX score and relative risk of early relapse (< 1 year after ASCT) occurred at day +180. In multivariate analysis, in addition to high-risk cytogenetics (hazard ratio [HR] 3.55, 95% confidence interval [CI] 2.34-5.43, $p < 0.01$) and poor response to induction therapy (< very good partial response, HR 4.31, 95% CI 2.32-7.14, $p < 0.01$)), high EASIX score at day+180 (> 2.0, HR 2.45, 95% CI 1.43-3.67, $p < 0.01$) was also an independent risk factor for early relapse after ASCT.

Conclusions: The change of EASIX after ASCT for MM is dynamic. Assessment of dynamic EASIX score may be useful in predicting septic shock related to endothelial injury along the neutropenic period and early relapse after ASCT, especially EASIX at day+180. Future investigations are necessary to validate the kinds of conclusions that can be drawn from this study.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P495

STEM CELL MOBILIZATION AND AUTOLOGOUS STEM CELL TRANSPLANTATION AFTER INDUCTION WITH BENDAMUSTINE, PREDNISONE AND BORTEZOMIB (BPV) IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS WITH RENAL IMPAIRMENT

Susann Fricke[1], Wolfram Pönisch[1], Tanja Holzhey[1], Madlen Holzvogt[2], Marc Andrea[2], Vladan Vucinic[1], Georg-Nikolaus Franke[1], Simone Heyn[1], Saskia Hell[1], Birthe Schetschorke[1], Madlen Jentzsch[1], Sebastian Schwind[1], Thomas Zehrfeld[3], Leanthe Braunert[4], Thomas Edelmann[4], Cornelia Becker[5], Franz-Albert Hoffmann[5], Kolja Reifenrath[6], Maik Schwarz[7], Andreas Schwarzer[8], Franziska Flade[8], Dorren Hammerschmidt[9], Markus Scholz[10], Uwe Platzbecker[1], Maximilian Merz[1], Song-Yau Wang[1]

University of Leipzig, Leipzig, Germany, [2]Hospital Weißenfels, Weißenfels, Germany, [3]Hospital Torgau, Torgau, Germany, [4]Hematology Practice, Schkeuditz, Germany, [5]Hematology Practice, Leipzig, Germany, [6]Hospital Oberlausitzer Bergland, Zittau, Germany, [7]Medical Care Centre, Schöneck, Germany, [8]Hematology Practice, Leipzig-Probstheida, Germany, [9]Hospital Plauen, Plauen, Germany, [10]Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Leipzig, Germany

Background: High-dose therapy followed by autologous stem cell transplantation (ASCT) is the standard first line treatment for younger patients (< 70 years) with multiple myeloma (MM). Approximately 20–50 % of all patients already display an impaired kidney function at diagnosis. However, MM patients with severe renal dysfunction are excluded from most ASCT studies. Bortezomib and bendamustine have both been identified as quickly acting and well-tolerated drugs for patients with MM-induced renal failure. In this retrospective study we analyzed the efficacy of a BPV induction therapy prior ASCT in newly diagnosed MM patients depending on the severity of renal impairment.

Methods: Between October 2008 and November 2019, 135 patients with newly diagnosed MM were treated with a BPV-induction therapy consisting of bendamustine 60mg/m^2 on days 1 and 2, bortezomib 1.3mg/m^2 on days 1, 4, 8 and 11 and prednisone 100mg on days 1, 2, 4, 8 and 11 followed by chemomobilization with cyclophosphamide (1-4 g/m^2) and ASCT.

Results: The majority of patients ($n = 117$; 87%) responded after the BPV-induction with median of 2 (range 1–6) cycles with 9 sCR (7%), 3 CR (2%), 12 nCR (9%), 39 VGPR (29 %), and 54 PR (40%). Stem cell counts of CD 34^+ ≥20x10^6/L in the peripheral blood were achieved in 131 (97%) patients after a median of 12 (range 9–17) days. Further four patients with poor stem cell mobilization on day 15 received additional plerixafor. After first ASCT ORR increased to 99% with 33 sCR (24%), 10 CR (7%), 32 nCR (24%), 41 VGPR (30%) and 17 PR (13%). With a median observation time of 51 months, median PFS was 47 months and 60 months OS was 67%. Transplant related mortality was 0.7% ($n = 1$). Patients were divided into four groups depending on the severity of renal impairment: group A 13 patients with eGFR <15 mL/min, group B 15 patients with eGFR 15–29 mL/min, group C 19 patients with eGFR 30–59 mL/min and group D 88 patients with eGFR ≥60 mL/min. At the time of diagnosis, 8 of 13 patients in group A were dialysis dependent. We observed no significant difference in the median PFS between patients with normal/mild (D), moderate (C), severe renal dysfunction (B) and renal failure/dialysis (A) (50 vs 47 vs 34 vs 24 months, $p = 0.053$) and in the 60 months OS (69 vs 72 vs 58 vs 70%, $p = 0.23$). In 23 of 38 patients with eGFR ≤50mL/min, we found rapid recovery of renal function during the first two BPV cycles, with four of eight dialysis-dependent patients reverting to independence. BPV induced a rapid reduction in light chain production in the first few days of treatment, potentially preventing the development of irreversible renal failure. Following the ASCT, the renal response rate improved from 61% after BPV induction to 74% with 18 CRrenal (47%), 3 PRrenal (8%) and 7 MRrenal (18%).

Conclusions: Our results indicate that the BPV induction followed by high-dose therapy and ASCT is feasible, effective and well tolerated in patients with MM-induced renal failure.

Clinical Trial Registry: Ethics Committee of the Medical Faculty, Leipzig University (IRB 00,001,750; registration number 118/18-e)

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P496

THE OUTCOMES OF AUTOLOGOUS BONE MARROW TRANSPLANTATION IN ELDERLY MULTIPLE MYELOMA PATIENTS: A DOUBLE-CENTERED RETROSPECTIVE STUDY

Meral Ulukoylu Menguc[1], Hasim Atakan Erol[2], Ozlem Ozdemir[1], Secil Salim[1], Fatma Arikan[1], Derya Demirtas[1], Ahmet Mert Yanik[1], Asu Fergun Yilmaz[1], Tayfur Toptas[1], Isık Atagunduz[1], Ozgur Mehtap[2], Tulin Firatli Tuglular[1]

[1]Marmara University, Istanbul, Turkey, [2]Kocaeli University, Kocaeli, Turkey

Background: Autologous bone marrow transplantation (ABMT) is a standard of care consolidation treatment in Multiple Myeloma(MM). Eligibility for ABMT requires evaluation of functional status,organ functions,comorbidities and psychosocial condition of the patient. Advanced age and existing comorbidities were considered as contraindications for transplantation until last decade but in the current transplantation practice physiological age rather than chronological age is accepted as a criteria for transplantation decision. In this retrospective study we evaluated the outcomes of elderly MM patients who had ABMT in 2 different university hospitals in Turkey.

Methods: Twenty three patients who had ABMT at the age of 65 or older for MM in 2 transplantation centers between October 2016 and July 2022 were evalauted retrospectively. Patients younger than 65 at the time of ABMT were excluded. Pre-transplant and post-transplant treatment responses were assessed by using International Myeloma Working Group (IMWG) response criteria. All data were collected and processed online.

Results: After data processing 13 male and 10 female patients were enrolled in the study. Median age was 66 (65-70) years. Immunglobulin G kappa MM (39 %) and non-secretory MM (17.4%) were the most common types respectively. International staging system (ISS) score revealed 34.8 % stage I, 47.8 % stage II and 17.4 % stage III patients. Sixty-nine % patients had comorbidities of mainly hypertension and diabetes mellitus. Three out of 23 patient received bortezomib based induction therapy. Pre-transplant 5 patients had complete response (CR), four patients had very good partial response (VGPR) and fourteen patients had partial response (PR). All patients except 1 received melphalan 200 mg/m^2 as conditioning chemotherapy. Sixteen patients experinced complications of febrile neutropenia and diarrhea in the pre-engraftment period. Median duration was 10 (9-20) days for neutrophile engraftment and 13 (10-25)days for platelet engraftment. Response evaluation was not available for 2 patients by day 100 because of 1 early death due to SARS CoV-19 infection and one for lost to follow up. Day 100 responses were 28.6 % CR, 42.9 % VGPR and 28.6 % PR in response- available patients. In statistical analysis pre-transplant response and ISS both were not predictive of day 100 response. Four patients (17.4 %) relapsed at a median 40 months follow up. In 45 months follow up 82.6 % of patients were still alive.

Conclusions: ABMT is a safe and feasible consolidation therapy for MM patients older than 65. Although complications in the periengraftment period occurs, adequate management of complications improve transplant outcomes.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P497

REAL-WORLD SAFETY AND EFFICACY OF DARATUMUMAB BASED INDUCTION QUADRUPLETS IN TRANSPLANT ELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS (TE-NDMM): A SINGLE CENTRE EXPERIENCE

Vasiliki Douka[1], Sotiria Dimou-Besikli[1], Eleni Papchianou[1], Michael Iskas[1], Chrysaygi Lalayanni[1], Maria Papathanasiou[1], Alkistis-Kyra Panteliadou[1], Nikos Spyridis[1], Rita Avramidou[1], Asimina Bouinta[1], Aggeliki Gripelaki[1], George Papaioannou[1], Anastasia Athanasiadou[1], Damianos Sotiropoulos[1], Ioanna Sakellari[1]

General Hospital "George Papanikolaou", Thessaloniki, Greece

Background: Duration of response in multiple myeloma (MM) patients has been substantially ameliorated through incorporating novel agents in early treatment lines. The addition of daratumumab in first-line treatment regimens has been recently approved. The aim of this study is to assess the safety and efficacy of the addition of daratumumab in the already existing induction triplet regimens prior to autologous transplantation in everyday clinical practice.

Methods: Our cohort consists of 18 TE-NDMM patients, diagnosed since 2021, F/M:10/8, of median age 59(49-68). MM type was IgG:9/IgA:4/sFLC:1/macrofocal:2/non-secretory:1/solitary plasmocytoma with minimal bone marrow infiltration:1 patient. In 6/18 patients available ISS and R-ISS at diagnosis was I/II/III in 7/6/5 and 8/8/2 patients respectively. Extramedullar plasmocytoma was detected in 6/18 patients. Skeletal lesions in MRI were evident in 14 patients (> 7 lesions=9/2-7 = 3/ < 2 = 2 patients). Cytogenetics were available in all patients. Conventional karyotype was unsuccessful in 2 patients. Eleven patients had normal karyotype, 1 hypodiploid and 3 hyperdiploid. FISH was normal in 10/18 patients, 1/18 had del17p, 5/18 del1p/add1q and 2/18 t(4;14), 1/18 t(14;16). One patient had both del17p and del1p. Overall, 7/18(39%) patients had adverse cytogenetics. Median plasma cell infiltration at diagnosis was 60%(5-95). In 12/18 (67%) patients proteinuria >200 mg/24h was detected;3/12 > 1.5 g/24h. Renal function was impaired in 8/18(44%) patients (< 60 ml/min MDRD). Three out of 18(17%) patients presented with hypercalcemia and 2/18(11%) with elevated serum LDH levels.

Results: Daratumumab was intented to be administered in combination with Bortezomib – Thalidomide – Dexamethasone (VTD) in 16 patients. In two patients D-VCD at treatment start was considered safer due to concurrent COVID-19 infection. In 7/16(44%) patients, thalidomide had to be switched to cyclophosphamide (D-VCD) due to eventual toxicity. Fourteen patients (78%) experienced sensory peripheral neuropathy grade 1-2. Nine patients had additional gastrointestinal neuropathy, constipation/ileus;8/1. Rash occurred in 5/18(28%) patients treated with D-VTD. Infection occurred in 7/18(39%) patients, respiratory/urinary;5/2. Two patients contracted COVID-19. Infection outcome was favorable in all 4 COVID-19 patients (2-pretreatment/2-posttreatment). Pre-ASCT disease assessment was sCR:4, CR:2, VGPR:7,PR:4 and PD:1 patients. In 5/6 patients in CR, bone marrow MRD was undetectable at a level of 10^{-5}.

CD34 peripheral stem cell mobilization was attempted in 11/17 patients (one patient denied ASCT), all initially with G-CSF. Eventually plerixafor was required in 9/11 patients. Collection was successful in 10/11 patients. Median stem cell yield was 3.56x10^6 (2.00-7.11)/kg BW. Eight patients have already been treated with ASCT. Post ASCT response and MRD data are available so-far in 5 patients. Two pre-ASCT CR patients remain MRD-undetectable. Two out of 3 patients pre-ASCT MRD (+) patients achieved 1-log reduction in MRD and one patient remained MRD stable and subsequently relapsed.

Conclusions: Conclusively, D-VTD quadruplet is an effective induction regimen but thalidomide switch to cyclophosphamide was required due to intolerance in 44% of patients in real practice. The impact of drug switch remains to be assessed in longer follow up. Stem cell mobilization was not impaired. However, most patients required plerixafor. The addition of daratumumab with alternative established induction regimens such as VRD is greatly anticipated to refine safety and efficacy.

Clinical Trial Registry: Department of Hematology and BMT Unit, General Hospital of Thessaloniki "George Papanikolaou", Greece https://aimatologiko-pap.gr

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P498

UP-FRONT HIGH DOSE MELPHALAN AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR NEWLY DIAGNOSED MULTIPLE MYELOMA: SINGLE CENTER RETROSPECTIVE ANALYSIS OF 124 CASES

Nobuhiro Tsukada[1], Moe Nomura[1,1], Yuki Kasuya[1], Yuki Oda[1], Tomomi Takei[1], Kota Sato[1], Mizuki Ogura[1], Taku Kikuchi[1], Yu Abe[1], Kenshi Suzuki[1], Tadao Ishida[1]

Japanese Red Cross Medical Center, Tokyo, Japan

Background: IFM/DFCI group reported that VRd induction followed by up-front ASCT and maintenance therapy lead to median PFS of 50 months. We conducted a retrospective analysis on the outcomes of patients received triplet induction treatment followed by up-front ASCT in our institution.

Methods: Total of 124 patients received ASCT between Nov 2016 and Dec 2021 at Japanese Red Cross Medical Center. Patient characteristics, treatment response before and after ASCT, PFS, and OS were retrospectively analyzed.

Results: Median age was 57.5 (36-70) and 77 patients were male. Myeloma subtypes were IgG 67, IgA 17, IgD 2, and BJ 38. Revised ISS 1, 2, and 3 were 37, 70, and 16, respectively. 94% of patients received VRD-based induction treatment. Among 118 evaluable patients, 116 (98%) patients received either consolidation and/or maintenance. Response before ASCT and best response at anytime were ≥CR 31% and ≥VGPR77%, and ≥CR 77% and ≥VGPR 94%, respectively. Sixty-eight out of 104 patients obtained MRD-negativity by multiparameter FCM. Median PFS of all cases were not reached. 5-year estimated PFS and OS were 54.7% and 80.2%, respectively. Age ≥65, high-risk chromosome, and <VGPR before ASCT were identified as worse prognostic factors on PFS. PFS for patients obtained MRD-negativity was significantly better than others ($p = 0.0048$, 4-yr PFS 86.4% vs. 49.8%).

Conclusions: Treatment outcome is improved by triplet induction treatment, especially combination of PI and IMiDs. Post ASCT consolidation/maintenance may lead to improved response. MRD-negativity was correlated with extended PFS.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P499

ISATUXIMAB INTERFERENCE OF ALLOGENEIC CROSSMATCH IMPACTING IMMUNOLOGICAL ASSESSMENT IN MULTIPLE MYELOMA TRANSPLANTATION

Milda Rudzianskiene[1], Daiva Urboniene[2], Ruta Dambrauskiene[1], Domas Vaitiekus[1], Migle Kulboke[1], Viktoras Rudzianskas[1], Rolandas Gerbutavicius[1]

[1]Oncology Institute of LUHS, Kaunas, Lithuania, LUHS, Kaunas, Lithuania

Background: The treatment of multiple myeloma (MM) has changed dramatically due to the introduction of novel agents in the last decade. However, the treatment of patients who had been treated with two or more previously lines of therapy remains challenging. Monoclonal antibodies against CD38 are a suitable option in disease progression. Immunotherapies are under clinical investigations and not available in multiple countries. The allogeneic stem cell transplantation (SCT) still remains the option to treat selected patients. Crossmatching by flow cytometry (FCXM) and complement–dependent lymphocytotoxicity (CDCXM) are used to identify the alloimmune pre-transplant risk which is associated with worse allograft outcome.

Methods: We report the first case of Isatuximab interference of allogeneic crossmatch assessment causing false-positive results in heavily pre-treated patient with multiple myeloma.

Results: 42-year-old male diagnosed with MM in 2018. Diagnose was based on positive serum kappa/lambda free light chain (FLC) ratio of 0.02 (kappa 5.91 mg/l; lambda 310 mg/l), monoclonal protein on serum protein electrophoresis and IgG lambda positive immunofixation. Bone marrow biopsy revealed infiltration of 15 % of plasma cells. On fluorescence in situ hybridization any specific genetic aberrations were not detected. The patient was treated with 4 courses of VTD (Bortezomib, Thalidomide, Dexamethasone) and tandem autologous SCT was done. The complete remission continued 20 months. After the first relapse the patient was treated with KRD (Carfilzomib, Lenalidomide and Dexamethasone). During the treatment the multiple plasmacytomas in bones and organs were detected and treatment was switched to PACE (Cisplatin, Doxorubicin, Cyclophosphamide, Etoposide). After two courses the disease progression was revealed and treatment with Isa-Pom-Dex regiment (Isatuximab, Pomalidomide, Dexamethasone) was started in named patient program. After four courses of Isa-Pom-Dex the partial remission was achieved. After consolidation with salvage autologous SCT, allogenic matched related donor SCT were performed. Patient received conditioning regiment of Fludarabine and 8 Gy TBI.

Pre-transplant crossmatching was done using two techniques. CDCXM was done between donor T and B lymphocytes and recipient sera with and without dithiothreitol (DTT) and ¼ dilutions, according to guidelines of the American Society for Histocompatibility and Immunogenetics. FCXM was done on a BD FACSLyric flow cytometer using FACSuite software (BD Biosciences, San Jose, CA, USA). Median channel shift (MCS) was used for results evaluation. A cutoff value for positive FCXM assay was defined as more than 2 SD. Unexpected results were obtained – CDCXM was negative but FCXM was positive with T and B cells. We hypothesized that FCXM results were falsely positive. Subsequently, antibodies against HLA (anti-HLA) were tested by Luminex (Luminex, Austin, TX) using single-antigen bead ® xMAP® technology (LIFECODES LSA Class I and Class II kits, Immucor Inc., USA). The results revealed the absence of either anti-HLA class I or anti-HLA class II antibodies.

Conclusions: Isatuximab is a chimeric humanized IgG1 monoclonal antibody which binds the CD38. CD38 is present on plasma cells and expressed on T and B lymphocytes, and can contribute to variability in FCXM results. The false-positive results of FCXM assessment after treatment with Isatuximab can be caused by anti-CD38 monoclonal antibodies binding to donor cell surface CD38.

Clinical Trial Registry: n/a

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P500

EXPERIENCE IN THE USE OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH SYSTEMIC AMYLOID LIGHT CHAIN AMYLOIDOSIS: A SINGLE-CENTRE OBSERVATIONAL EVALUATION

Jorge Illarramendi Esteban[1], Ivan Quispe Cuba[1], Gisell Gabaldon Limas[1], Amaia Aldea Garcia de Vicuña[1], Leire Armesto Aguado[1], Idoia Mugica Muñagorri[1], Adrian Casamayor Garcia[1], María Cruz Viguria Alegría[1], Jose María Arguiñano Pérez[1], Amaya Zabalza San Martín[1], María Carmen Mateos Rodríguez[1], María Teresa Zudaire Ripa[1], Ana Margarita Redondo Izal[1]

[1]University Hospital of Navarra, Pamplona, Spain

Background: Diagnosis and treatment are a challenge in patients with systemic amyloid light chain (AL) amyloidosis. High-dose systemic treatment followed by autologous hematopoietic stem cell transplantation (ASCT) is the standard of care. Despite this, ASCT is associated with great toxicity and a high number of complications.

The objective is to analyse our experience with the use of ASCT in patients with systemic AL amyloidosis.

Methods: Retrospective study of cases with AL amyloidosis who were deemed candidates to receive ASCT. Setting: 1,200 beds University-tertiary hospital. All patients fulfilled the criteria of Mayo Clinic for ASCT. Study period: 2018-2021. The patients signed an informed consent for ASCT. Also sign EBMT ProMise inclusion.

Results: 7 patients received ASCT. Median age at the diagnosis of AL amyloidosis: 63 years (59-66). Male/female: 5/2. Lambda light chain: 5. Kappa light chain: 2. Concomitant multiple myeloma (MM): 3. Concomitant Waldenström disease: 1 (also MM). ECOG status prior ASCT: 0:2, 1:3, 2:2. Organ involvement at diagnosis: Cardiac: 5. Renal: 4. Gastrointestinal: 3. Multiple organs (+): 4. Cardiac +: 3. Renal +: 3. Gastrointestinal +: 3. Median of involved organs: 2 (1-3). Conditioning regimen: melphalan 200 mg/m2: 4, melphalan 140 mg/m2: 3.

Median survival of AL amyloidosis: 16 months (8-150). Median survival after ASCT: 12 months (0.33-135). Median of time since diagnosis and ASCT: 15 months (1-17). Survival after ASCT: 30 days: 4/7. 100 days: 4/7. 1 year: 3/7. 5 years: 1/7. Median survival. Patients with cardiac involvement: Median survival: 13 months (8-39). Median survival after ASCT: 0.33 months (0.33-32). Patients with multiple organs affected: Median survival: 14.5 months (8-39). Median survival after ASCT: 6.2 months (0.33-32). Hematologic relapse: 2/7 (median time: 15.5 months (13-18)). Median survival with melphalan 200 mg/m2: 10.16 months (0.33-32). Median survival with melphalan 140 mg/m2: 12 months (0.33-135). Median glomerular filtration rate in patients receiving melphalan 140 mg/m2: 34 (32-60). 1 patient with severe cardiac disease and chronic renal failure receive melphalan 140 mg/m2. Preconditioning levels of brain natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP) and glomerular filtration rate were analysed to compare survival between patients with pathologic and normal levels. No significant results were obtained. Deaths: 6/7. Causes of death: Bleeding 2 (gastrointestinal and brain), COVID pneumonia 1, multiorganic failure: 2, suicide: 1.

Most used regimens were those based on proteosome inhibitor + immunomodulators + steroids. First line treatments administered bortezomib 4, melphalan 1, thalidomide 1, daratumumab 1, cyclophosphamide 2, lenalidomide 1, rituximab 1, dexamethasone 6, direct ASCT 1 (is the patient with longer survival).

TABLE 1.

Patients included	7
Median age at the diagnosis of AL amyloidosis	63 years (59-66)
Male/female	5/2
Light chain type	
• Lambda	5
• Kappa	2
Organ affection at diagnosis	
• Heart/ +	5/3
• Renal/ +	4/3
• Gastrointestinal/ +	3/3
• Multiple organs (+)	4
• Median of organs affected	2 (1-3)
ECOG prior ASCT	
• 0	2
• 1	3
• 2	2
Conditioning regimen (Melphalan 200/140 mg/m2)	4/3
Median survival of AL amyloidosis	16 months (8-150)
Median survival after ASCT	12 months (0.33-135)
• Survival 30 days	4/7
• Survival 100 days	4/7
• Survival 1 year	3/7
• Survival 5 years	1/7
Median of time since diagnosis and ASCT	15 months (1-17)
Median survival patients with cardiac involvement • Median survival after ASCT	13 months (8-39) 0.33 months (0.33-32)
Median survival patients multiple organs affected • Median survival after ASCT	14.5 months (8-39) 6.2 months (0.33-32)
Median survival with melphalan 200 /140 mg/m2*	10.16 months (0.33-32)/12 (0.33-135)
Hematologic relapse (median time to relapse)	2/7 (median time: 15.5 months
Deaths	6/7

+: More than one organ affected.
* Patients that receive melphalan 140 mg/m2 presented impaired filtration rate or cardiac comorbidities.

Conclusions: ASCT in patients with systemic AL amyloidosis can help to consolidate the hematological and organic response. However, the mortality rate associated with ASCT is higher than in other conditions. As daratumumab has shown to be more effective, it should be more carefully considered whether patients may benefit from early ASCT if they meet the selection criteria. Additionally, it may be advisable to wait for a response of cardiac involvement before proceeding with ASCT to increase the likelihood of a better outcome.

Disclosure: No disclosures.

27 - Multiple Myeloma

P501

SAFETY, FEASIBILITY AND OUTCOMES OF STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA PATIENTS WITH UNDERLYING CHRONIC RENAL FAILURE

Akshay Lahoti[1], Vinay Anand Guntiboina[1], Jeevan Kumar[1], Arijit Nag[1], Saurabhjayant Bhave[1], Rizwan Javed[1], Vivek Radhakrishnan[1], Mammen Chandy[1], Reena Nair[1]

[1]Tata Medical Center, Kolkata, India

Background: Renal failure (RF) is a frequent complication in patients with multiple myeloma. Use of Stem Cell Transplant (SCT) has improved the disease outcome, however safety and efficacy of SCT is patients with RF has been the subject of debate. Very often affected patients with RF are excluded from stem cell transplant (SCT) with the concern of higher drug toxicity and increased transplant related mortality (TRM). There is a paucity of data on

safety of SCT in patients of Multiple Myeloma (MM) with chronic renal failure (CRF).

Methods: With the objective to assess safety of stem cell transplantation (SCT) in patients of Multiple Myeloma (MM) with chronic renal failure (CRF), we retrospectively analyzed patients of MM with pre-existing CRF who underwent SCT at our center between 2012 to 2022.

Results: Out of 132 patients that had undergone SCT for MM, 10 had CRF (eGFR<60ml/min) at the time of transplant. Nine underwent ASCT and 1 alloSCT. The one who underwent alloSCT had a relapsed/refractory disease on maintenance hemodialysis (MHD) pre-transplant, and had received Melphalan 140 mg/m^2 (Mel140) as conditioning regimen but succumbed to refractory shock 4 months after transplant. Of the 9 patients who underwent ASCT, median age was 54 years (range: 41-64) with a male:female ratio of 3.5:1. At the time of transplant, 3 were in complete response (CR), 3 in stringent CR (sCR), 2 in very good partial response (VGPR) and 1 in partial response (PR). Seven (77.7%) of them received Bortezomib Thalidomide Dexamethasone (VTD) and 2 received Bortezomib Cyclophosphamide Dexamethasone (VCD) as prior induction therapy with a median baseline creatinine of 2 mg/dl (1.4-4 mg/dl) and estimated glomerular filtration rate (eGFR) of 36 ml/min (18-54 ml/min). Renal dose plerixafor was used along with granulocyte colony-stimulating factor (G-CSF) for mobilization in 55.5% (n = 5) of patients, yielding a median of 5.69x10^6 CD34+ cells/kg, all of whom received Mel140 as the conditioning regimen. No transplant related mortality was reported at our center. Median time for neutrophil and platelet engraftment was 11 and 10 days, respectively. The most common non hematological toxicity noted in this cohort was ≥ grade 3 mucositis (77.7%) followed by neurological events (22.2%), including 1 patient who had developed encephalopathy and another who had generalized tonic clonic seizures (GTCS). Only 1 patient (11.1%) had a temporary dialysis requirement in the immediate peri transplant period. Median event free survival (EFS) was 3.5 years (95% CI: 1.47-5.59 years), while overall survival (OS) was not reached in this cohort. At a median follow up of 5 years, the cumulative OS and EFS was 68.6% and 29.2%, respectively.

Conclusions: Autologous SCT can be safely done for patients of MM with pre-existing CRF with reasonable overall survival.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

P502

TWO CASES OF B-ALL IN MYELOMA PATIENTS RECEIVING LONG MAINTENANCE IMID THERAPY AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION

Gülşah Akyol[1], Mustafa Baydar[1], Kemal Fidan[1], Nesibe Taşer Kanat[1], Neslihan Mandaci Şanli[1], Muzaffer Keklik[1], Ali Ünal[1]

[1]Erciyes University, Kayseri, Turkey

Background: Introduction: Patients with multiple myeloma (MM) have a higher risk of developing myeloid neoplasm compared to the general population, but acute lymphoblastic leukemia (ALL) is rarely seen. It is considered to develop as a treatment-related leukemia (1).

Objective: We present 2 cases of B-ALL that developed after MM treatment.

Methods: Case 1:

A 58-year-old female patient was admitted to our hospital with complaints of fatigue and widespread pain. With the evaluation, the rate of CD38 positive plasma cells in Bone Marrow Biopsy was determined as 40%. In addition, a pathological fracture line and an increase in hypermetabolism were detected in the right 5th rib on PET CT, and a diagnosis of MM was made. 4 cycles of VCD were given. Afterwards, autologous HCT was performed with Melphalan 200 mg/m2 preparation regimen to the patient who had a complete response. After the transplant, it was determined that the patient was in remission, and lenalidomide 15 mg maintenance was started. After the deepening and prolongation of neutropenia at 33 months of treatment, the dose was reduced to 10 mg, at 45 months to 7.5 mg, and at 46 months to 5 mg. At the last follow-up at 47 months, blasts compatible with 78% CALLA + B-ALL were detected in peripheral flow cytometry, and a diagnosis of Ph (-) B-ALL was made. The patient was in remission with the Hyper-CVAD regimen. The patient is scheduled for a 2nd Autologous HCT.

Case 2:

A 40-year-old male patient was admitted to our hospital with complaints of weakness and widespread pain. As a result of the evaluation, the patient was diagnosed with IgG Lambda type MM. After 4 courses of VAD, partial response was obtained, followed by autologous HCT with Melphalan 200 mg/m2 priming regimen. When it relapsed 2 years later, 6 courses of VCD and then 2 courses of Len-Dex were given. Second autologous HCT was performed on the patient who was in remission. Afterwards, the patient who took lenalidomide for 6 months was followed up in remission by taking thalidomide for 89 months. The patient was diagnosed with Ph (-) B-ALL, in which 75% lymphoid blasts were detected in the bone marrow at the last control. Allogeneic HCT was performed from a fully matched donor to the patient who went into remission with Hyper-CVAD treatment.

Results: Discussion: Secondary malignancies that develop after MM are most commonly encountered as AML and MDS (2). In a study by Aldos et al., it was reported that the development of ALL after MM does not occur from a clonal cause, but is secondary to the long-term IMiD treatments given (1). One of our 2 cases developed B-ALL after 89 months of use with Thalidomide and the other after 47 months of Lenalidomide. Both of our patients were in remission for MM when ALL developed. In addition, both of our patients were normal in terms of Ph (-) and cytogenetics.

Conclusions: Sonuç olarak ALL gelişebileceği için uzun süreli IMID tedavisi alan hastalar sekonder maligniteler açısından daha dikkatli izlenmelidir.

Clinical Trial Registry: no

Disclosure: There is no conflict of interest.

27 - Multiple Myeloma

P503

TANDEM VS SINGLE ASCT FOR MM PATIENTS - CLINICAL EXPERIENCE OF CIC 859 – FIRST RESULTS

Penka Ganeva[1], Kameliya Milcheva[1], Krasen Venokov[1], Lidia Garcheva[1], Iglika Mihaylova[2], Dimcho Georgiev[2], Georgi Mihaylov[1]

[1]Specialized Hospital for Active Treatment of Hematological Diseases, Sofia, Bulgaria, [2]University Specialized Hospital for Active Oncology Treatment, Sofia, Bulgaria

Background: Autologous stem cell transplantation (ASCT) has been established as standard consolidation therapy for MM patients eligible for transplantation, resulting in improvement in both PFS and OS, however patients with high-risk disease remain a therapeutic challenge. Tandem ASCT may be associated with better clinical results compared with single ASCT, especially for patients with suboptimal response to induction therapy.

The aim of our study was to evaluate safety and efficacy of tandem ASCT using sequentially total marrow irradiation (TMI) at the dose of 12 Gy (4Gy on days -3,-2,-1) and second ASCT with Melphalan 200 mg/m^2 and to compare it with matched group of patients who went through single ASCT.

Methods: The analysis included 2 groups of patients : A group with tandem ASCT and B group with single ASCT. Patients in group A were scheduled to receive tandem ASCT in sequencing mode TMI and subsequent Melphalan 200 mg/m^2 within 3-6 months, and group B patients were scheduled to receive single ASCT with Melphalan conditioning. Mobilization was performed with growth factor only or AraC 2 x 400 mg/m^2 (1600 mg total dose) for 2 days in combination with growth factor. Criteria for selection of patients for tandem ASCT was PR after induction and/or high risk disease.

Results: Patient's and disease characteristics are shown in Table 1. Group A included 15 patients with median age 48.6 years (37-62 years); male / female ratio = 13/2. The median time between Melphalan and TMI was 116 days (range 96-185 days). Group B included 15 patients (male / female ratio = 12/3), with median age 55.8 years (45-66 years). Before first ASCT in group A, 14 (93.4 %) were in PR, 1(6.6%) in PD. Proportion of patients who achieved at least VGPR after 1st ASCT was 4 (26%) and after 2nd transplantation - 6 (40 %). One patient died with extramedullary progression 3 months after first ASCT. All of the patients continue with lenalidomide maintenance. Till 11.2022 we have 3 patients with PD at the 8th, 13th and 6th month after tandem ASCT and 8 (61.5%) in CR/VGPR.

In group B response before ASCT was: PR13 (86.8%), SD 1 (6.6%) and PD 1(6.6%); response after ASCT; in CR/VGPR – 9 (60%), 6 in PR(40%) ; 2 from them died because on +14th month and 16th month after ASCT.

TMI was resulted with absolute neutropenia in all patients, no serious adverse events reported according to CTCAE v5.0.

Table 1. Patient's and disease characteristics

CHARACTERISTIC	Group A n = 15	Group B n = 15
Sex male/female	13/2	12/3
Median age,yr	48.6	55.8
ISS 1/2/3	2/7/6	7/5/3
Cytogenetic risk Standard/high	2/13	4/11
Number of lines before ASCT 1/2/3 more	10/4/1	9/5/1
Median time from diagnosis to first ASCT	12.9 m	12

Conclusions: Conditioning with TMI/Melphalan is a valuable treatment option for MM with suboptimal induction response and/or high-risk disease. The use of TMI as part of conditioning in tandem ASCT did not affect hematological recovery and did not increase the incidence of early non-hematological toxicity in our small group of patients compared to standard conditioning.

Disclosure: Nothing to declare.

22 - Myeloproliferative Neoplasm

P504

LONG-TERM SURVIVAL AFTER DONOR LYMPHOCYTE INFUSION FOR MOLECULAR AND HEMATOLOGICAL RELAPSE AFTER HEMATOPOIETIC CELL TRANSPLANTATION FOR MYELOFIBROSIS

Nico Gagelmann[1], Christine Wolschke[1], Evgeny Klyuchnikov[1], Anita Badbaran[1], Susanna Carolina Berger[1], Francis Ayuk[1], Nicolaus Kröger[1]

[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Allogeneic stem cell transplantation (HCT) is a curative treatment approach for myelofibrosis patients but besides non-relapse mortality, relapse is the major cause of treatment failure. Donor T-cells can induce graft-versus-myelofibrosis effects in relapsed patients and induce molecular complete remission (mCR). Here, we evaluated the so far largest cohort to date of myelofibrosis patients with relapsed disease after HCT who received DLI as standard of care posttransplant management for either molecular relapse or hematological relapse. The aim of this study was to compare efficacy regarding achievement of molecular complete remission (CR), incidence of acute and chronic graft-versus host disease (GvHD) and survival between both approaches.

Methods: All patients received reduced intensity busulfan-fludarabine conditioning HCT, with anti T-lymphocyte globulin as graft-versus-host disease (GVHD) prophylaxis as recently reported. The usual starting dose of DLI after HLA identical sibling HCT was 1 x 10^{6}CD3+ cells/kg/ BW and 5 x 10^5 CD3+cells (kg/BW) after unrelated HCT resulting in a median dose of the first DLI of 1 x10^6 (range, 1 x10^5 - 1 x10^7) followed by a subsequent half-log escalated dose after at least 6 weeks if there was no response and no GVHD. We investigated the effect of DLI in 37 patients with either molecular relapse (n = 17) or hematological relapse (n = 20) after HCT. Patients received a median of 2 (range, 1-5) cumulative DLI (a total of 91 infusions). Median starting dose of first DLI was 1 x10^6 cells, escalated by half-log after ≥6 weeks if no response nor GVHD occurred.

Results: Median time from HCT to first DLI was 68 weeks and significantly shorter for molecular relapse (40 weeks) versus hematological relapse (145 weeks). Overall mCR at any time was 73% (n = 27) and mCR rate was significantly higher for patients with initial molecular relapse (88%) versus hematological relapse (60%; P = 0.05). Overall survival according to initial indication for DLI was 77% (95% CI, 57-97%) for molecular relapse compared with 32% (95% CI, 10-54%) for hematological relapse after HCT (P = 0.03). Outcome appeared to be impacted rather by initial relapse after HCT than by achievement of response (P = 0.05). Overall survival for responders versus non-responders to first DLI was 88% versus 68% for molecular relapse compared with 60% versus 12% for hematological relapse. All patients who experienced subsequent relapse after having achieved mCR after first DLI could be salvaged with subsequent DLI, showing long-lasting mCR and overall survival.

Conclusions: This is the largest and most comprehensive report of DLI for relapsed myelofibrosis after first HCT. In conclusion, DLI for relapsed myelofibrosis after HCT showed excellent survival, particularly for patients with molecular relapse and who showed molecular CR at any time. Furthermore, molecular monitoring enabled to treat early and to target molecular CR, even after several infusions, resulting in long-lasting response and survival. Our results underscore the need for molecular monitoring and

targeted treatment in relapsed myelofibrosis and provide evidence for DLI as standard of care for these patients.

Disclosure: None.

22 - Myeloproliferative Neoplasm

P505

EFFICACY OF PACRITINIB FOR SPLEEN REDUCTION IN PATIENTS WITH MYELOFIBROSIS ACROSS THE CYTOPENIC SPECTRUM

Nico Gagelmann[1], Vikas Gupta[2], Donal McLornan[3], Philipp Treskes[4], Sarah Buckley[4], Karisse Roman-Torres[4], Bart Scott[5]

[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2]Princess Margaret Cancer Centre, Toronto, Canada, [3]University College Hospital London, London, United Kingdom, [4]CTI BioPharma Corp, Seattle, United States, [5]Fred Hutchinson Cancer Research Center, Seattle, United States

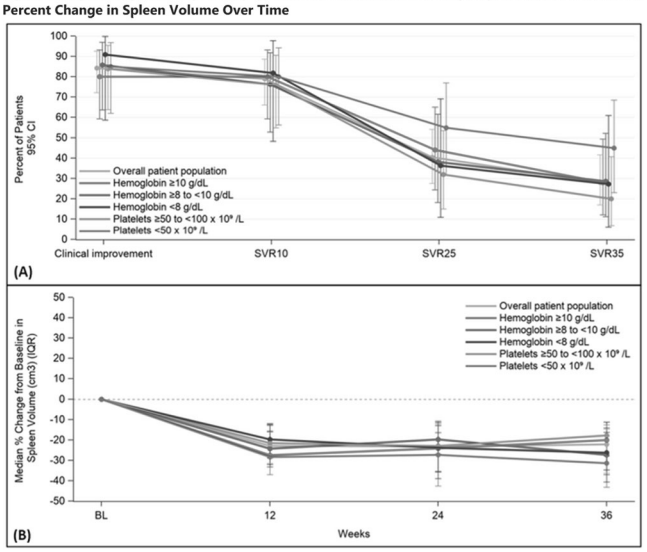
Background: In patients with myelofibrosis (MF), bulky splenomegaly prior to allogeneic hematopoietic stem cell transplant (allo-HCT) is a potential risk factor for worse post-transplant outcomes, including delayed engraftment, poor graft function, and a possible increase in non-relapse mortality. While the JAK1/2 inhibitors ruxolitinib and fedratinib may reduce spleen volume, their dosing, and therefore their effect on spleen reduction, is limited in cytopenic MF patients. Pacritinib is a novel JAK2/IRAK1/ACVR1 inhibitor with no detectable inhibition of JAK1. Pacritinib received accelerated approval in the United States (Feb2022) for adults with myelofibrosis who have a platelet count <50 x 10^9/L. However, clinical studies of pacritinib included patients across the cytopenic spectrum (including any grade of anemia or thrombocytopenia). Here we present data on spleen volume reduction achieved by patients receiving pacritinib 200 mg twice daily (BID) on the phase 3 PERSIST-2 study stratified by degree of baseline anemia and thrombocytopenia.

Methods: Evaluable patients treated with pacritinib 200 mg BID on PERSIST-2 were analyzed. Patients were stratified by baseline platelet count (< 50 and 50 to <100) and hemoglobin (< 8, 8 to <10, and ≥10 g/dL). All groups were analyzed for depth of spleen volume response (SVR), median dose intensity, and hematologic stability (based on median hemoglobin and platelet count over time). Spleen volume was assessed throughout the study by MRI or CT scan with central review.

Results: Of 57 evaluable patients, mean age was 67 years, 75% had primary MF, 42% were previously treated with a JAK2 inhibitor, and median baseline palpable spleen length was 14 cm below the left costal margin. Distribution across blood count groups was 37% and 42% for platelet subgroups of <50 and 50 to <100 respectively and 18%, 37% and 46% for hemoglobin subgroups of <8, 8 to <10, and ≥10 g/dL respectively. Overall, 28% achieved ≥35% SVR (SVR35), 40% achieved SVR25, 79% achieved SVR10, and 84% achieved any spleen reduction. Patients experienced spleen responses regardless of baseline cytopenias (**Figure 1a**). Clinical improvement occurred consistently in 80-91% of patients regardless of cytopenias. SVR35 occurred at the highest rate (45%) in patients with a baseline platelet count <50x10^9/L. Spleen reduction occurred by week 12 across all subgroups, with modest additional improvement beyond week 12 (**Figure 1b**).

Patients across all subgroups maintained a median dose intensity of 100%, and median hemoglobin and platelet counts remained stable over time, regardless of degree of baseline cytopenia.

Figure 1. Depth of Spleen Response by (a) Blood Count at Baseline Subgroups at Week 24 (b) Media Percent Change in Spleen Volume Over Time



Conclusions: Pacritinib demonstrates a consistent efficacy profile on spleen response across different degrees of thrombocytopenia and anemia in patients with MF, likely related to high dose intensity seen with pacritinib treatment regardless of cytopenias. These findings suggest that pacritinib may be an effective option to reduce spleen volume prior to allo-HCT, potentially leading to improved post-transplant outcomes in patients with MF and thrombocytopenia regardless of the degree of baseline cytopenias. These data warrant further evaluation in transplant-eligible MF patients.

Clinical Trial Registry: NCT02055781

Disclosure: **NG** has no conflicts of interest to declare.

VG has consulted for Novartis, BMS Celgene, Sierra Oncology/GSK, AbbVie, Constellation BioPharma, and Pfizer, received payment for lectures or speakers bureaus from Novartis, BMS Celgene, and Constellation BioPharma, and participated on data safety monitoring or advisory boards for BMS Celgene, Roche, AbbVie, and Pfizer.

DPMcL has participated on speakers bureas for AbbVie, Celgene BMS, Jazz Pharmaceuticals, and Novartis; has received research funding from Celgene BMS and Novartis, and has received honoraria from Jazz Pharmaceuticals and Novartis.

PT, SB, and **KR-T** are employed and hold stock in CTI BioPharma,

BS has consulted for Acceleron Pharma, Celgene, and Novartis; has served on speakers' bureaus for Alexion Pharmaceuticals, Celgene, Jazz Pharmaceuticals, and Novartis; has received honoraria from BMS, Incyte, and Taiho Oncology, and reports his institution receiving research funding from Celgene.

22 - Myeloproliferative Neoplasm

P506

THIOTEPA-TREOSULFAN-FLUDARABINE (TTF) AS CONDITIONING REGIMEN IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLOHSCT) FOR MYELOFIBROSIS

Filippo Antonio Canale[1], Gaetana Porto[1], Chiara Verduci[1], Maria Celentano[2], Barbara Loteta[1], Marta Pugliese[1], Virginia Naso[1], Tiziana Moscato[1], Giuseppe Irrera[1], Giuseppe Console[1], Anna Ferreri[1], Alessandra Picardi[2,3], Massimo Martino[1]

[1]Stem Cell Transplantation and Cellular Therapies Unit, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy, [2]Stem Cell Transplant Program, AORN A. Cardarelli, Naples, Italy, Tor Vergata University, Rome, Italy

Background: AlloHSCT remains the only potentially curative option for patients affected by myelofibrosis (MF) but there is no consensus on the best conditioning regimen. The use of treosulfan as alkylating agent in a RIC regimen demonstrated low toxic profile; on the other hand, the combination of two alkylating agents with the addiction of thiotepa seems to increase the chance of achieving engraftment with full donor chimerism in MF patients. Therefore a treosulfan-based dual alkylator regimen with thiotepa and fludarabine (TTF) could be a promising toxicity-reduced but myeloablative conditioning regimen for a kind of patients characterized by an advanced median age and usually with high comorbidity index (HCTI), at high risk of relapse and transplant-related mortality. No data are reported about the use TTF in alloHSCT for myelofibrosis: here we show the initial findings of our multi-centric prospective observational study regarding TTF in this setting.

Methods: A total of 9 patients (median age: 57, range 44-69, 55% male) affected by MF underwent alloHSCT with TTF conditioning (treosulfan 30 g/m^2, fludarabine 150 mg/m^2, thiotepa 5mg/kg) between January 2021 and November 2022. Six patients had primary disease, 1 patient had MF secondary to PV and 2 patients had a MF associated to LMC and MDS, respectively. DIPSS-plus was "intermediate-2" in 55% and "high" in 33,3% of cases respectively, while 44,4% of patients were at "very-high" risk according to myelofibrosis transplant scoring system (MTSS). The median time from diagnosis to alloHSCT was 13 months (range, 4-158). Graft source was PBSC in all patients. Donor types were HLA-matched related (n = 2), haploidentical (n = 1) matched unrelated (n = 2) and mismatched unrelated (n = 4). GVHD-prophylaxis consisted of a calcineurin inhibitor plus methotrexate and ATG for 5 patients, while combination of cyclosporine with micophenolate and PTCy was used in 4 patients who underwent HSCT from mMUD or haploidentical donor.

Results: Full donor early engraftment was achieved in all cases except one. The median time to neutrophil recovery was 17 days (range, 15-21). The median time to achieve platelet engraftment >20 G/L was 21 (range, 14-31) days. Median follow-up was 7.2 (range, 0.5-22.8) months. Complications after HSCT included mucositis grade 4 in one patient, 2 cases of transient mild hyperbilirubinemia, one grade 3 systolic disfunction, neutropenic fever with 2 BSI, 2 cases of grade 3 myalgia. Two patients died early during aplasia: 1 for cerebral hemorrhage (at day 12) and 1 due to acute kidney disease and subsequent multi-organ failure (at day 32). One patient experienced grade II acute GVHD at day 35 which evolved in overlap chronic GVHD with atypical involvement of central nervous system and subsequently he died at day 342. Mild chronic GVHD occurred in another patient. No relapse was seen. There was an association between death and presence of MTSS "very-high" (p = 0.048).

Conclusions: These data suggest feasibility of TTF myeloablative regimen for alloHSCT in myelofibrosis, with manageable transplant-related toxicity. We will further evaluate TTF conditioning expanding patients cohort and with a longer follow-up, which are prerequisites mandatory for efficacy evaluation and for GRFS analysis.

Disclosure: Nothing to declare.

22 - Myeloproliferative Neoplasm

P507

RUXOLITINIB AND DLI AS EARLY SALVAGE THERAPY FOR MYELOFIBROSYS RELAPSE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

Alessia Ripamonti[1], Paola Perfetti[1], Beatrice Manghisi[1], Sara Tarantino[1], Marilena Fedele[1], Elisabetta Terruzzi[1], Andrea Aroldi[1], Elena Elli[1], Carlo Gambacorti Passerini[1], Matteo Parma[1]

[1]Ospedale San Gerardo, Monza, Italy

Background: Allogeneic stem cell transplantation (allo-SCT) is the only potentially curative treatment for myeolofibrosis (MF). The 5-years overall survival (OS) rates after allo-SCT ranges from 47% to 62%. However, relapse after transplantation remains a frequent cause of death with rates ranging from 10-43%. Increasing mixed chimerism and contemporary detection of a driver mutation after SCT are strong predictors of relapse and potential markers for guiding adoptive immunotherapy. Association of JAK2 inhibitor Ruxolitinib and Donor Lymphocytes Infusion (DLI) can lead to complete remission by obtaining a full donor chimerism and the complete disappearance of the driver mutation. We report a single centre experience of salvage therapy with Ruxolitinib + DLI as early salvage therapy for MF relapse.

Methods: We report on 3 patients (pts) who experienced MF relapse after allo-SCT. The first evidence of relapse was mixed increasing chimerism which appeared 8, 34 and 51 months after allo-SCT. The disease was also confirmed with the presence of the driver mutation (JAK2-V617F). 1 pt also showed an initial decrease in the blood cells counts but none presented atypical cells in blood stain or bone marrow.

Immediately they started therapy with Ruxolitinib at doses of 20 mg, 10 mg and 10 mg respectively.

DLI infusion was performed with a fixed scheduled of 4 doses, starting to 1 x 10^6/Kg progressing till to 5 x 10^7/Kg with a semi-log increase. Ruxolitinib-DLI treatment is ongoing on a fourth pt (Ruxolitinib 20 mg and 1st dose of DLI).

Results: All the 3 pts obtained a full donor chimerism within 7, 7 and 8 months respectively. We observed also the disappearance of the driver mutation between the third (2 pts) and the fourth (1 pt) dose of DLI without any successive relapse (time to observation 6, 21 and 29 mths). 2 patients experienced a late-onset GvHD (grade 2, MAGIC CRITERIA) which was treated with steroid-Ruxolitinib-Extracorporeal Photoapheresis and steroid-Ruxolitinib-MMF respectively with complete response. No opportunistic infections were detected in our pts. 2 pts are still continuing Ruxolitinib treatment, 1 stopped 5 months after obtaining a full donor chimerism, none of them relapsed again and actually all are maintaining JAK2 negativity.

Conclusions: Ruxolitinib-DLI seems to be an effective treatment for MF relapse after allo-SCT. GvHD remains the major expected complication. Continuation of Ruxolitinib treatment after obtaining complete chimerism could be a valid option either to maintain the remission or to control the GvHD. It remains a matter of debate how long the Ruxolitinib treatment should be continued.

Disclosure: Nothing to disclose.

22 - Myeloproliferative Neoplasm

P508

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH MYELOFIBROSIS IN A RETROSPECTIVE COHORT – CHALLENGES AND UNMET NEEDS

Blanca de Felipe Noguerales[1], María Luisa Palacios Berraquero[1], Valentín García Gutiérrez[1], Anabelle Chinea Rodríguez[1], Alejandro Luna de Abia[1], Lucía Bolea Jarreta[1], Pablo Palomo Rumschisky[1], Pilar Herrera Puente[1], Javier López Jiménez[1]

[1]Hospital Universitario Ramón y Cajal, Madrid, Spain

Background: To date, allogeneic transplant of hematopoietic progenitors is still the sole curative treatment for patients with myelofibrosis. Despite recent advances in the approach to this disease, there are still challenges and unmet needs in the management of these patients.

Methods: We conducted a unicentric retrospective study enrolling 10 patients with myelofibrosis who underwent allogeneic stem cell transplant (HSCT) between 2014-2022. We included patients with primary or secondary myelofibrosis. All patients received antifungal and antiviral prophylaxis, as well as prophylaxis against *Pneumocystiis jirovecii* regardless of their serological status. Letermovir was given as prophylaxis for cytomegalovirus (CMV) reactivation in seropositive recepients. They all received prophylaxis against graft versus host (GVHD) with mycophenolate and cyclosporine; patients who received haploidentical transplantation also received post transplant cyclophosphamide as per protocol. We followed EBMT definitions for poor graft function and graft failure.

Results: Most patients suffered from secondary myelofibrosis: 4 of them had progressed from essential-thrombocytemia and 2 from polycitemia-vera; the other 4 patients had primary myelofibrosis. All patients presented intermediate-2 or high risk DIPSS and DIPSS plus scoring. Furthermore, three patients included in the study also presented high-risk molecular alterations (*ASXL1*, *IDH1*, *EZH2*); however, information about molecular alterations of patients diagnosed before 2015 was not available.

Splenomegaly was present in 6 patients, with a spleen size over 20cm in 2 of them.

Six of these patients were exposed to ruxolitinib (JAKi) before transplantation: only 1 of them achieving a lasting response, three of them did not respond and two of them achieved initial response and then lost it.

All of them received reduced intensity conditioning with busulfan and fludarabine.

The mean time to engraftment for platelets was 31 days (haploidentical-37; identical-26) and 20 days for neutrophils (haploidentical-23; identical-17).

The rate of graft failure/poor graft function was high, presenting in four patients (40%). Only one is currently alive after 15,4months follow up, having received a second HSCT.

Of the three deceased, one received a CD34+ boost of the same donor but did not achieve engraftment, another one died while programming apheresis of his donor and the last one died due to an infection within secondary graft failure. Interestingly, two of these patients presented massive splenomegaly (> 20cm) prior to HSCT.

The most relevant complication observed besides graft failure was CMV reactivation. Rates of GVHD were similar to those described in literature.

Table-1: Descriptive data of our series. MUD: Matched Unrelated Donor. MRD: Matched Related Donor. Haplo: haploidentical. Id:identical. aGVHD: acute graft versus host disease. cGVHD: chronic graft versus host disease.

Conclusions: Our cohort shows how the management of allogeneic transplant in patients with myelofibrosis has changed through the years. We can see the growing importance of the molecular alterations in risk stratifications and the increasing role of haploidentical donors, as well as the importance of JAKi treatments peri transplantation. Graft failure remains the most relevant post-transplant complication, constituting the main cause of post-transplant mortality; however management of this problem remains an important clinical challenge, as outcomes are still poor.

Disclosure: Nothing to declare.

Descriptive data of our series appears in Table-1.

	Age (years)	HCT Score	Driver mutation	Risk (DIPSS /DIPSS+)	Molecular alteration	Spleen Size (cm)	Exposure Ruxolitinib (response)	Donor (HLA)	Year Trasplant	Neu-Engraftment (day)	Plt-Engraftment (day)	Complications	Overall Survival (months)	Graft failure/poor graft function management
1.	61	0	JAK2	Int-2(3/3)	-	15	Yes	MUD (id)	2014	16	19	-	Alive (104,6)	
2.	53	0	TN	Int-2(3/3)	-	17	Yes (lost response)	MRD (id)	2014	15	32	aGVHD, CMV reactivation	DEP (4,5)	
3.	60	1	JAK2	Int-2(3/3)	-	17	No	MRD (id)	2017	23	26	cGVHD	Alive (70,4)	
4.	69	0	JAK2	Int-2(3/3)	-	12	No	Haplo	2017	21	34	CMV reactivation	Alive (67,9)	
5.	58	1	JAK2	High(5/5)	-	15	No	Haplo	2017	14	27	Secondary graft failure	DEP (2)	
6.	60	1	JAK2	Int-2(3/3)	-	15	Yes (no response)	MUD (id)	2017	20	37	-	Alive (60,8)	
7.	64	0	JAK2	High(3/4)	ASXL-1, EZH2	16	No	Haplo	2019	20	32	aGVHD, CMV reactivation	Alive (39,7)	
8	57	4	JAK2	Int-2(3/3)	KMT2A, MLL	23	Yes (lost response)	Haplo	2021	23	44	Primary graft failure, CMV reactivation	Alive (15,4)	Second transplant
9.	62	3	JAK2	High(3/4)	ASXL1, IDH1	17	Yes (no response)	MRD (id)	2021	-	-	Primary graft failure	DEP (1,2)	
10.	64	3	JAK2	High(4/4)	EZH2	26	Yes (no response)	Haplo	2022	30	-	Poor graft function	DEP (2,5)	CD34+ boost

7 - New Drugs and Cell-based Immune Therapies

P509

IDALLO STUDY: A RETROSPECTIVE MULTICENTER STUDY OF THE SFGM-TC EVALUATING THE EFFICACY AND SAFETY OF IVOSIDENIB, IN RELAPSED AML AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

Adrien Caillet[1], Marion Simonet- Boissard[1], Edouard Forcade[2], Marie Robin[3], Ibrahim Yakoubagha[4], Natacha Maillard[5], Raynier Deviller[6], Marie-Anne Couturier[7], Anne HUYNH[8], Jean-Henri Bourhis[9], Celestine Simand[10], Sylvain Chantepie[11], Ana Berceanu[1]

[1]CHU Besancon, Besancon, France, [2]CHU Bordeaux, Bordeaxu, France, [3]Hôpital St Louis, Paris, France, [4]CHRU Lille, Lille, France, [5]CHU Poitiers, Poitiers, France, [6]IPC, Marseille, France, [7]CHU Brest, Brest, France, [8]IUCT, Toulouse, France, [9]IGR, Villejuif, France, [10]ICANS, Strasbourg, France, [11]CHU, Caen, France

Background: Acute myeloblastic leukemias (AMLs) are heterogeneous hematological malignancies and their prognosis depends on molecular and cytogenetic.

AML is the main indication for allogeneic stem cell transplantation (Allo SCT) but many relapses persist. The prognosis of these patients is poor with a median overall survival is estmated between 6 and 7 months.

IDH1 and IDH2 are proteins that regulate DNA methylation and can also be targeted by specific treatments. These proteins are mutated in 6-10% of AMLs. Ivosidenib is a treatment targeting the IDH1 protein. In a cohort of R/R AML ivosidenib resulted in 41,6% overall response and and 21,6% complete remission. Even if this cohort included patients in relapse after allogeneic transplantation, few data are available in this setting.

Methods: We conducted a retrospective study of behalf of the Francophone Society of Marrow Transplantation and Cell Therapy (SFGMTC). 22 patients received ivosidenib for a relapse of AML after a allo SCT; these patients were treated in 12 transplantation centers in France and received ivosidenib in a compassionate use.

All the patients gave their to consentement to use their transplantation data via the PROMISE European Data Base; the centers verified recorded data and were asked to provide missing information.

Overall response rate, event free survival and tolerance of ivosidenib were evaluated in these patients.

Statistical modelling was performed on the pvalue.io website, and the comparison of mortality rates was performed using the Logrank test.

Results: We included 15 females and 7 males. The median age was 47 years. The majority had intermediate cytogenetic and molecular risk according to the ELN 2017 classification. The most common molecular abnormality associated with the IDH1 mutation was the NPM1 mutation (5 patients). Most patients were transplanted in first complete remission and most grafts were derived from peripheral stem cells (19 patients). 50% of the grafts were matched-unrelated, 23% matched-related and 27% haplo-identical. The median time to relapse after alloSCT was 9.3 months. 8 patients received azacitidine therapy (before or after ivosidenib). Azacitidine was combined with venetoclax in 3 patients. Patients received ivosidenib in the a median time of 4,9 month after transplantation. 68% of the patients did not present graft versus host disease.

The follow-up period was 19 months. The overall response rate was 40.6% with 36% in complete response. The median time to response, assessed in 7 patients, was 42 days, and the median duration of response, assessed in 9 patients, was 17.6 months.

The overall survival rate at 6 months is 72%, at 12 months 59% and the median overall survival is 18 months. The relapse type (cytological, molecular or extra-medular) was not associated with differences in overall survival.

The tolerance of ivosidenib was good ; no patient had to discontinue the treatment due to toxicity.

Conclusions: This study evaluating ivosidenib after alloSCT showed interesting results in terms of overall response and overall survival with few serious adverse events. The impact of associated treatments, remains to be determined. Further andomized studies could provide more precise answers to the role of this treatment in this setting.

Disclosure: Nothing to declare.

7 - New Drugs and Cell-based Immune Therapies

P510

IMPROVED SURVIVAL SINCE THE INCORPORATION OF NEW THERAPIES FOR THE TREATMENT OF RELAPSED-REFRACTORY AGGRESSIVE B-CELL LYMPHOMA. ANALYSIS BASED ON RELINF REGISTRY OF THE GELTAMO GROUP

María José Llácer Ferrandis[1], Mariana Bastos-Oreiro[1], Ana Jiménez Ubieto[2], Sonia González de Villambrosia[3], Raúl Córdoba Mascuñano[4], Elena Pérez Caballos[5], Belén Navarro Matilla[6], Ana Muntañola Prat[7], Eva María Donato Martín[8], Lourdes Escoda Teigell[9], Hugo Luzardo Henríquez[10], María Jesús Peñarrubia Gómez[11], Daniel García Belmonte[12], Emilia Pardal de la Mano[13], Claudia Juliana Salazar Lozada[14], Alejandro Martín García-Sancho[15]

[1]Hospital Gregorio Marañón, Madrid, Spain, [2]Hospital 12 de Octubre, Madrid, Spain, [3]Hospital de Valdecillas, Santander, Spain, [4]Hospital Fundación Jiménez Díaz, Madrid, Spain, [5]Hospital Morales Meseguer, Murcia, Spain, [6]Hospital Puerta de Hierro, Madrid, Spain, [7]Hospital Mutua Terrassa, Terrassa, Spain, [8]Hospital Doctor Peset, Valencia, Spain, [9]Hospital Joan XXIII, Tarragona, Spain, [10]Hospital Doctor Negrín, Las Palmas de Gran Canaria, Spain, [11]Hospital de Valladolid, Valladolid, Spain, [12]Hospital de la Zarzuela, Madrid, Spain, [13]Hospital Vírgen del Puerto, Plasencia, Spain, [14]Instituto Valenciano de Oncología, Valencia, Spain, [15]Hospital de Salamanca, Salamanca, Spain

Background: Several new therapeutic agents has been approved In recent years for the treatment of relapsed/refractory (r/r) diffuse large B cell lymphoma (DLBCL) and high-grade B cell lymphomas (HGBCL) such as new monoclonal antibodies (MA), bispecific antibodies (BA) and CAR-T therapy. The objective of our study was to evaluate the epidemiology and the use of these new therapies (NT) in Spain, and to analyse the impact on survival. From the initial registry RELINF from the GELTALMO group, we focused on patients with diagnosis of DLBCL and HGBCL.

Methods: This is a multicentre retrospective study including 15 centres in Spain, 2 of them are CAR-T cell providers. We identified patients with histologic diagnosis of DLBCL and HGBC from the RELINF platform. Cases were included from January, 2014 to December, 2021.

Results: A total of 2162 patients were included in the analysis, with a median age of 69 years, and 49.8% were female. 1891 DLBCL (51% germinal centre, 41% activated phenotype, 8% indeterminate), 271 HGBCL (45% double/triple HIT).

Four hundred and ninety four patients relapsed, 174 between 2014 and 2017 (1st period), and 311 between 2018 and March 2021 (2nd period) and the median number of lines fort them was 3 (2-7). In 353 patients, any NT was used. In the 2nd period, 111 patients received NT (and 30 in the 1st period). New MA were use

in 88 (28%) patients, polatuzumab vedotin was the most frequently used antibody (54%), and BA in 28 (9%) all of them within a clinical trial. Twenty patients received NT in 1st relapse, 14 MA and 7 BA. For 211 patients that received > 2 lines of treatment, 128 were in the 2nd period, 60 (47%) received CAR-T cell therapy, and 39 (30%) of these patients did not receive any NT.

Five-year progression free survival (PFS) for the entire cohort was 71% (CI 69-74), and median overall survival (OS) was 90 months (IC: 76-NR), 33 months (CI: 25-44) ≥ 70 y/o patients and 170 months (IC: 170-NR) for patients < 70. Median OS for relapsed patients was 22 months (CI: 19- 26), and for the group of patients with > 2 lines was 23 months (CI; 19-27). Median OS since first relapse for patients with > 2 lines treated with CAR-T cell was 31 months vs 11 months for patients who did not receive CAR-T ($p = 0.002$). With a median follow up of 25 months, (50 months for the 1st period and 20 months for the 2nd period) OS was superior for patients relapsed in the 2nd period (26 month [CI: 22-38]), compared with those relapsed in the 1st period (18 month [IC: 16-22], $p = 0.016$).

Conclusions: According to our analysis, the incorporation in recent years of NA for the treatment of r/r DLBCL and HGBCL provide more treatment options, improving the OS. In this sense, for r/r patients with at least 2 previous lines of treatment, having received CAR-T therapy has been associated with a significant improvement in OS.

Disclosure: Nothing to declare.

7 - New Drugs and Cell-based Immune Therapies

P511

IMPACT OF (LEUKAEMIA-DERIVED) DENDRITIC CELLS GENERATED FROM AML-PATIENTS' WHOLE BLOOD- VERSUS WHOLE BONE MARROW CELLS ON THE MEDIATION OF ANTILEUKAEMIC PROCESSES AFTER MIXED LYMPHOCYTE CULTURE

Marianne Unterfrauner[1], Hazal Aslan[1], Anne Hartz[1], Sophia Bohlscheid[1], Elias Rackl[1], Tobias Baudrexler[1], Xiaojia Feng[1], Lin Li[1], Giuliano Filippini Velazquez[2], Andreas Rank[2], Christoph Schmid[2], Jörg Schmohl[3], Peter Bojko[4], Helga Maria Schmetzer[1]

[1]University Hospital of Munich, Munich, Germany, [2]Augsburg University Hospital, Augsburg, Germany, [3]Diakonieklinikum Stuttgart, Stuttgart, Germany, [4]Rotkreuzklinikum Munich, Munich, Germany

Background: There are virtually no treatment options for therapy-refractory or relapsed AML and high rates of relapse in successfully treated patients. The combination of the (clinically approved) immune-modulatory compounds GM-CSF and PGE-1 (Kit-M) converts myeloid blasts into dendritic cells of leukaemic origin (DC_{leu}). After stimulation with DC_{leu}, antileukaemic immune cells are activated. Kit-M treatment may be an attractive tool for immunotherapy in myeloid leukaemia. Kit-M mediated antileukaemic effects on whole bone marrow (WBM) were evaluated and compared to WB to evaluate potential differences in efficacy of Kit-M mediated reactions.

Methods: WB and WBM samples from 17 AML patients at first diagnosis, in persisting disease or at relapse after allogeneic stem cell transplantation (SCT) were treated in parallel with Kit-M to generate DC/DC_{leu}. Untreated samples served as controls. After a mixed lymphocyte culture enriched with patients' T-cells (MLC), the antileukaemic effects were assessed through the degranulation- (CD107a+ T cells), the intracellular IFNγ production- and the cytotoxicity fluorolysis assay. Quantification of cell subtypes was performed via flow cytometry.

Results: In both WB and WBM significantly higher frequencies of (mature) DC_{leu} were generated without induction of blast proliferation in Kit-M treated samples compared to control. After MLC with Kit-M treated vs. not pretreated WB or WBM, frequencies of immunoreactive cells (e.g. non-naive T-cells, NK-cells) were (significantly) increased, of regulatory T-cells (T_{reg}, CD152 + T-cells) were (significantly) decreased and of degranulating and IFNγ producing activated T-cells (e.g. central memory CD107a+ T-cells, CD3+Integrinβ7+ cells) were (significantly) increased. The cytotoxicity fluorolysis assay showed a significantly improved blast lysis in Kit-M treated WB and WBM compared to control.

A parallel comparison of WB and WBM samples revealed no significant differences in frequencies of cell subtypes and achieved antileukaemic processes.

Conclusions: Kit-M showed to have comparable effects on WB and WBM samples regarding the generation of DC_{leu} and activation of (antileukaemic) immune cells after MLC. This was true for samples before or after SCT. A potential Kit-M in vivo treatment could lead to antileukaemic effects in WB as well as WBM in vivo and to stabilization of the disease or remission in patients before or after SCT. A clinical trial is currently being planned.

Disclosure: Modiblast Pharma GmbH (Oberhaching, Germany) holds the European Patent 15 801 987.7-1118 and US Patent 15-517627 'Use of immunomodulatory effective compositions for the immunotherapeutic treatment of patients suffering from myeloid leukemias', with whom Helga Maria Schmetzer is involved with.

7 - New Drugs and Cell-based Immune Therapies

P512

NEXT GENERATION THERAPY: INNOVATIVE AND SAFE RNA DELIVERY MEDIATED BY LENTIFLASH® PARTICLES FOR AN EFFICIENT CRISPR/CAS9-MEDIATED GENE KNOCKOUT IN HUMAN INDUCED PLURIPOTENT STEM CELLS

Christine Duthoit[1], Joffrey Mianne[2], Nicolas Martin[1], Alexandra Iche[1], Regis Gayon[1], Florine Samain[1], John De-Vos[3], Pascale Bouille[1]

[1]Flash Therapeutics, Toulouse, France, [2]IRMB, Univ Montpellier, INSERM, CHU, Montpellier, France, Univ Montpellier, CHU, Montpellier, France

Background: Old and new successful gene therapy approaches show that there is no universal delivery tool for all therapeutic strategies. As DNA delivered-therapies mediated by integrative lentiviral vectors and AAV have become widespread in the market, RNA therapies are expected to be more versatile, and to cover a broad range of applications with minimal regulatory concerns and thus address a large variety of diseases. The technology targets specific applications in which a transient expression is expected to trigger a cellular process which will remove a genetic sequence or will commit cells into a specific pathway. Once engineered, patient's cells become the effective medicine.

Depending on the target disease, RNA must be designed to fit with the therapeutic approach: vaccination, gene-editing or regenerative medicine. The design of the transferred RNA must also be selected depending on ex vivo or in vivo approach, the required expression level and its duration.

Methods: Biological RNA delivery mediated by a lentiviral particle is an attractive approach as it combines most of the

inherited properties of lentiviral vectors (cell entry and tropism) without the potential adverse effects from long-lasting expression or genomic integration (size limitation, insertional mutagenesis). From a therapeutic perspective, a great advantage of such system is its ability to carry different RNA species, of biological origin and naturally protected from degradation, to trigger fine, specific cell responses.

The combination of CRISPR/Cas9 technology with human induced pluripotent stem cells (hiPSC) has tremendous potential for basic research and cell-based gene therapy. However, fulfilling these promises relies on our capacity to efficiently deliver exogenous nucleic acids into these cells and harness the repair mechanisms induced by the nuclease activity. Since gene editing systems require low and short-term expression in order to avoid off-target effects, RNA delivery is favored over DNA delivery.

Here, we investigated the potential of bacteriophage-chimeric retrovirus-like particles, called LentiFlash®, for the delivery of CRISPR/Cas9 technology as biological RNA molecules in hiPSC.

Results: We found that LentiFlash® particles efficiently convey biological RNA molecules for transient expression in hiPSC, with minimal toxicity and without affecting cell pluripotency and subsequent differentiation. We then used this system to transiently deliver the CRISPR-Cas9 components (Cas9 mRNA and sgRNA) to generate a gene knockout with a high indel level (up to 85%) at several loci into hiPSC. Strikingly, when using an allele-specific sgRNA, the targeted allele was not altered by NHEJ/MMEJ, but was repaired at high frequency using the homologous wild type allele, suggesting interallelic gene conversion.

Conclusions: Our results highlight the potential of LentiFlash® particles to deliver biological RNA molecules efficiently and safely in hiPSC. Harnessing this DNA repair mechanism could facilitate the therapeutic correction of human genetic disorders in hiPSC.

All these properties, as well as the ability to produce LentiFlash® using lentiviral production platforms already validated in clinical settings offer additional safety considerations making it certainly the most versatile, flexible, and safe mean for the next generation of human therapy.

Disclosure: none.

7 - New Drugs and Cell-based Immune Therapies

P513

A REAL-WORLD STUDY OF LENALIDOMIDE COMBINED WITH LOW-DOSE VENECLA IN MAINTENANCE THERAPY AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR RECURRENT AND REFRACTORY HEMATOLOGICAL MALIGNANCIES

Zhihui Li[1], Qinglong Zheng[2], Keyan Yang[2], Xianxuan Wang[1], Fan Wu[1], Xiaopei Wen[1], Caiyan Zhang[2], Tong Wu[1]

Beijing Gaobo Boren Hospital, Beijing, China, Beijing Gaobo Boren Hospital, Beijing, China

Background: HSCT is the only cure option for patients with r/r hematological malignancies. However, many patients still relapse after HSCT. Therefore, we conducted a study to retrospectively analyze the recurrence and survival of patients after HSCT who received Lenalidomide combined with low-dose ven maintenance therapy.

Methods: Our study retrospectively analyzed 141 patients who received HSCT in Beijing Gaobo Boren hospital from August 2019 to April 2022. After HSCT, 119 patients did not receive any maintenance treatmentand, 22 patients received maintenance treatment. Patients who received maintenance treatment within a median time of 5 months (1-40 months) after transplantation. Children or children weighing less than 25kg received lenalidomide 5mg/d; Children or adults weighing more than 25kg received lenalidomide 10mg/d. Low dose venecla 10mg orally for Qd. The median follow-up time was 22.4 months (95% CI: 17.5-25.7 months).

A total of 141 patients with r/r hematological malignancies were enrolled in the cohort, including 66 cases of B-ALL (46.8%), 37 cases of AML (26.2%), 30 cases of T-ALL (21.3%), and 7 cases of NHL-B (5%). Male: female =30:27, median age 12 (1-58 years old). Before transplantation, 80 patients (56.7%) had CR, 14 patients (9.9%) had PR, 47 patients (13.3%) had NR. The types of transplant were haploidentical (94, 66.7%), unrelated (8, 5.7%), and identical siblings (39, 27.7%). RTC with either TBI/FLU (52, 36.9%) or BU/FLU (89, 63.1%) were applied. Comparing the baseline differences between two groups, there was no significant difference.

Results: Among the 22 patients who received maintenance treatment, 2 patients died, and both of them died of recurrence. Eight patients (34.8%) developed aGVHD° after lenalidomide; Two cases of III-IV ° were relieved after drug withdrawal and anti-GVHD treatment. Infection occurred in 12 cases, and all patients were effective in antibiotic treatment. Grade 2 AES occurred,no AES ≥ grade 3 was observed. All toxicity was tolerable and reversible.

we analyzed the patients according to different conditioning regimen. It can be seen that lenalidomide combined with ven significantly prolonged the relapse free time and survival of patients conditioned with TBI/FLU regimen ($P = 0.05$; $P = 0.039$). The 1-year recurrence rate of TBI/FLU patients with maintenance treatment was 14.3% (95% CI: 2.1-66.6%), and the survival rate was 100% (95% CI:NA-NA); The 1-year recurrence rate of patients without maintenance treatment was 42.3% (95% CI: 27.4-61.3%), and the survival rate was 60.5% (95% CI: 45.5-80.3%).

In addition, we also analyzed the impact of maintenance therapy on the prognosis of patients with BU/FLU. Whether it was first transplant or not, the 1-year recurrence rate was higher than 50% with maintenance treatment, which was significantly higher than that of patients who did not receive maintenance treatment ($P = 0.0076$; $P = 0.026$).

Conclusions: In this study, We observed that lenalidomide combined with ven could significantly improve the prognosis of HSCT patients with TBI/FLU as a conditioning regimen. The results needs to be further studied in a prospective clinical trial with an expanded sample in the future.

Disclosure: Noting to declare. The authors declare that they have no competing interests.

7 - New Drugs and Cell-based Immune Therapies

P514

USE OF MESENCHIMAL STROMAL CELLS IN COMBINATION TREATMENT FOR SEVERE STEROID REFRACTORY GRAFT VERSUS HOST DISEASE: A SINGLE CENTRE EXPERIENCE

Beatrice Manghisi[1], Marilena Fedele[1], Giuseppe Gaipa[2], Daniela Belotti[3], Sara Tarantino[1], Alessia Ripamonti[1], Paola Perfetti[1], Elisabetta Terruzzi[1], Andrea Aroldi[1], Carlo Gambacorti Passerini[1], Matteo Parma[1]

[1]Ospedale San Gerardo, Monza, Italy, [2]Fondazione Tettamanti, Monza, Italy, [3]Università di Milano-Bicocca, Monza, Italy

Background: Graft versus host disease (GvHD) is the most frequent complication of allogeneic hematopoietic stem cell transplantation (HSCT). Steroid treatment is the first line therapy

with a response rate of 50%; second line treatment in steroid refractory patients is not clearly defined but it includes several immunosuppressive drugs (Ruxolitinib, Micofenolate-Mofetile, m-TOR inhibitors, MoAbs) and Extracorporeal Photoapheresis (ECP). Recently, a growing interest in cell therapy has prompted the use of intravenous infusion of mesenchymal stromal cells (MSC). In vitro MSC can exert a strong immunosuppressive/immunomodulatory effect against aberrant inflammatory responses typical of acute GvHD. Despite this, definitive proof of their efficacy "in vivo" remains lacking so far.

We hereby report on our experience in the use of MSC for management of severe steroid refractory GvHD.

Methods: We treated 4 patients affected by severe (stage III-IV) steroid-refractory acute GvHD with MSC in compassionate use, in combination with other second line therapies. MSC, derived from the third part of donor marrow, were collected and preserved according to GMP criteria in our Institution's Cell Factory.

MSC were administered with the following schedule: 1 x 10^6 cells once a week for a maximum of 8 doses, in association to other second or subsequent lines of therapy.

Two patients were affected by acute myeloid leukemia and two by T-cell acute lymphoblastic leukemia. Three patients received a MUD HSCT (1 full matched and 2 mismatched for a single locus); one patient received a Haplo-HSCT.

All patients experienced severe (grade III-IV) GvHD according to MAGIC criteria; gastrointestinal tract was the most frequent system involved; one patient experienced severe pulmonary chronic GvHD. Patients were treated with MSC after failure of multiple lines of therapy, and MSC were always combined with other immunosuppressive or immunomodulatory drugs. Interestingly, 3/4 patients received concomitantly Ruxolitinib therapy.

Results: Three patients received a complete cycle of 8 MSC infusions. Treatment was well tolerated by all the patients, without any adverse event or complication related to the infusion. One patient received a single MSC infusion because of early death in the context of TA-TMA overlapping GvHD.

We observed a complete GVHD response in 1 patient and a partial response in 2 patients. The fourth patient was not evaluable for response.

Among the 3 patients who completed the scheduled MSC treatment, one patient is alive in absence of GVHD (nine months after ending the treatment) one died of invasive aspergillosis during the immunosuppressive treatment, one died of septic shock unrelated to GVHD treatment.

Conclusions: In our experience MSC were administered as compassionate use in association with other drugs and ECP in the setting of steroid refractory GVHD. Treatment with MSC proved to be a safe, well tolerated and effective option in second-line therapy.

In the context of the combined treatment it's difficult to establish the real impact of MSC therapy: further research with comparative studies and larger cohorts are certainly needed.

At last, the association of Ruxolitinib/MSC could be a valid option as second line therapy, especially for patients not eligible to ECP.

Disclosure: Nothing to disclose.

7 - New Drugs and Cell-based Immune Therapies

P515

UTILIZATION OF NK CELLS IN PREVENTION OF RELAPSE AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION – CLINICAL STUDY PHASE IB/II

Jiri Sramek[1,2], Monika Holubova[3,1], Daniel Lysak[1], David Chena[1], Michal Karas[1], Marcela Hrabetova[1], Katerina Steinerova[1], Radka Boudova[1], Jana Vrbova[1], Iveta Paurova[3,1], Pavel Jindra[1]

University Hospital Pilsen, Pilsen, Czech Republic, Pilsen, Charles University, Pilsen, Czech Republic, [3]Biomedical Center, Charles University, Pilsen, Czech Republic

Background: Relapse is the most common cause of death in patients after allogeneic hematopoietic cell transplantation (AlloHSCT). Patients with a high-risk disease according to the disease risk index (DRI) or patients with measurable residual disease after AlloHSCT have a high risk of disease relapse with limited therapeutic options. Adoptive immunotherapy using ex vivo expanded and activated NK cells represents a potential treatment modality for relapse prevention.

This unicentric phase Ib/II clinical study (EudraCT 2018-001562-42) aims to confirm the safety of advanced therapy medical product (ATMP) application from cultured NK cells and evaluate the composition variability of produced ATMP. The secondary objectives are to monitor the immune reconstitution and evaluate MRD, RFS, OS, and the occurrence of GvHD during the 12-month follow-up.

Methods: Patients with hematological malignancy after AlloHSCT with a high/very high-risk disease according to the DRI, or patients with proven MRD after transplantation, were included in the clinical study. NK cells were isolated from the fraction of autologous mononuclear cells (MNC) obtained by leukapheresis 2-4 months after AlloHSCT. This was followed by in vitro cultivation, expansion, and activation using IL-2 and feeder cells (irradiated MNCs from healthy donors) for 3 weeks. The application of ATMP NK cells was preceded by lymphodepleting chemotherapy (cyclophosphamide 300 mg/m2 and fludarabine 30 mg/m2 on days -6 to -3). Administration of 3 doses of NK cells (0.5-1.5x10e7/kg) was infused on day +0, +14 and +30.

Results: 11 patients were included, and the application was implemented in 9 (5xAML, 1xALL, 2xMM, 1xcHL), median age was 55 years, DRI high/very high in 5/9, MRD pos. in 6/9. The parameters of 25 products were (all medians): dose 1.5x10e7/kg, viability 99.5%, purity 99.0%, expression of the NKG2D activation mark 100%, and cytotoxic activity (percentage of dead K562 cells) 84.15%. No infusion toxicity and clinically significant AEs related to ATMP administration were observed. The kinetics of lymphocyte populations showed over a period of weeks, a gradual rise of NK cells with a high representation of activation features. Median RFS and OS from NK-cell infusion were 5 months and 12.4 months, respectively. The onset of new GvHD activity was observed in 2 patients (25%).

Conclusions: Adoptive NK cell immunotherapy in the stated clinical trial design was safe, and no infusion toxicity was observed. The production of NK-cell ATMP was highly standardized, with low inter-individual variability. The effectiveness of immunotherapy could not be assessed due to the small number of patients, however, a relatively high number of late relapses was observed, which can be expected in the given patient population. To ensure higher efficacy, a combination with chemotherapy and/or targeted therapy to affect leukemic stem cells or gene manipulation with the preparation of CAR-NK cells will probably be necessary.

Clinical Trial Registry: EudraCT 2018-001562-42

Disclosure: Nothing to declare.

8 - Non-haematopoietic Stem Cells and Regenerative Medicine

P516

SARS-COV-2 FAILS TO INFECT MESENCHYMAL STROMAL CELLS (MSCS) AND DOES NOT ACTIVATE COAGULATION –

PRE-CLINICAL INVESTIGATIONS IN SUPPORT OF THERAPEUTIC USE OF MSCS FOR SEVERE COVID-19

Lisa-Marie Pfeffermann[1], Sabine Hünecke[2], Melanie Bremm[2], Natascha Piede[2], Denisa Bojkova[3], Joshua Kandler[3], Selim Kuci[2], Zyrafete Kuci[2], Holger Neb[4], Sabine Harenkamp[1], Halvard Bönig[1], Peter Bader[2]

[1]Institute for Transfusion Medicine and Immunohematology, Frankfurt, Germany, [2]University Hospital, Clinic for Children and Adolescents, Frankfurt, Germany, [3]University Hospital, Institute of Medical Virology, Frankfurt, Germany, [4]University Hosital, Clinic for Anesthesiology, Intensive Care Medicine and Pain Therapy, Frankfurt, Germany

Background: Severe COVID with adult respiratory distress syndrome (ARDS) is characterized by hyperinflammation and small vessel endothelitis. Mesenchymal stromal cells (MSCs) have shown therapeutic effects in a pathogenetically not dissimilar disease, graft-versus-host disease (GvHD) after stem cell transplantation. MSCs could thus be, in principle, therapeutically efficacious in severe COVID ARDS.

Methods: MSC were cultivated and infected with virus at MOI 0.1. Quantification of viral RNA and expression of inflammatory mediators was done by PCR. MSCs were analysed by flow cytometry for specific receptors and coagulometry was assessed via Clotpro® system.

Results: Obnitix MSCs were analysed for the expression of potential (co)receptors for SARS-CoV-2, namely ACE-2 and TMPRSS2. Staining was performed 72 h after incubation with and without virus and in the presence or absence of IFN-γ. Obnitix MSCs remained negative for the SARS-CoV-2 receptors ACE-2 and TMPRSS, importantly, also under inflammatory conditions as Obnitix MSCs may encounter in vivo in COVID-19 or GvHD patients.

The immunophenotype of Obnitix MSCs was not affected by the virus and the MSCs showed an inflammatory signature after stimulation, with up-regulated HLA class I and II antigen expression. This is the same with/without virus.

Obnitix mRNA was analysed for expression of a panel of inflammation-mediated genes. The IFN-γ activated MSC samples showed an inflammation signature with up-regulated IL-8, IL-12a and IL-15, but the presence of SARS-CoV-2 did not noticeably affect inflammatory gene expression. Between Obnitix batches, cytokine and phenotypic patterns were remarkably similar in quality and particular also quantity, confirming the overwhelming dose-to-dose similarity of Obnitix MSCs.

Next the infectibility of Obnitix MSCs was evaluated. Supernatants and cells exposed to SARS-CoV-2 from three independent MSC Obnitix batches were collected after 2 and 72 hours post exposure and tested for viral RNA in triplicates. No increase in intracellular nor extracellular viral RNA over the time course was detected, suggesting, that MSC Obnitix are not permissive for SARS-CoV-2 replication. Low levels of viral RNA found in the cells after 2 hours, are most likely reflecting spontaneous, vesicle-associated viral uptake. Such uptake was not detected in IFNγ-treated cells, presumably reflecting the known anti-viral activity of IFNγ. Moreover, supernatants collected at the 72 h time point failed to infect SARS-CoV-2 target cells. Obnitix MSCs are thus resistant to SARS-CoV-2 infection and cannot serve as reservoir for the virus.

Random healthy donor whole blood coagulation was tested in the presence of Obnitix MSCs or diluent control. Most parameters were unaffected by the presence of Obnitix MSCs at all concentrations. At concentrations approximating predicted peak MSC in vivo concentrations ($0.04x10^6$ Obnitix MSCs/mL) all tests yielded normal values, indistinguishable from diluent controls demonstrating that Obnitix MSCs do not trigger coagulation and can be designated "hemocompatible".

Conclusions: In summary, because of the lack of SARS-CoV2 surface receptors ACE2 and TMPRSS, Obnitix MSCs cannot be infected with SARS-CoV-2. We consistently observe an inflammatory cellular phenotype and transcriptome which is, however, entirely unaffected by the presence of SARS-CoV-2. These studies support the expectation of safety of Obnitix use in COVID-ARDS.

Disclosure: Zyrafete Kuci, Selim Kuci, Halvard Boenig and Peter Bader own intellectual property related to the MSC preparation and have received royalties there for.

8 - Non-haematopoietic Stem Cells and Regenerative Medicine

P517

EXPLORING THE THERAPEUTIC POTENTIAL OF AUTOLOGOUS BONE MARROW MONONUCLEAR CELLS *VERSUS* ALLOGENIC WHARTON JELLY-DERIVED MESENCHYMAL STEM CELLS IN CHRONIC LIMB-THREATENING ISCHEMIA IN DIABETIC PATIENTS

Martha L. Arango-Rodríguez[1], Claudia L. Sossa[2], Ligia C. Mateus[3], Miguel Enrique Ochoa[4], Lady T. Giratá[1], Silvia M. Becerra-Bayona[4], Víctor Solarte-David[4], Ana M. Vera Berrio[1], Oliverio Vargas[3], Alape Benitez[3], German Rangel[3]

[1]Banco Multitejidos y Centro de Terapias Avanzadas, Clínica FOSCAL Internacional, Floridablanca, Colombia, [2]Programa para el Tratamiento y Estudio de Enfermedades Hematológicas y Oncológicas de Santander (PROTEHOS), Floridablanca, Colombia, [3]Fundación Oftalmológica de Santander, Floridablanca, Colombia, [4]Facultad de Ciencias de la Salud, Universidad Autónoma de Bucaramanga - UNAB, Bucaramanga, Colombia

Background: Chronic limb-threatening ischemia (CLTI) represents the final stage of peripheral arterial disease. Approximately one-third of patients with CLTI are not candidates for conventional surgical treatment. Patients in the severe stages of CLTI are prone to amputation and death.

There is an urgent need to develop an effective therapeutic strategy to treat this disease. In this context, autologous bone marrow mononuclear cells (auto-BM-MNC) and allogeneic mesenchymal stem cells have emerged as promising therapeutic approaches for CLTI. We compare auto-BM-MNC *vs*.allogeneic Wharton jelly-derived mesenchymal stem cells (allo-WJ-MSCs), evaluating their safety and beneficial therapeutic effect in comparison with the placebo group in diabetic patients with CLTI.

Methods: We performed a double blind and controlled pilot study. Twenty-four diabetic patients in the most severe stages of the CLTI (4 or 5 in Rutherford's classification) and transcutaneous oxygen pressure ($TcPO_2$) below 30 mmHg were randomizedto receive 15 injections of (i) auto-BM-MNC ($7.197x10^6 \pm 2.984$ $x10^6$cells/mL) ($n = 7$), (ii) allo-WJ-MSCs (1.333 $x10^6$cells/mL) ($n = 7$) or (iii) placebo solution (1 mL) ($n = 10$), which were administered into the periadventitial layer of the walls arteries. The follow-up visits were at months 1, 3, 6, and 12, to evaluate the following parameters: (i) Rutherford's classification, (ii) $TcPO_2$, (iii) percentage of wound closure, (iv) pain, (v) pain-free walking distance, (vi) revascularization and limb-survival proportion, and (vii) the quality of life (EQ-5D questionnaire).

Results: No adverse events were reported. Patients with CLTI that received auto-BM-MNC and allo-WJ-MSCs presented an improvement in Rutherford's classification, a significant increase in $TcPO_2$values, clinical changes in the lesion size in a shorter time, a decrease in the pain score and an increase in the pain-free

walking distance, in comparison with the placebo group. In addition, the participants treated with auto-BM-MNC and allo-WJ-MSCs kept their limbs during the follow-up period, unlike the placebo group, who had a marked increase in the amputation.

Conclusions: Our results suggest that auto-BM-MNC and allo-WJ-MSCs in patients with CLTI lead to significant clinical changes, being more noticeable in a shorter time with allo-WJ-MSCs, unlike the placebo group where the participants increased their classification to a more severe stage of the disease.

Clinical Trial Registry: The study was registered at ClinicalTrials.gov (NCT05631444)

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P518

MANAGEMENT OF SINUSOIDAL-OCCLUSION-SYNDROME IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION AFTER INTRODUCING DIAGNOSIS BY EBMT CRITERIA AND TREATMENT WITH DEFIBROTIDE: A SINGLE CENTER EXPERIENCE

Hirotoshi Sakaguchi[1], Yoshihiro Gocho[1], Yuji Yamada[1], Yoko Shioda[1], Chikako Kiyotani[1], Takao Deguchi[1], Keita Terashima[1], Akihiro Iguchi[1], Motohiro Kato[1,2], Daisuke Tomizawa[1], Kimikazu Matsumoto[1]

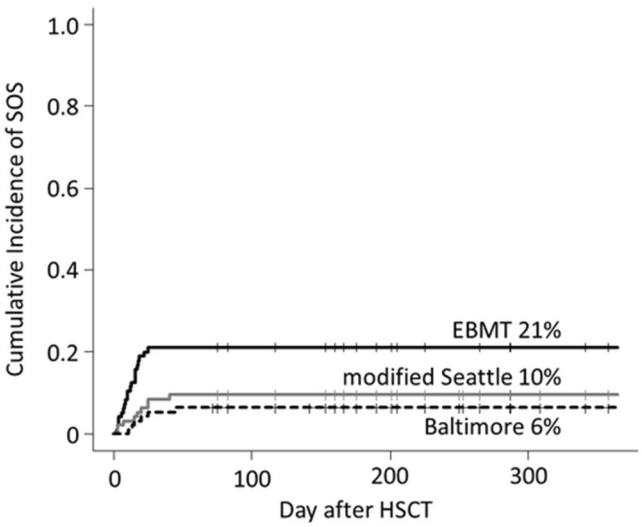
[1]National Center for Child Health and Development, Tokyo, Japan, [2]The University of Tokyo, Tokyo, Japan

Background: Sinusoidal obstructive syndrome (SOS) is a life-threatening complication of hematopoietic stem cell transplantation (HSCT). The proposal of EBMT criteria and severity classification of childhood SOS in 2018, and the Japanese marketing of defibrotide as a treatment for SOS in 2019, has brought about a major change in the management of SOS. Herein, we report our experience with commercially available defibrotide as treatment for childhood SOS.

Methods: We conducted a retrospective survey of SOS with the approval of the Ethics Review Board in National Center for Child Health and Development, Tokyo, Japan. From October 2019 to September 2022, 91 consecutive patients underwent 100 HSCTs in our center; patient's characteristics were summarized in Table. The median observation period for survivors was 561 days after HSCT (range, 71–1106 days). Medical records were reviewed to assess the incidence of SOS by conventional diagnostic criteria and EBMT criteria, and to detail the treatment of SOS.

Gender	**Female**	**35**	**Donor Source**	**Autologous PBSCT**	**28**
	Male	56		Related BMT	15
Age at HSCT, years	Median	5		Unrelated BMT	28
	Range	0.2–19		Unrelated CBT	7
Disease	Benign	37		Haploidentical BMT or PBSCT	22
	Hematological Malignancy	28	GvHD prophylaxis	None	28
	Solid Tumor	26		Cyclosporin A + MTX	8
Conditioning	Myeloablative	76		Tacrolimus + MTX	38
	Reduced Intensity	24		PT-Cy alone	5
				PT-Cy + Tacrolimus + MMF	21

Results: Twenty patients (21%) met the EBMT criteria (median days after HSCT that met the criteria, 11 days; range, 2–25 days), of whom 13 were clinically diagnosed with SOS; nine patients fulfilled the modified Seattle criteria (17 days; range, 3–41 days) and six met the Baltimore criteria (17.5 days; range 11–45 days), as shown in Figure. The seven patients who met the EBMT criteria but were not clinically diagnosed with SOS all no longer met the criteria within a few days. Of the 13 clinical SOS patients, the percent meeting each of the EBMT criteria were as follows: transfusion-refractory thrombocytopenia in 100% (13/13), unexplained weight gain > 5% above baseline in 77% (10/13), hepatomegaly in 54% (7/13), ascites in 38% (5/13), and bilirubin increase lasting 3 consecutive days in 85% (11/13). The highest severity by EBMT grading criteria for the 13 clinical SOS patients was 1 mild, 3 moderate, and 9 very severe (2 with delirious). All 13 patients were treated with defibrotide and/or recombinant human thrombomodulin (rhTM); seven with defibrotide alone, four with defibrotide following rhTM, and the other two with rhTM alone. The median interval between SOS diagnosis and treatment initiation was 0 days (range, 0–3 days), and the median duration of drug administration was 36 days (range, 10–97 days). Three of the patients with very severe SOS underwent continuous drainage to control ascites and pleural effusions, and were able to continue defibrotide administration without hemorrhagic events. Complete resolution of SOS occurred in 38% (5/13) and 92% (12/13) of patients at 28 and 100 days after SOS onset. Day +365 transplantation-related mortality was 1.3% for all HSCT patients and 0% for those with any grade of SOS. Severe hemorrhagic adverse events occurred in one patient with very severe SOS (gastrointestinal bleeding).



Conclusions: The EBMT diagnostic criteria are useful for early diagnosis of clinical SOS cases, although there is a risk of overdiagnosis of SOS. Our findings suggest that treatment with DF and/or rhTM along with early diagnosis by EBMT criteria is a promising therapeutic strategy that can cure even very severe SOS.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P519

EFFECT OF THE KNOCKOUT OF GSTA1 ON HEPATIC CELLS AND CELLULAR RESPONSE TO DRUGS USED IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

Vid Mlakar[1], Isabelle Dupanloup[1], Yvonne Sylvie Gloor[1], Laurence Lesne[1], Fabienne Gumy-Pause[2,1], Tiago Nava[2,1], Marc Ansari[2,1]

[1]University of Geneva, Geneva, Switzerland, [2]University Geneva Hospitals, Geneva, Switzerland

Background: GSTA1 and GSTM1 encode enzymes that add glutathione (GSH) to target electrophiles, including carcinogens, drugs, environmental toxins, and oxidative stress products. Previously, we demonstrated that several SNPs in the promoter region of GSTA1 modulate gene expression and affect the pharmacokinetics of busulfan (Bu), which is used in the conditioning regimen before hematopoietic stem cell transplantation (HSCT) in children. In this study, we investigated the effect of the knockout of GSTA1 on the functioning and sensitivity of hepatic cells to different alkylating agents, Bu and Treosulfan (Treo) commonly used in HSCT.

Methods: CRISPR/Cas9 was used to generate GSTA1 knockout (KO) HepaRG cell lines. The expression of proteins was assessed by western blot. We used 1-chloro-2,4-dinitrobenzene and GSH-Glo™ Glutathione Assay to measure GST activity and GSH concentration, respectively. CellTiter2.0 was used to measure cell viability after treatment with selected drugs used in HSCT. RNAseq and Proteome profiler Kinase assays were used to evaluate gene expression profiles and kinase phosphorylation profiles of GSTA1 KO HepaRG cells, respectively.

Results: The knockout of GSTA1 results in the downregulation of GSTM1 and has a strong effect on cell viability after both Bu or Treo treatment. Our results demonstrate that the resistance to alkylating agents is correlated with the absence of GSTM1 and the regulation of the GCLC/GCLM expression which results in a 1.5-fold increase in intracellular GSH concentrations. The comparison of wild-type and knockout cell lines showed that cells with downregulated GSTM1 expression also present altered expression profiles of genes involved in the regulation of transcription, translation, cell migration, and cell cycle. Further deletion of GSTA1 has only a minor effect on the global transcription profile except for the regulation of transcription by RNA polymerase II. The kinase phosphorylation profiles showed changes in the phosphorylation of ERK1/2, p53, and RSK1/2/3 in GSTM1 down-regulated cells.

Conclusions: We successfully created GSTA1 KO HepaRG cell lines and confirm previous evidence which showed that GSTA1 is involved in the cellular response to Bu. In addition, we also demonstrate a correlation between the consequent GSTM1 down-regulation and an increase in GCLC expression resulting in increased GSH levels. This increase leads to a higher cellular resistance to various drugs. The analysis of the gene expression profiles and the kinase phosphorylation profiles revealed that the downregulation of GSTM1 correlates with more changes in cell signaling than the KO of GSTA1.

Disclosure: All authors declare no conflict of interest.

14 - Non-infectious Early Complications

P520

NON-INFECTIOUS COMPLICATIONS AFTER THE USE OF POST-TRANSPLANT CYCLOPHOSPHAMIDE OR ANTI-T-LYMPHOCYTE GLOBULIN AS GVHD PROPHYLAXIS

Juan Manuel Cerezo Martín[1], Rodrigo Cantera[1], Ana Tobalina[1], Irene Francés[1], Ana Gea[1], Sara Fernández-Luis[1], Miriam Sánchez-Escamilla[1], Guillermo Martin[1], M. Aránzazu Bermúdez[1], Lucrecia Yañez[1]

[1]Marqués de Valdecilla University Hospital, Santander, Spain

Background: Infectious complications associated with the use of post-transplant cyclophosphamide (PT-Cy) and Anti-T-lymphocyte globulin (ATLG; Grafalon) as graft-versus-host-disease (GVHD) prophylaxis are well described. However, other side effects such as cardiac (CE), pulmonary (PE) or renal toxicity (RE) have not been deeply investigated.

Methods: We conducted a single-center retrospective study to analyze the cumulative incidence of CE, PE and RE after the use of PT-CY (total dose of 100 mg/Kg) or ATLG (total dose 21 mg/Kg) in allogeneic hematopoietic stem cell transplantation (HSCT) on day+100 and one year post HSCT. We also evaluate the risk factors associated with them. CE was defined as: cardiac failure, pericarditis, arrythmia and acute coronary syndrome. PE was defined as: alveolar damage without a pre-existing cause, obliterans bronchiolitis in absence of GVHD, pneumonitis, and a decrease in DLCo and/or FEV1 of ≥15%. RE was defined as acute renal injury (Decrease of GFR >30mL/min).

Results: We analyzed 156 patients (PT-CY, n = 92; ATLG, n = 64) who underwent HSCT between 2012-2022. The median follow-up was 37 months. Donor in all PT-CY patients was haploidentical and in the ATLG group was an HLA 10/10 matched unrelated.

There were no differences ($p > 0,05$) regarding the age, HCT-CI, and cardiovascular risk factors between both groups. (Table 1).

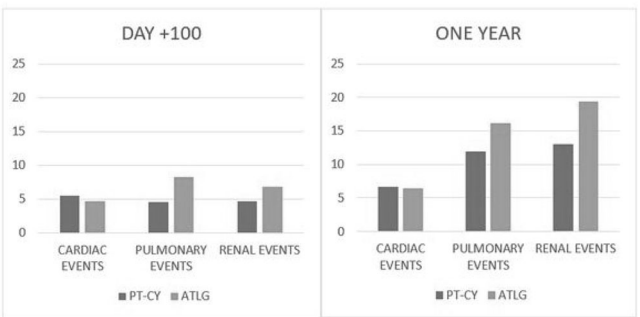
Cumulative incidence of CE at day +100 and 1 year was 5,5% and 6,7% in the PT-Cy group and 4,7% and 6,4% in the ATLG group, respectively ($p = 0,7$). Cardiac failure was the main CE in both groups (PT-CY, n = 5; ATLG, n = 4), followed by arrythmia (PT-CY, n = 2; ATLG, n = 1) and acute coronary syndrome (PT-CY, n = 1; ATLG, n = 1). The presence of pre-transplant cardiovascular risk factors was related to a higher CE (HR 4,36, CI 95% 0,96-18,6) but not reached statistical significance ($p = 0,06$).

Cumulative incidence of PE at day +100 and at one year-post HSCT were 4,5% and 12% in the PT-Cy group and 8,2% and 16,1% in the ATLG group, respectively ($p = 0,6$). In the PT-Cy group main PE were decrease in DLCo and/or FEV1 (10), pneumonitis (1) and bronchiolitis (1) and in the ATLG group were decrease in DLCo and/or FEV1 (8) and alveolar damage (1).

Cumulative incidence of RE at day +100 and 1 year-post HSCT were 4,7% and 13% in the PT-Cy group and 6,8% and 19,4% in ATLG group, respectively ($p = 0,7$).

In multivariate analysis, age>60y, myeloablative conditioning, diagnosis, and the type of donor were not associated with a higher incidence of CE, PE, or RE. On the other hand, smoking exposure and cardiovascular risk factors were not associated with a higher incidence of PE or RE, respectively.

Figure 1. Cardiac, pulmonary, and renal events at day +100- and one-year post HSCT.



Conclusions: Non-infectious complications may affect, at least, 5% of patients within the first year after PT-CY or ATLG. Renal impairment is the most frequent adverse event, especially in the setting of ATLG. There were no differences in terms of CE, PE or RE

GENDER	PT-CY n = 92 (%)	ATLG n = 64 (%)	p-value		PT-CY = 92	ATLG n = 64	p-value
Female	35 (38)	25 (39)	0,898	HYPERTENSION	20 (21,7)	17 (26,5)	0,486
AGE							
<60	55 (59,8)	36 (56,3)	0,661	DIABETES	8 (8,7)	7 (10,9)	0,641
60-70	37 (40,2)	28 (43,7)					
DIAGNOSIS							
AML	37 (40,2)	26 (40,6)	<0,01	DYSLIPIDEMIA	20 (21,7)	14 (21,9)	0,984
ALL	9 (9,7)	13 (20,3)					
MDS	8 (8,7)	5 (7,8)					
NHL	15 (16,3)	4 (6,3)					
HL	14 (15,2)	0					
MF	3 (3,3)	8 (12,5)					
OTHER	6 (6,6)	8 (12,5)					
DRI							
Low	18 (19,6)	4 (6,3)	0,049	SMOKE EXPOSURE	46 (50)	25 (39)	0,3822
Intermediate	41 (44,6)	39 (60,9)					
High	23 (25)	17 (26,5)					
Very High	6 (6,5)	4 (6,3)					
Not applicable	4 (4,3)	0					
HCT-CI							
<3	43 (45,7)	31 (48,5)					
>=3	47 (50)	32 (50)	0,862				
Unknown	4 (4,3)	1 (1,5)					
PREVIOUS ASTC	18 (19,5)	8 (12,5)	0,232				
SOURCE							
Peripheral blood	48 (52,2)	64 (100)	<0,01				
Bone Marrow	44 (47,8)						
CONDITIONING							
Myeloablative	37 (40,2)	43 (67,2)	0,01				

within the first-year post HSCT in the PT-Cy group or ATLG group regardless of age, intensity of conditioning, diagnosis, donor or cardiovascular risk factors.

Clinical Trial Registry: Not applicable

Disclosure: I have been found in terms of travelling and congress registration by Fresenius Kabi.

14 - Non-infectious Early Complications

P521

EFFECTS OF HYPERBARIC OXYGEN THERAPY ON SALIVARY AND FECAL MICROBIOTA IN PATIENTS WITH MULTIPLE MYELOMA UNDERGOING AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

Bassil Said[1], Armin Rashidi[2], Ann Gill[3], Kaitlyn Burrows[4], Eric Huselton[4], Jane Liesveld[4], Steven Gill[3], Omar Aljitawi[4]

[1]Stony Brook Cancer Center, State University of New York at Stony Brook, Stony Brook, United States, [2]Fred Hutchinson Cancer Center, Seattle, United States, [3]University of Rochester, Rochester, United States, [4]Wilmot Cancer Institute, University of Rochester, Rochester, United States

Background: We previously reported hyperbaric oxygen therapy (HBOT) decreases serum erythropoietin and may promote homing of transplanted umbilical cord stem cells to the bone marrow. Inspired by those results, we recently completed a multi-center randomized trial of HBOT vs. no intervention in patients with multiple myeloma (MM) undergoing autologous HCT. Given the high incidence of microbiota disruptions in these patients and their association with worse survival (Khan et al. Blood 2021), we conducted a supplementary pilot study to profile the microbiome in longitudinal samples from patients enrolled in the trial. Here we report our findings.

Methods: In this supplementary pilot study conducted at the Wilmot Cancer Institute, 10 patients with MM were randomized to HBOT (n = 4) before cell infusion on the day of transplant. vs. no intervention (n = 6). Melphalan 200 mg/m2 was given on day -1. Antibacterial prophylaxis (oral vancomycin and ciprofloxacin) was administered from the onset of neutropenia (days 5-8 in this trial) until neutrophil recovery to 0.5 k/uL or fever. Cefepime and metronidazole were used for neutropenic fever. Salivary samples were collected in both groups on days -1 (before melphalan), 0 (one sample before HBOT and one up to 8 hours after HBOT for the HBOT group), +1, +3, +7, +13, +30, and +100. Fecal samples were collected in both groups on days +1, +3, +7, and +13. The V3-V4 hypervariable regions of the 16S rRNA gene were profiled. Alpha and beta diversity were estimated using Shannon index and Aitchison distance. SplinectomeR was used to compare the longitudinal course of alpha diversity between the two arms. ALDEx2 was used for differential abundance analysis.

Results: A total of 123 samples (89 salivary and 34 fecal) were profiled. The main determinant of microbiota variation in both

salivary and fecal samples was collection day, with maximal compositional departure from baseline occurring at day 13 post-HCT. Treatment arm was another significant determinant of microbiota composition ($P < 0.001$ for saliva and $P = 0.03$ for stool, Adonis test with 999 permutations. While the baseline diversity of salivary microbiota was not significantly different between the 2 arms (Wilcoxon's $P = 0.26$), the longitudinal trajectory of diversity in the two arms diverged after the intervention, reaching a significant difference on days 3 and 9-10 post-HCT ($P = 0.02$ and 0.04, respectively, from 999 permuted splines. Although a similar trend was apparent in the stool microbiota, the difference between the arms did not reach statistical significance, likely due to smaller sample size. *Alloprevotella* and *Porphyromonas* genera were enriched in the saliva of the intervention arm. There was a trend for enrichment of obligate anaerobic commensal genera (e.g., *Faecalibacterium*, *Ruminococcus*, *Subdoligranulum*, *Agathobacter*), some of which are potent butyrate producers, in the stool of the intervention arm.

Conclusions: HBOT may affect salivary and fecal microbiota composition. HBOT appeared to decrease microbiota diversity loss after autologous HCT. Increased oxygen pressure near the intestinal epithelium after HBOT may make the lumen a more favorable habitat for obligate anaerobic commensals, hence their enhanced fecal detection.

Clinical Trial Registry: ClinicalTrials.gov #NCT03398200

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P522

LOW PLASMA CONCENTRATIONS OF INSULIN-LIKE GROWTH FACTOR-I ARE ASSOCIATED WITH INCREASED GUT DAMAGE DURING PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Maria Ebbesen Sørum[1], Katrine Kielsen[1], Marte Kammersgaard[1], Marianne Ifversen[1], Anders Juul[1], Klaus Müller[1]

[1]Copenhagen University Hospital Rigshospitalet, København Ø, Denmark

Background: Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) are challenged with severe side effects, which are propagated by mucosal barrier disruption causing microbial translocation and systemic inflammation. Insulin-like growth factor-1 (IGF-I) is a key factor in the repair of most tissues and have been found to protect against damage of the gut mucosa in rodents treated with chemotherapy, and reduced IGF-I plasma concentrations are found to be predictive of sinusoidal obstruction syndrome (SOS) following pediatric HSCT. To explore the underlying mechanisms of these associations we investigated the impact of IGF-I levels on gut mucosal integrity following HSCT by measurements of circulating citrulline as a marker of functioning enterocytes.

Methods: In this prospective population-based study we included 121 children undergoing HSCT. Median age was 8.8 years (range: 1.1-17.6), and 59% had a malignant diagnosis. Donors were matched siblings (28%) or matched unrelated donors (72%), and grafts were either BM (88%), PB (7%) or UCB (5%).

Conditioning groups were defined as high-intensity myeloablative conditioning (cyclophosphamide plus busulfan or TBI 12Gy) and low-intensity myeloablative conditioning (other chemotherapy-regimens with or without TBI 2Gy). Plasma concentrations of IGF-I and citrulline were measured before conditioning, at day of HSCT (day 0), at day +7, +14 and +21 post transplantation. Statistical analyses were performed with a mixed model with a compound symmetry covariance matrix and simple and multiple linear and logistic regression models. Sex- and age-adjusted SD-scores were calculated for IGF-I to account for the natural variations related to age and sex.

Results: IGF-I levels before as well as after conditioning were significantly reduced compared with healthy sex- and age-matched children, and low IGF-I levels at day of transplant (day 0) were associated with higher levels of maximum C-reactive protein (25% per IGF-I SDS decrease (95% CI 12–35%, $P < 0.001$)), number of platelet transfusions post-HSCT (22% per SDS decrease (13–29%, $P < 0.001$)), and increased risk of developing hyperbilirubinemia (OR = 1.7 (1.2–2.3, $P < 0.001$)) and SOS (the pediatric EBMT criteria: OR = 1.7 (1.3–2.5, $P = 0.001$)/SDS decrease). Citrulline levels declined significantly following conditioning reflecting a decrease in viable enterocytes with a nadir at day +7-14. Low levels of IGF-I at day 0 were associated with lower citrulline levels at day +7 and day +14, also after adjustment for type of conditioning (day +7: 1.2 µmol/L/IGF-I SDS (95% CI 0.6–1.7, $P < 0.001$) and day +14: 2.6µmol/L/IGF-I SDS (1.6–3.6, $P < 0.001$)). Furthermore, lower levels of citrulline at day +7 and day +14 were associated with increased risk of SOS diagnosed by the pediatric EBMT criteria (day +7: OR = 1.2 (1.1–1.3, $P = 0.003$) and day +14: 1.2 (1.1–1.2, $P < 0.001$) per µmol/L decrease in citrulline level).

Conclusions: These data suggest that high levels of IGF-I may protect against cytotoxic damage of the gastrointestinal epithelium, thereby ameliorating severity of systemic inflammation and the risk of SOS. Hence, the IGF-I pathway may represent a target for new preventive strategies to limit toxicity of HSCT.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P523

VON WILLEBRAND FACTOR AS A POTENTIAL PREDICTIVE BIOMARKER OF EARLY COMPLICATIONS OF ENDOTHELIAL ORIGIN AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Guillaume Dachy[1], Marine Vankeerbegen[1], Nicolas Vanlangendonck[1], Catherine Lambert[1], Nicole Straetmans[1], Xavier Poiré[1]

[1]Cliniques Universitaires Saint-Luc, Brussels, Belgium

Background: Early complications of endothelial origin after allogeneic hematopoietic cell transplantation (alloHCT) include a range of life-threatening complications. It is crucial to develop new tools to detect patients with endothelial vulnerability at risk of early mortality.

Methods: We conducted a retrospective study in order to assess the role of von Willebrand factor (VWF) as a potential predictive biomarker of transplant-related endothelial dysfunction.

We included all adult patients (n = 127) having received an alloHCT from February 2019 to November 2021. Diagnosis of transplant-related endothelial dysfunction, i.e., transplant associated thrombotic microangiopathy (TA-TMA), lung endothelial injuries (idiopathic pneumonia syndrome and diffuse alveolar hemorrhage), engraftment (ES) and capillary leak (CLS) syndromes, was assigned based on laboratory values and clinical features by performing systematic retrospective chart review. Turbidimetric assays of VWF antigen levels (VWF:Ag) and

of binding capacity of VWF to GPIbIX (VWF:RCo) were performed on day -4, day 0 and day +28 of the alloHCT.

Results: Median follow-up was 659 days (IQR: 430 - 905 days). The probability of relapse-free survival was 65% and overall survival (OS) was 67% at two years. 28 patients (22%) had at least one endothelial-related complication within a four-week window after alloHCT: 18 CLS, 10 TA-TMA and 7 ES. Lung-specific complications affected 11 patients. All conditioning regimens induced both synthesis and activation of VWF. Using univariate analyses, we found that a high VWF:RCo level on day -4 was associated with the occurrence of endothelial complications (Odds ratio, OR: 2.62, $p = 0.033$, for values above 200%), as well as elevated EASIX score and C-reactive protein level at day 0. Multivariate analyses showed that only VWF:RCo retained an independent impact on the occurrence of endothelial complications, with an OR of 2.44 ($p = 0.052$, 95% CI: 1.01 – 6.15). EASIX-pre had a more modest impact, with an OR of 2.33 ($p = 0.076$, 95% CI: 0.90 – 5.90). Interestingly, VWF:RCo elevation was also associated with a higher risk of sepsis.

Survival was strongly influenced by the occurrence of endothelial-related complications. In univariate analyses, VWF:RCo-pre, EASIX and CRP constituted risk factors for both survival and non-relapse mortality, even in patients not developing endothelial-related complications. Multivariate analyses confirmed the impact of the biomarkers. Regarding non-relapse mortality, we observed an elevation of the incidence of fatal acute lung injury in the elevated VWF:RCo group (5/12 NRM in VWF:RCo group, 0/8 in the low VWF:RCo group, $p = 0.054$).

Conclusions: Conditioning regimens increase VWF:Ag and VWF:RCo in alloHCT. Moreover, VWF:Rco > 200% four days before transplant appears to be a biomarker of endothelial vulnerability and a risk factor for the development of endothelial-related complications. Our data suggest also that CRP level and EASIX score on day 0 are important risk factors for these complications. Beyond being predictive for such severe complications, they were associated with survival and all causes' non-relapse mortality. If confirmed in a larger, multicentric clinical cohort, this could lead to the development of a revised EASIX-pre score, including VWF:RCo and CRP, to evaluate the degree of endothelial vulnerability, the probability of transplant-associated endothelial dysfunction and the risk of death after alloHCT.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P524

OPTIMIZING THE EASIX CAPACITY FOR PREDICTING NRM IN ADULTS UNDERGOING ALLO-HCT USING POST-TRANSPLANT CYCLOPHOSPHAMIDE

Silvia Escribano Serrat[1,2], Luis Gerardo Rodríguez-Lobato[2], Paola Charry[2], Andrea Rivero[2], Nuria Martínez-Cibrian[2], María Suárez-Lledó[2], Alexandra Pedraza[2], Jordi Arcarons[2], María Teresa Solano[2], Meritxell Nomdedeu[3], Joan Cid[3], Miquel Lozano[3], Laura Rosiñol[2], Jordi Esteve[2], Álvaro Urbano-Ispizua[2], Maribel Díaz-Ricart[4], Enric Carreras[5], Francesc Fernández-Avilés[2], Carmen Martínez[2], Montserrat Rovira[2], María Queralt Salas[2]

Hospital Clínico San Carlos, Madrid, Spain, Clinical Institute of Hematology and Oncology (ICMHO), IDIBAPS, Hospital Clínic Barcelona, Barcelona, Spain, [3]Apheresis & Cellular Therapy Unit, ICMHO, IDIBAPS, Hospital Clínic, Barcelona, Spain, [4]Hematopathology, CDB, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain, [5]Fundació i Institut de Recerca Josep Carreras contra la Leucèmia (Campus Clínic), Barcelona, Spain

Background: Higher Endothelial Activation and Stress Index (EASIX) values, measured before and after allo-HCT, have been correlated with higher NRM. However, a cut-off value of EASIX for a more accurate classification of high-risk patients for NRM has yet to be determined.

Since creatinine, LDH, and platelets, which are the variables included in the EASIX formula, vary during the post-transplant period, EASIX values will differ depending on the time-point when they are calculated. This study explores the predictive ability of EASIX for NRM in patients undergoing PTCY-based allo-HCT, including their classification into high and low-risk of NRM according to this prognostic index, considering that EASIX evolves over time.

Methods: Between 2014 and 2020, 201 consecutive adults undergoing allo-HCT using PTCY were included. EASIX [(creatinine*LDH)/platelets] was calculated before allo-HCT and on days 0, +7, +14, +21, +28, +100, and +180, and transformed to a base-2 logarithm to perform the statistical analysis.

Log2-EASIX trends were described using medians. The predictive ability for 2-years NRM was examined using the continuous variable log2-EASIX and a dichotomous "high EASIX value" calculated using maximally selected rank statistics, for distributing patients into high and low-risk groups. EASIX discriminatory ability was estimated using C-Index.

Results: The median age was 52, 40.3% patients received MAC regimens, and 54.2% received mismatched donor grafts. The 2-year OS and NRM were 69.0% and 16.4%.

Log2-EASIX values increased rapidly from days 0 to +7, peaked at day +21, and decreased progressively until day +180.

Higher values of log2-EASIX, measured before and after allo-HCT, correlated significantly with a higher risk for NRM, and with an increasing discriminative accuracy from day 0 to +180 (60.0% to 69.6%). The optimal cut-off for discriminating high-risk patients when EASIX was measured before allo-HCT (EASIX-PRE) was 3.0 (Log2-EASIX equivalence: 1.6). Patients with EASIX-PRE > 3.0 had higher NRM than those with ≤3.0 values (2-year NRM 33.7% vs. 12.1%, HR 3.00, $P = 0.0019$) (**Table 1**).

Using the cut-off value defined for discriminating high-risk patients before allo-HCT (EASIX-PRE: 3.0), patients were classified into two groups according to their respective EASIX values calculated from day 0 to +180. Next, the same classification was repeated using new cut-offs estimated from EASIX values measured at successive time-points. The maximum discriminating cut-offs for identifying high-risk patients were different from the EASIX-PRE cut-off, as expected considering that EASIX values varied along the transplant period. Moreover, using the recalibrated cut-off points the accuracy in the classification of high-risk patients increased (**Table 1**).

Conclusions:

- In patients receiving PTCY, patients with EASIX-PRE > 3.0 had an increased risk for NRM during the first two years after allo-HCT.
- EASIX trends varied throughout the first 180 days after allo-HCT, and higher values of EASIX correlated with a higher risk for NRM. These results support that EASIX is a dynamic biomarker capable to detect patients at high risk for mortality from day 0 to +180.
- The variation of EASIX during the post-transplant period recommends the recalibration of the cut-off values for stratifying high-risk patients for NRM at different time-points after allo-HCT.

Table 1. EASIX correlation with post-transplant outcomes and complications in adults receiving PTCY.

	Pre-Transplant N = 201	Day 0 N = 201	Day +7 N = 201	Day +14 N = 200	Day +21 N = 199	Day +28 N = 197	Day +100 N = 179	Day +180 N = 164
EASIX and Log2-EASIX trends during the early post-transplant period								
Median								
Creatinine (mg/dL)	0.75	0.67	0.56	0.60	0.69	0.83	0.90	0.90
LDH (U/L)	295	237	206	202	272	329	309	267
Platelets (x10^9/L)	162	123	25	25	31	55	85	120
Median (IQR)								
EASIX	1.30 (0.77-2.46)	1.35 (0.77-2.47)	4.68 (2.19-9.39)	4.94 (2.06-11.10)	5.95 (2.44-12.49)	5.73 (2.22-12.66)	3.21 (1.77-7.68)	1.88 (1.16-3.63)
Log2-EASIX	0.38 (-0.36-1.30)	0.43 (-0.37-1.30)	2.22 (1.13-3.23)	2.30 (1.04-3.47)	2.57 (1.28-3.64)	2.51 (1.15-3.66)	1.68 (0.82-2.94)	0.91 (0.22-1.86)
Correlation between Log2-EASIX value (continuous variable) and NRM								
2-year NRM Continuous value								
HR (95% CI)	1.27 (1.06-1.54)	1.41 (1.21-1.64)	1.70 (1.28-2.25)	1.41 (1.15-1.72)	1.44 (1.14-1.81)	1.39 (1.09-1.78)	1.51 (1.13-2.02)	1.99 (1.18-3.38)
P value	0.009	<0.001	<0.001	<0.001	0.001	0.008	0.005	0.010
C-index	0.594	0.655	0.678	0.665	0.680	0.666	0.707	0.703
Correlation between Log2-EASIX value and NRM according to the optimal cut-off for each time-point								
EASIX								
Cut-off points	3.0	2.1	9.5	6.3	19.6	9.0	5.7	1.9
Log2-EASIX	1.6	1.0	3.2	2.7	4.3	3.8	2.5	0.9
2-year NRM								
HR (95% CI)	3.00 (1.49-6.01)	3.28 (1.64-6.56)	6.78 (1.71-26.79)	2.56 (1.25-5.23)	3.52 (1.69-7.33)	3.26 (1.53-6.93)	3.75 (1.25-11.27)	7.50 (0.93-60.07)
P value	0.001	<0.001	0.006	0.009	<0.001	0.002	0.018	0.057
C-index	0.603	0.647	0.65	0.627	0.624	0.662	0.671	0.696
Estimated 2-year NRM								
Low-risk	12.1 (7.5-17.7)	10.3 (5.9-16.2)	10.2 (5.9-15.7)	10.4 (5.6-16.8)	11.6 (7.1-17.3)	9.4 (4.9-15.6)	5.4 (2.2-10.9)	1.2 (0.1-6.0)
High-Risk	33.7 (19.1-49.0)	30.0 (18.9-42.0)	34.8 (21.7-48.3)	24.1 (15.3-34.0)	34.3 (19.1-50.1)	25.1 (15.4-35.9)	14.0 (6.5-24.4)	10.3 (4.8-18.4)
P value	0.001	<0.001	<0.001	0.009	<0.001	0.001	0.034	0.018
Correlation between Log2-EASIX value and NRM using a permanent cut-off (Log-EASIX PRE > 1.6 / EASIX > 3.0)								
2-year NRM								
HR (95% CI)	Not applicable	2.61 (1.27-5.36)	4.12 (1.44-11.73)	1.94 (0.84-4.47)	2.65 (1.03-6.84)	2.27 (0.87-5.91)	2.18 (0.66-7.14)	1.49 (0.34-6.41)
P value		0.009	0.008	0.12	0.043	0.093	0.2	0.59
C-index	Not applicable	0.585	0.622	0.573	0.600	0.579	0.607	0.566

EASIX Endothelial Activation and Stress Index; *log2-EASIX* EASIX base-2 logarithm; *LDH* lactate dehydrogenase; *IQR* interquartile range; *NRM* non-relapse mortality; *HR* hazard ratio; *CI*: confidence interval; *C-index* concordance index.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P525

ELTROMBOPAG IS AN EFFECTIVE TREATMENT OF POOR GRAFT FUNCTION AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A GITMO SURVEY

Maura Faraci[1], Filomena Pierri[1], Simona Sica[2], Sabrina Giammarco[2], Maurizio Musso[3], Alessandra Crescimanno[3], Alessandra Biffi[4], Elisabetta Calore[4], Fabio Benedetti[5], Martina Montagnoli[5], Raffaella Cerretti[6], Anna Paola Iori[7], Irene Maria Cavattoni[8], Franca Fagioli[9], Francesco Saglio[9], Angela Cuoghi[10], Arcangelo Prete[11], Carlo Borghero[12], Veronica Tintori[13], Maria Chiara Sanvito[13], Francesco Paolo Tambaro[14], Stefania Bramanti[15], Cristina Skert[16], Gaetana Porto[17], Nicola Mordini[18], Alessandra Piccardi[19], Francesco Merli[20], Luca Facchini[20], Fabrizio Pane[21], Giorgia Battipaglia[21], Matteo Pelosini[22], Maria Cristina Menconi[22], Bianca Serio[23], Valentina Giudice[24], Michele Cimminiello[25], Eliana Degrandi[26], Angela Gheorghiu[27], Massimo Martino[28], Fabio Ciceri[29]

[1]IRCCS Istituto G. Gaslini, Genova, Italy, [2]A. Gemelli University Hospital Foundation IRCCS, Rome, Italy, [3]La Maddalena Hospital, Palermo, Italy, [4]Padua University Hospital, Padova, Italy, [5]Verona Integrated University Hospital, Verona, Italy, [6]Tor Vergata University Hospital, Rome, Italy, [7]Sapienza University of Rome, Rome, Italy, [8]Santa Chiara Hospital, Trento, Italy, [9]AOU City of Health and Science of Turin, Torino, Italy, [10]AOU of Modena Policlinico, Modena, Italy, [11]IRCCS University Hospital of Bologna, Bologna, Italy, [12]S. Bortolo Hospital, Vicenza, Italy, [13]AOU Meyer, Firenze, Italy, [14]Santobono Pausilipon Hospital, Napoli, Italy, [15]Humanitas Clinical Institute, Milano, Italy, [16]Ospedale dell'Angelo, Venezia, Italy, [17]Grande Ospedale "Bianchi-Melacrino-Morelli, Reggio Calabria, Italy, [18]S. Croce e Carle Hospital, Cuneo, Italy, [19]A. Cardarelli Hospital, Napoli, Italy, [20]Arcispedale S. Maria Nuova AUSL-IRCCS, Reggio Emilia, Italy, [21]AOU Federico II, Napoli, Italy, [22]Pisa University Hospital, Pisa, Italy, [23]University Hospital "San Giovanni di Dio e Ruggi D'Aragona", Salerno, Italy, [24]University Hospital "San Giovanni di Dio e Ruggi D'Aragona, Salerno, Italy, [25]S. Carlo Hospital, Potenza, Italy, [26]Trial Office GITMO, Bologna, Italy, [27]San Raffaele, IRCCS San Raffaele Scientific Institute, Milano, Italy, [28]Grande Ospedale "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy, [29]University Vita-Salute San Raffaele, IRCCS San Raffaele Scientific Institute, Milano, Italy

Background: Poor Graft function (PGF) is defined as poor or absent bone marrow function after allogeneic Hematopoietic Stem Cell Transplantation (HSCT). PGF is characterized by the persistence of at least 2 of the following conditions: hemoglobin (Hb) level less than 10 g/dl, neutrophil granulocytes (N) less than 1000 /mmc and platelets (Plt) less than 30.000/cm^3 occurring from day 30 after HSCT in patients with full donor chimerism and without graft versus

host disease (GvHD). The aim of this survey was to describe different therapeutic approaches for PGF in pediatric and adult GITMO (Gruppo Italiano Trapianto di Midollo Osseo) centers.

Methods: 25 Italian HSCT centers (28,5% pediatric) participated to this survey including 14 questions. The response to PGF therapies was defined as complete response (CR) when Hb level, N and Plt increase above normal range; partial response (PR) when transfusion independence occurred but the hematological value was lower than normal; no response (NR) in absence of hematological response.

Results: 24/25 Centers reported PGF. PGF was reported more frequently after haploidentical or Matched Unrelated Donor (MUD) transplant performed for acute leukemias, MDS or lymphoma after a Myeloablative CR. PGF was more frequent in adult patients (64%).

G-CSF was administered in 21/25 HSCT centers, in 84% at dose of 5 gamma/Kg, in 8% at dose of 10 gamma/Kg and in 8% centers at dose of 30 gamma/Kg.

Spontaneous resolution of PGF was reported in 32%.

The infusion of boost of Hematopoietic Stem Cells (HSC) was performed in 15/25 centers (60%) followed by CR in 53% of cases, PR in 20% and NR in 27%. In 6/15 GvHD occurred after this procedure.

Danazole was used only in one center to cure PGF.

Eltrombopag was administered off-label in 18/25 centers. During Eltrombopag therapy were reported mild side effects including gastrointestinal symptoms (61% of centers), psychiatric symptoms (22%), muscle-skeletal symptoms (22%), hepatic dysfunction (16%), and ocular problems (16%). Overall response after Eltrombopag was 73%, CR was reported in 66% and PR in 55 % NR in 27% with eltrombopag therapy.

Conclusions: The most practiced treatments for PGF were G-CSF (84% of centers), eltrombopag (72%) and boost of donor HSC (60%). Eltrombopag efficacy warrants a prospective trial in this specific setting of bone marrow aplasia.

Disclosure: no conflict of interest.

14 - Non-infectious Early Complications

P526

VENO-OCCLUSIVE DISEASE AFTER HSCT: THE IMPACT OF NEW DIAGNOSTIC CRITERIA, ULTRASOUND AND ELASTOGRAPHY FINDINGS

Alba Puyuelo[1], Pablo Prieto Martínez[1], Teresa Fontanilla[1], Javier Minaya[1], Iñigo Pérez-González[1], Ana Belén Bocanegra[1], Carlos de Miguel[1], María Esther Martínez-Muñoz[1], Rosalía Alonso[1], Guiomar Bautista[1], Rafael Francisco Duarte[1]

[1]Puerta de Hierro Majadahonda University Hospital, Majadahonda, Spain

Background: The diagnosis of veno-occlusive disease (VOD) remains primarily based on clinical features. As the profile of allogeneic HSCT and recipients changes, new clinical presentations of VOD are becoming more common and require revised criteria with the support of novel diagnostic tools. Our aim is to revise our VOD experience using newer diagnostic criteria, and our findings from radiology techniques, including ultrasound, doppler and elastography (UDE).

Methods: We retrospectively collected clinical, laboratory, and UDE data of allogeneic HSCT recipients diagnosed with severe VOD at our center treated with defibrotide over a ten-year period (2012-2022). We applied both EBMT's 2016 and Cairo's 2020 criteria. Statistical analysis complies with EBMT guidelines.

Results: The incidence of severe VOD in our series is 15.5% (39 out of 252 allogeneic HSCT). At baseline, VOD cases had a median CIBMTR risk score of 2.02% (range 0.52-6.25), median EASIX score of 4.1 (range 0.4-49.5), and none of them had abnormal liver function tests or known liver disease. Most patients had UDE performed at baseline (37, 95%; median stiffness 4.9 kPa, IQR 4.2-5.9), and thereafter as required clinically. Only a minority had pretransplant UDE abnormalities. The use of the new Cairo criteria led to the diagnosis of a relatively large percentage of anicteric VOD cases (61.5%; median overall bilirubin 1.4, IQR 0.6-2.2), which fulfill VOD diagnosis a median of two days earlier than using the current EBMT criteria (IQR 0-4). Diagnostic UDE were suggestive or confirmatory of VOD in 23 cases (59%), with an increased liver stiffness of 17.3 kPa (11.9-25.3). These patients started defibrotide within one day from diagnosis. Of note, for the whole set of cases, treatment delay from VOD diagnosis to initiation of defibrotide was one day (IQR 0-2.5), but for the group of VOD cases with normal UDE imaging, it was four days (IQR 1.8-6.8; $p = 0.003$). Median defibrotide treatment duration was 15 days (IQR 10.5-22). Thirteen VOD patients required ICU admission (33%) at a median of four days from diagnosis (IQR 1.5-5). Most VOD cases responded to defibrotide (29,74%). Nine patients died from VOD (23%), for a total all-cause mortality of 26% at day +90. Thirty-one cases (80%) were monitored following the initial UDE diagnostic test, with a median of two additional tests (IQR 1-3). Five out of eight patients with a normal first diagnostic UDE (62.5%) developed imaging abnormalities in the following 10 days. Clinical improvement with defibrotide associated to improvement in radiological findings. Finally, in patients who died from VOD, liver stiffness did not improve from 15.1 kPa (IQR: 6.3-18.6) at diagnosis to 16.3 kPa (IQR: 12-36.6) during follow-up.

Conclusions: The traditional features of VOD do not accurately reflect current clinical presentations of this disease. Our data support the need for updated diagnostic criteria that include an increasing percentage of anicteric presentations, that incorporate novel radiological results to help diagnosis, and that recognize the dynamic nature of these clinical and imaging findings, in order to identify patients timely, avoid delays in treatment and improve patient outcomes.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P527

OUTCOMES OF VENO-OCCLUSIVE DISEASE (VOD) IN INFANTS AND TODDLERS POST-HEMATOPOIETIC STEM CELL TRANSPLANT (HCT)

Miki Nishitani[1], Kyle Hebert[2], Donna Neuberg[2], Kathleen Doherty[2], Emily Bakinowski[2], Christine N. Duncan[1]

[1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, United States, [2]Dana-Farber Cancer Institute, Boston, United States

Background: Younger age is a recognized VOD risk factor, yet no prior studies have focused on outcomes of VOD in the infant and toddler population.

Methods: This retrospective study compared the overall survival (OS) in young children clinically diagnosed with and without VOD, and additionally compared OS for those with clinical VOD, those not diagnosed with clinical VOD but retroactively met either EBMT, modified Seattle (MS), or Baltimore criteria (BC), and those without clinical VOD nor met VOD criteria. Described are also the acute care utilization in those with clinical VOD. Included were patients who received their first HCT for any indication at age ≤ 3 years between January 1, 2016 and October 31, 2021. The pediatric EBMT, MS, and BC were used to retroactively determine if subjects met VOD criteria by Day +100, +21, and +20 post-HCT. Autologous and allogeneic HCT recipients were analyzed separately. Post-HCT characteristics and outcomes were described for allogeneic recipients only, due to insufficient follow-up in the autologous recipients.

Results: Of 150 HCT recipients [89 allogeneic and 61 autologous], 18 were clinically diagnosed with VOD [14 (15.7%) allogeneic, 4 (6.6%) autologous] at a median of 14d [2-23d] post-HCT. Defibrotide was given to 15 (83%) patients. All patients survived to hospital discharge. Age at HCT was lower in patients who developed VOD than those who did not in autologous recipients [median 1.1y vs 2.5y, $P = 0.02$]. All allogeneic recipients who developed VOD received a busulfan-based conditioning regimen. Recipient sex, race, ethnicity, graft type, conditioning intensity, and use of cyclophosphamide and TBI were similar between the cohorts in both autologous and allogeneic HCT recipients.

In allogeneic recipients, OS at Day +365 [100% vs 98.7%, $P = 0.69$], cumulative incidence of acute GVHD at Day +100 [21.4% vs 17.6%, $P = 0.70$], and chronic GVHD at Day +365 [22.1% vs 22.0%, $P = 0.87$] were similar between those with and without clinical VOD. Median length of stay was longer in those with VOD versus those without [60.5d vs 38d]. More patients with VOD were admitted to the intensive care unit [79% vs 15%]. Of the 14 patients with VOD, 11 (79%) required peritoneal fluid drainage, 3 (21%) required pleural effusion drainage, and 9 (64%) developed respiratory failure requiring intubation.

More patients retroactively met criteria for VOD than were clinically diagnosed, with EBMT criteria capturing the most patients (Table 1).

Table 1. Clinical Diagnosis of VOD Compared to Retrospective EBMT, Modified Seattle, and Baltimore Criteria in HCT Recipients

	Autologous HCT Recipients (n = 61)	Allogeneic HCT Recipients (n = 89)
Clinically diagnosed VOD, no. (%)		
No	57 (93)	75 (84)
Yes	4 (7)	14 (16)
EBMT criteria met, no. (%)		
No	50 (82)	44 (49)
Yes	11 (18)	45 (51)
Modified Seattle (MS) criteria met, no. (%)		
No	55 (90)	65 (73)
Yes	6 (10)	24 (27)
Baltimore criteria (BC) met, no. (%)		
No	55 (90)	74 (83)
Yes	6 (10)	15 (17)

Conclusions: While VOD in young children can be highly morbid, the majority have promising survival probabilities at 1-year post-HCT. Retroactive evaluation demonstrates that only a portion of patients who met various VOD criteria were captured. Further work is needed to understand the sensitivity and specificity of these definitions in this younger aged cohort.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P528

HIGH-RISK TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY (TA-TMA), SINGLE CENTRE EXPERIENCE

Maria Gabelli[1,2], Manuela Tumino[1], Chiara Mainardi[1], Antonio Marzollo[1], Elisabetta Calore[1], Marta Pillon[1], Anna Colpo[1], Piero Marson[1], Giovanni Montini[3], Enrico Vidal[1], Germana Longo[1], Davide Maneghesso[1], Annalisa Angelini[2], Gianluigi Ardissino[3], Alessandra Biffi[1,2]

[1]Padova University Hospital, Padova, Italy, [2]University of Padova, Padova, Italy, [3]Ospedale Maggiore Policlinico, Milano, Italy

Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is a significant cause of morbidity and mortality in patients after hematopoietic stem cell transplantation (HSCT). TA-TMA incidence is not precisely known, also because a consensus on diagnostic criteria has been lacking until recently. A recent work (*Schoettler M et al, TCT 2022*) provided harmonized diagnostic and risk stratification criteria that can be applied also when sC5b9 measurement, essential for risk stratification by Jodele criteria, is not available (*Jodele S et al, TCT 2022*). We report our single centre experience in TA-TMA, diagnosed and stratified based on these revised criteria.

Methods: We included children transplanted at our Institution between Jan 2020 and Jan 2022, when sequential screening for TA-TMA was implemented, although sC5b9 determination was not available. Informed consent for data collection was signed by legal guardians.

Results: Among 41 children who received allogeneic HSCT, TA-TMA was diagnosed in 5 (12%). Table I shows the characteristics of the patients and the transplants. TA-TMA was diagnosed at median 182 days post HSCT. Confirmatory renal biopsy was performed at diagnosis in patients 4 and 5, and during treatment in patients 2 and 3. All 5 children presented at least one high-risk feature: elevated LDH (4/5), refractory hypertension (3/5), proteinuria (2/5), acute kidney injury (2/5), concurrent graft versus host disease (GVHD) (2/5), concurrent viral infection (2/5). One patient presented with polyserositis (cardiac, pleural and ascitic fluid). Four patients were diagnosed with GVHD before the onset of TA-TMA; in these patients the first intervention was to interrupt treatment with calcineurin inhibitors and administer mycophenolate mofetil and methylprednisolone 1-2 mg/kg/day. Eculizumab was initiated as first line treatment in all patients within 1 week from diagnosis, with a response in 2/5 patients (40%). The other 3 patients presented very difficult-to-treat TA-TMA and underwent multiple lines of treatment (Table I). Eventually, a response to treatment was seen in all patients: cessation of hemolysis (4 responders out of 4 affected patients), blood pressure control (3/3), normalization of platelet counts (2/4), improvement of renal function and reduced proteinuria (3/4). In patient 5 a slow improvement of renal function in terms of reduction of dialysis need was observed 4 months after the initiation of the last line of treatment. At a median follow up of 362 days from HSCT, 3/5 (60%) patients are alive; patient 1 died of leukemia relapse, patient 3 died of sepsis following multiple lines of treatment with concurrent remission of TA-TMA.

Conclusions: Following implementation of screening, 12% of our allogeneic HSCT patients could be diagnosed with TA-TMA with high risk features, even without sC5b9 assessment. Despite the timely administration of Eculizumab, more than half of them did not respond and required multiple lines of treatment, including an experimental drug under compassionate program (Narsoplimab). This intense approach allowed resolution of TA-TMA in all the patients at the cost of important toxicity and morbidity, including a death of sepsis. There is an unmet need for efficacious treatments for TA-TMA; the implementation of diagnostic criteria that can be widely applicable poses the bases for robust clinical trials.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P529

INCIDENCE OF LGL AFTER USING DUAL T CELL DEPLETION (ATG AND PTCY) AND ITS' CORRELATION WITH LONG TERM OUTCOME

Ptn°	gender	Age at HSCT	Diagnosis	Conditioning	Donor type, source	GVHD prophylaxis	aGVHD, organ and maximal grade	cGVHD	Days from HSCT to TA-TMA	Diagnosis	HR features	First line treatment	Time from Ta-TMA diagnosis (days)	Second line treatment	Time from TA-TMA diagnosis (days)	Third line treatment	Time from TA-TMA diagnosis (days)	Fourth line treatment	Time from TA-TMA diagnosis (days)	Fifth line treatment	Time from TA-TMA diagnosis (days)	Sixth line of treatment	Time from TA-TMA diagnosis (days)	Outcome	Follow up from HSCT (days)
1	F	17.4	Secondary MDS/AML	TBI, Melphalan, ATG, Rituximab	Haplo, CD19 and TCR αβ depletion PBSC	none	Skin, grade II	no	95	Clinical	Elevated LDH, concurrent viral infection, concurrent GVHD	Eculizumab	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Death, AML relapse. No GVHD nor TMA at time of death	214
2	F	9.6	ALL, HR	TBI, TT; Cy, ATG	MUD 11/12, PBSC (cryopreserved)	CSA, MTX	Skin, grade I	no	111	Histological	Nephrotic proteinuria, refractory hypertension, elevated LDH, polyserositis	Eculizumab, (Switch CSA to MMF)	5	Methylprednisolone 2 mg/kg/die	39	Defibrotide	73	Narsoplimab	102	Methylprednisolone, 20 mg/kg for 3 days and plasma exchange	116	Rituximab	156	Death, sepsis. Improvement of hypertension and hemolysis	307
3	M	8.4	ALL, relapse	TBI, TT; Cy, ATG	MUD 11/12, PBSC (cryopreserved)	CSA, MTX	Skin and gut, grade III	Moderate, Skin, lung	330	Histological	Nephrotic proteinuria, refractory hypertension, elevated LDH	Eculizumab + Methylprednisolone 2 mg/kg/die (Switch CSA to MMF)	5	Rituximab and plasma exchange	58	Defibrotide	89	NA	NA	NA	NA	NA	NA	Alive, off therapy, residual proteinuria with normal renal function, stable cGVHD	776
4	M	14.8	XLP2	Treo, TT, Flu, ATG, Rituximab	Haplo, CD19 and TCR αβ depletion PBSC	none	no	no	328	Histological	Acute kidney injury	Eculizumab	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Alive, off therapy, residual proteinuria and mild chronic renal disease	668
5	F	9.2	ALL, HR	TBI, TT; Cy, ATG	MUD 11/12, BM	CSA, MTX	Skin, grade II	Moderate, skin and lung	182	Histological	Refractory hypertension, acute kidney injury, elevated LDH, concurrent viral infection, concurrent GVHD	Eculizumab (Switch Tacrolimus to MMF)	2	Plasma exchange	8	Defibrotide	25	Methylprednisolone 10 mg/kg (only 1 dose due to positive Adenovirus DNA)	47	Narsoplimab	55	NA	NA	Alive, off therapy, severe chronic renal disease	362

Vered Stavi[1], Rawan Al-Omari[2], Eshetu G. Atenafu[2], Auro Viswabandya[2]

[1]Soroka Medical Center, Beer Sheva, Israel, [2]Princess Margaret Cancer Centre, Toronto, Canada

Background: Large granular lymphocytosis (LGL) is a chronic mature lymphoproliferative disorder of T or NK cells. Patients post allogeneic stem cell transplant (Allo-HSCT) may develop LGL presenting either with cytopenia or lymphocytosis or a combination of both. In several retrospective studies association of LGL post-transplant appear to have improved transplant outcomes, however the results have not been consistent.

Our standard GVHD prophylaxis since 2015 is dual T-cell depletion using a combination of ATG and Post Transplant Cyclophosphamide (ATG+ PTCy).

Methods: This is a single centre retrospective analysis of all consecutive Allo-HSCT patients between Jan 2015-March 2020. LGL was diagnosed with their characteristic flow cytometry results.

Results: Out of 726 transplanted patients, 110 patients developed LGL (15.44%). Median follow-up was 25.25 months (Range: 0.43-88.04). Table 1 shows the characteristics of patients who developed LGL and those who didn't. Incidence of LGL was higher in patients using dual T cell depletion. as GVHD prophylaxis (74.55% vs 64.29%, $p = 0.0196$). There was no other statistically significant differences between both groups (LGL vs Non-LGL). Clonality study was done in 39/110 patients and monoclonality was detected in 84.7%.

2-years OS was significantly better in those who developed LGL vs. who did not(85.4% vs 53.1%, $P < 0.0001$), even after censoring the data for patients who died before Day +100, the OS was still superior in the LGL group (OS in 12, 24 and 60 months 91.8%, 85.4% and 78.6% vs. 69.3%, 60.4% and 52% $P < 0.0001$).

Patients with LGL also had a superior 2-year RFS (76.3% vs 48.4%; $p < 0.0001$) and 2-year GRFS (71.1% vs 40.1%; $p < 0.0001$) with lower NRM (6.4% vs 28%; $p < 0.0001$) compared to non-LGL group.

The GRFS in 12, 24 and 60 months was 0.854, 0.767, 0.690 Vs 0.792, 0.625, 0.573 in the dual vs non dual groups.

There was no significant difference in the cumulative incidence of acute GVHD grades II-IV, III-IV and overall chronic GVHD at 2 years between the two groups.

Only 12 (10.9%) patients needed treatment for significant cytopenia.

Table 1. Patient Characteristics comparing LGL with NON-LGL patients

	LGL (N = 110)	NON-LGL (N = 616)	P-value
Age at Diagnosis (Years)			0.2406[1]
Median (Range)	58.13 (22.86, 70.90)	56.50 (-86.75, 76.43)	
Diagnosis, n (%)			0.1148[2]
Others	33 (30.00%)	228 (37.01%)	
AML	65 (59.09%)	298 (48.38%)	
MDS	12 (10.91%)	90 (14.61%)	

	LGL (N = 110)	NON-LGL (N = 616)	P-value
Gender, n (%)			0.0840[2]
Female\ Male	56 (50.91%) \54 (49.09%)	259 (42.05%) \357 (57.95%)	
Donor_Type, n (%)			0.1797[2]
Haplo	20 (18.18%)	78 (12.66%)	
MRD	26 (23.64%)	185 (30.03%)	
URD	64 (58.18%)	353 (57.31%)	
Source, n (%)			0.1588[2]
BM	1 (0.91%)	21 (3.41%)	
PB	109 (99.09%)	595 (96.59%)	
GVHD_PROPH, n (%)			0.0196[2]
dual T-cel depletion	82 (74.55%)	396 (64.29%)	
single T-cell depletion	24 (21.82%)	145 (23.54%)	
others	4 (3.64%)	75 (12.18%)	

[1]Unequal variance two sample t-test; [2]Chi-Square p-value;

Conclusions: With the limitation of the retrospective nature of our study, our study showed that patients who got dual T cell depletion had higher incidence of LGL. Patients with LGL had superior outcome (better OS, RFS, GRFS and less NRM) in comparison to those who did not.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P530

INTENSIVE CARE UNIT UTILIZATION AND OUTCOMES IN STEM CELL TRANSPLANT PATIENTS DURING INITIAL TRANSPLANT HOSPITALIZATION

Rachel Cook[1], Staci Williamson[1], Jessie Myers[1], LeeAnn Farestrand[1], Alexandria Hodges Dwinal[1], Robert Ahrenkiel[1], Chi Phan[1], Maryam Rezaie[1], Brandon Hayes-Lattin[1], Arpita Gandhi[1], Jennifer Saultz[1], Jessica Leonard[1], Yazan Migdady[1], Andy Chen[1], Levanto Schachter[1], Laura Newell[1], Jennifer Smith[1], Gabrielle Meyers[1], Richard Maziarz[1]

[1]Oregon Health and Science University, Portland, United States

Background: Intensive Care Unit (ICU) access and utilization is a potentially lifesaving resource for patients undergoing stem cell transplant (SCT). Utilization patterns and patient outcomes have evolved over time. This single-institution retrospective study provides evidence of improved survival over time and identification of risk factor for ICU deaths in a large academic center.

Methods: Between 1/1/2016 and 9/16/2022, 1527 adult subjects underwent SCTs. All transfers to ICU during initial transplant admission were recorded and analyzed to evaluate overall survival and outcome status. Pre-transplant factors assessed included age, sex, transplant type, co-morbidity (HCT-CI) score and type, and performance status. ICU length of stay and intubation status were used to categorize all patients transferred to the ICU to determine if any of these factors or events were predictive of overall survival. Subjects who did not require ICU care and those who received outpatient preparative regimen were not included.

Results: 102/1527 (6.7%) subjects were transferred to the ICU during initial transplant admission. Demographic table below:

	Patients who required ICU care during initial SCT admit (regardless of outcome) (n = 102)
SCT Type	65 Allogeneic (63.7%) 37 Autologous (36.3%)
Sex	Male: 53 (52.0%) Female: 49 (48.0%)
Age (Years)	18 – 77 (Median = 61)
KPS	30 – 100 (Median = 80; 7 Unknown)
Overall HCT-CI Score	0 – 10 (Median = 3; 4 Unknown)
Pre-SCT Pulmonary Comorbidity	14 Severe (13.7%) 32 Moderate (31.4%) 52 None (51.0%) 4 Unknown (3.9%)
Pre-SCT Cardiac Comorbidity	18 Yes (17.7%) 80 No (78.4%) 4 Unknown (3.9%)
ICU Length of Stay (Days)	1-54 (Median = 5)
Intubation in the ICU	47 Yes (46.1%) 55 No (53.9%)

Median Overall Survival = 1.09 years
1 Year Survival = 51.1%

Conclusions: Infrequent utilization of the ICU is seen in the adult SCT population during initial transplant admission. However in those patients requiring ICU care, there is a high level of early mortality with subjects requiring intubation and mechanical ventilation leading to a striking level of early death, particularly among patients requiring intubation. Of the patients requiring ICU care who died during initial admission, only 1 of 40 patients died of recurrent/persistent disease. All other (39/40) patients died as an early complication of transplant. Although this patient cohort spanned a wide range of ages, performance status and HCT-CI, all patients had a life expectancy greater than 100 days without transplant and consequently their lives were shortened by undergoing transplant. Risks for death in the ICU identified in multivariate analysis included HCT-CI of > 3, intubation and pulmonary comorbidity. Patients who survived the ICU stay were markedly more likely to be alive at 1 year if they had undergone autologous versus allogeneic transplant and if their ICU stay was 4 days or less. The finding that patient age did not influence outcome in the ICU may reflect the differing intensities of pre-transplant conditioning in different age cohorts with differing durations of cytopenias and intensity of tissue damage. Patient characteristics that are identified pre-transplant will help provide improved pre-transplant and peri-hospitalization guidance from SCT providers regarding risks and benefits of ICU care, including intubation. Further study of ICU care and decision making is warranted in this cohort of patients with resource intensive treatment.

Disclosure: Nothing to Declare.

14 - Non-infectious Early Complications

P531

PRE-TRANSPLANT ANTI-CD20 MONOCLONAL ANTIBODY THERAPY AFFECTS THE DONOR-DERIVED HEMATOPOIETIC COMPARTMENT IN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) RECIPIENTS

Dimana Dimitrova[1], Jennifer Sponaugle[1], Ruby Sabina[1], Mark Roschewski[1], Christopher Melani[1], Jennifer Kanakry[1]

[1]*National Institutes of Health, Bethesda, United States*

Background: Anti-CD20 monoclonal antibodies may be used as a low toxicity bridge to HCT for patients with low-grade B-cell neoplasms or B-cell-driven immune dysregulation, or as an adjunct to multiagent chemotherapy in patients with aggressive B cell malignancy. While delayed onset neutropenia (DON) is a known potential side effect, its occurrence in engrafted HCT recipients who only received the therapy prior to HCT and not after has not been well described or understood.

Methods: Children and adults with immune deficiency or dysregulation enrolled on either of two protocols at our center (clinicaltrials.gov: NCT02579967, NCT03663933) were included if they had a history of ever receiving anti-CD20 monoclonal antibody therapy and were alive and engrafted with at least 6 months follow up post-HCT (n = 23). Routine evaluations performed in follow up included complete blood counts and a bone marrow biopsy at 60 +/− 3 days post-HCT. All patients received reduced intensity conditioning, T-replete grafts, and post-transplantation cyclophosphamide-based GVHD prophylaxis. Twelve patients had a history of proximal anti-CD20 monoclonal antibody therapy within 90 days of HCT (approximately 4 rituximab half-lives), 7 within a year of HCT, and 4 over a year prior to HCT (Table 1). Post-engraftment grade 3-4 DON with nadir absolute neutrophil counts (ANC) below 500/mL with or without intervention or 500-1000/mL with intervention were recorded and attributed to prior CD20-directed therapy if clinical trajectory and ancillary evaluations did not reveal another clear and plausible etiology.

Results: Nine patients (39%) developed DON attributed to prior anti-CD20 therapy, in absence of otherwise poor graft function, with median post-HCT onset day of 108 (34-216) and at median 153.5 days (55-205) from last infusion (Table 1). Notably, DON occurred in 67% of patients with proximal anti-CD20 exposure and only one patient with more distal therapy. Nearly half of patients recovered without growth factor therapy, and only minor complications occurred: cellulitis treated with oral antibiotics in one patient and culture-negative short-lasting febrile neutropenia in another. Two patients coincidentally underwent their protocol-mandated bone marrow biopsies on the same day as DON onset. In both, a disrupted granulocyte maturation pattern was reported. CD20 + B cells were increased in the marrow of the first patient and noted in the periphery for the first time on the same day, so DON coincided with the beginning of marrow B cell output. In the second patient, CD20+ cells were absent in the marrow, while B cell precursors abounded and rare mature B cells were evident, but no peripheral B cells were detected. This patient initially responded to a single dose of filgrastim before developing agranulocytosis confirmed with repeat marrow evaluation. Agranulocytosis resolved 2 weeks after starting daily filgrastim and stopping trimethoprim-sulfamethoxazole. Given initial response followed by worsening, two separate processes were suspected in this patient.

Table 1. Patient, HCT, and Delayed Neutropenia Characteristics

	All patients (n = 23)	Timing of anti-CD20 therapy exposure prior to HCT		
		≤90 days (n = 12)	91-365 days (n = 6)	>365 days (n = 5)
PATIENT CHARACTERISTICS				
Age at HCT, median years (range)	25 (4-62)	24.5 (4-54)	25 (11-37)	42 (18-62)
Indication for HCT, n (%)				
IEI, known defect	13 (57%)	8 (67%)^	2 (33%)*	3 (60%)@
Cytopenias, unknown defect	2 (9%)	0	1 (17%)	1 (20%)
Lymphoma/LPD, unknown defect	7 (30%)	4 (33%)	2 (33%)	1 (20%)
Poor viral control, unknown defect	1 (4%)	0	1 (17%)	0
Indication for anti-CD20 therapy, n (%)				
Lymphoma/LPD	16 (70%)	10 (%)	4 (67%)	2 (40%)
Cytopenias	5 (22%)	2 (%)	1 (17%)	2 (40%)
Other immune dysregulation	3 (13%)	0	1 (17%)	2 (40%)
Anti-CD20 therapy, n (%)				
Rituximab	23 (100%)	12 (100%)	6 (100%)	5 (100%)
Obinutuzumab	1 (4%)	1 (8%)	0	0
Total no. infusions, median (range)	6 (2-29)	7 (2-29)	6 (3-16)	6 (2-8)
Days pre-HCT of last infusion, median (range)	90 (19-3650)	40 (19-90)	190 (112-270)	1195 (382-3650)
HCT CHARACTERISTICS				
Conditioning				
PC/Bu2	14 (61%)	8 (67%)	4 (67%)	2 (40%)
Equine antithymocyte globulin/ PC/Bu2	9 (39%)	4 (33%)	2 (33%)	3 (60%)
Graft, n (%)				
T-replete marrow	11 (48%)	6 (50%)	4 (67%)	1 (20%)
T-replete PBSC	12 (52%)	6 (50%)	2 (33%)	4 (80%)
Donor, n (%)				
Matched related donor	1 (4%)	0	0	1 (20%)
Matched unrelated donor (8/8)	16 (70%)	8 (67%)	5 (83%)	3 (60%)
Mismatched unrelated donor (7/8)	1 (4%)	0	1 (17%)	0
Haploidentical	5 (22%)	4 (33%)	0	1 (20%)
Chronic GVHD on systemic IS post-HCT, n (%)	0	0	0	0
Systemic IS at 6 months post-HCT, n (%)	3 (13%)	0	2 (33%)%	1 (20%)%
FEATURES OF POST-ENGRAFTMENT NEUTROPENIA ATTRIBUTED TO PRIOR ANTI-CD20 THERAPY (DON)$				
DON, n patients (%)	9 (39%)	8 (67%)	1 (17%)	0
Post-HCT day of onset, median (range)	108 (34-216)	99 (34-153)	216	-
Days from last infusion to onset, median (range)	159 (55-418)	153.5 (55-205)	418	-
Clinical features				
Duration ANC < 1000/mL, median days (range)	18 (6-63)	21.5 (7-63)	6	-
Duration ANC < 500/mL, median days (range)	10.5 (4-19)	11 (4-19)	6	-
Nadir, median cells/mL (range)	170 (0-600)	230 (0-600)	10	-
Growth factor therapy, n (%)	5 (55%)	4 (50%)	1 (100%)	-

Abbreviations: *ANC* absolute neutrophil count; *IEI* inborn error of immunity; *IS* immunosuppression; *LPD* lymphoproliferative disorder; *PC/Bu2* pentostatin, low dose cyclophosphamide, 2 days busulfan.

^Genetic defects: *PIK3CD* n = 3; n = 1 each: *RAG1/2, MAGT1, WAS, CTLA4*, 22q11.2 deletion.

*Genetic defects: *RAG1/2* n = 1; *CTLA4* n = 1; *IKZF1* n = 1.

@Genetic defects: *RAG1/2* n = 1; *LRBA* n = 1.

%Systemic steroids for cryptogenic organizing pneumonia (n = 1), acute GVHD (n = 1), GVHD prophylaxis (n = 1).

$Recorded if nadir <500/mL or 500-1000/mL with intervention.

Conclusions: The timeline of DON in this cohort of HCT recipients, as well as the minimal infectious complications, are consistent with that seen in the non-HCT setting. However, the occurrence of anti-CD20 therapy-associated DON affecting donor-derived hematopoiesis indicates complex and long-lasting consequences for the marrow milieu and thus merits further study.

Clinical Trial Registry: clinicaltrials.gov: NCT02579967, NCT03663933

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P532

RISK FACTORS FOR TRANSPLANT ASSOCIATED THROMBOTIC MICROANGIOPATHY (TA-TMA) AMONG PATIENTS WITH PHILADELPHIA POSITIVE (PH +) LEUKEMIAS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANT

Sachin Punatar[1,2], Komal Kumbhalwar[1], Siddhesh Kalantri[1], Anant Gokarn[1,2], Lingaraj Nayak[1,2], Akanksha Chichra[1,2], Sumeet Mirgh[1,2], Nishant Jindal[1,2], Libin Mathew[1], Sadhana Kannan[1], Navin Khattry[1,2]

[1]ACTREC, Tata Memorial Centre, Navi Mumbai, India, [2]Homi Bhabha National Institute, Mumbai, India

Background: We have previously reported that pre-transplant use of tyrosine kinase inhibitors (TKIs) is independently associated with the occurrence of transplant associated thrombotic microangiopathy (TA-TMA). However, the precise TKI related factors which predispose to occurrence of TA-TMA are unknown. In this retrospective analysis, we tried to identify the TKI related factors that are associated with the occurrence of TA-TMA in Ph+ leukemias undergoing allogeneic stem cell transplant (ASCT).

Methods: This was a single centre retrospective analysis of all patients with Ph+ leukemias who received BCR-ABL TKIs prior to transplant and underwent ASCT between January 2008 and March 2019. Demographic details of patient and donors, details of conditioning chemotherapy, cell doses infused, occurrence of acute or chronic GVHD, occurrence and timing of TA-TMA, and survival outcomes were retrieved. Definite TA-TMA was defined as per BMT-CTN criteria and probable TMA as per Cho criteria. Details about timing (date or month) of start and stop of TKI pre-transplant, dose of TKIs used and number of TKIs exposed pre-transplant were obtained. Imatinib >400 mg/day, dasatinib > 100 mg/day or nilotinib > 800 mg/day were considered as high dose TKI.

Results: Seventy-two patients with median age 28.5 years and 53 (74%) males underwent transplant in the above period. Patients were divided in 2 groups - those with TA-TMA and those without. These 2 groups were well matched with respect to all demographic parameters, donor characteristics and transplant characteristics. Overall, 13 (18%) patients had TA-TMA at a median of day+128 post-transplant; 9 definite TMA and 4 probable TMA. There was no difference between those with and without TMA with respect to the number of TKIs used pre-ASCT, median duration of use and timing of stop prior to transplant. Of the 67 patients with available data about the dose of TKI, 46 (68%) patients had received high dose TKI. Twelve (26%) of these 46 developed TMA compared to 1 (4.7%) of 21 who had not received high dose TKI ($p = 0.04$). Among the non-TKI related factors, acute GVHD was associated with increased risk of TA-TMA. On multivariate analysis, the use of high dose TKI was associated with an Odds Ratio (OR) of 4.6, although this did not remain statistically significant ($p = 0.16$). The accuracy of a model to predict occurrence of TA-TMA using high dose TKI and acute GVHD was 80%. Those with TA-TMA had a significantly worse 10-year survival (15% vs 60%, $p = 0.003$).

Conclusions: While our group has shown earlier that pre-transplant use of TKIs increased the risk of TA-TMA in patients undergoing ASCT, it is the interplay of the dose of TKI used with acute GVHD that predicts the highest risk of its occurrence. Prospective studies are warranted to confirm the impact of pre-transplant TKI dose and TA-TMA. TA-TMA was associated with significantly worse long-term survival.

Clinical Trial Registry: Not applicable

Disclosure: No conflicts of interest (for all the authors).

14 - Non-infectious Early Complications

P533

THE VALIDATION OF SIMPLIFIED COMORBIDITY INDEX FOR PREDICTION OF NON-RELAPSE MORTALITY

Eun-Ji Choi[1], Han-Seung Park[1], Jung-Hee Lee[1], Je-Hwan Lee[1], Kyoo-Hyung Lee[1], Young-Shin Lee[1], Young-A Kang[1], Mijin Jeon[1], Ji Min Woo[1], Hyeran Kang[1], Yunsuk Choi[1]

[1]Hematology Section, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of

Background: Allogeneic hematopoietic cell transplantation (HCT) outcomes have been improved year by year. HCT-comorbidity index (CI) has been used as a tool for predicting risks of non-relapse mortality (NRM) following HCT for many years. However, the new simplified CI was recently introduced and demonstrated to stratify risk groups for NRM at MSKCC and Sheba Medical Center cohorts. Thus, we aimed to validate the simplified CI in patients who had received HCT at our institution.

Methods: We retrospectively analyzed the HCT registry data of 1677 patients with hematologic malignancy or bone marrow failure syndrome who had undergone HCT with unmanipulated grafts between 2008 and 2019 at the Asan Medical Center, Seoul, Korea. We excluded patients who did not have comorbidity data. The simplified CI and HCT-CI were evaluated in our cohort on multivariate analyses for NRM and overall survival (OS).

Results: The median age was 46 years (range, 15-75). In all included patients, the NRM and OS rates after HCT were 19.4% and 46.8% at 5 years, respectively. The myeloablative and reduced intensity conditioning regimens were treated in 19.2% and 80.8% of patients, respectively. In the univariate analyses, the 5-year NRM rates according to the HCT-CI (0, 1, 2, 3, and ≥ 4) were 8.3%, 22.9%, 15.1%, 17.2%, and 23.4%, respectively ($P < 0.001$). The increase in HCT-CI did not correlate to the rise in NRM in the univariate and multivariate analyses. Although there were significant differences in NRM according to the simplified CI (0, 1, 2, 3, and ≥ 4) with 17.9%, 15.5%, 16.0%, 24.2%, and 28.5% at 5 years ($P < 0.001$), the score 0-2 of the simplified CI did not stratify the risks of NRM. In multivariate analysis, the simplified CI (≥ 3) was an independently significant factor for NRM (hazard ratio [HR], 1.68, $P < 0.001$) and OS (HR, 1.39, $P < 0.001$). In addition, donor age (≥ 50 years) was a significant adverse factor for NRM (HR, 1.37, $P = 0.22$) and OS (HR, 1.22, $P = 0.23$). Aplastic anemia (AA) (HR, 2.11, $P < 0.001$) and myelodysplastic syndrome (MDS) (HR, 1.96, $P < 0.001$) were associated with higher NRM risks compared to acute leukemia. Higher-risk disease was also a significant risk factor for NRM (HR, 1.79, $P < 0.001$) and OS (HR, 2.73, $P < 0.001$). (Table 1)

Table 1. Multivariate analysis for NRM and OS

	NRM HR (95% CI)	p-value	OS HR (95% CI)	P-value
Age				
≥ 60 vs. <60	1.21 (0.91-1.62)	0.190	-	
Simplified Comorbidity Index				
≥ 3 vs. 0-2	1.68 (1.34-2.12)	**<0.001**	1.39 (1.21-1.59)	**<0.001**
Diagnosis				
AML	1		1	
ALL	0.88 (0.62-1.26)	0.490	1.27 (1.07-1.51)	**0.006**
AA or PNH	2.11 (1.39-3.22)	**<0.001**	0.89 (0.43-0.81)	**0.001**
MDS	1.96 (1.44-2.66)	**<0.001**	0.79 (0.65-0.96)	**0.016**
Others	1.21 (0.85-1.73)	0.290	1.09 (0.90-1.33)	0.362
Disease risk				
High vs. Standard	1.79 (1.42-2.26)	**<0.001**	2.73 (2.38-3.13)	**<0.001**
Donor age				
≥ 50 vs. <50 years	1.37 (1.05-1.80)	**0.022**	1.22 (1.03-1.44)	**0.023**

Conclusions: In our cohort, the simplified CI could not subdivide the risk of NRM into four groups according to the score. However, the simplified CI (≥ 3), AA or MDS, higher risk disease status, and older donor age (≥ 50 year) were significant predictors for NRM and OS after HCT.

Disclosure: Nothing to disclose.

14 - Non-infectious Early Complications

P534

RELATIONSHIP OF FLUID OVERLOAD IN THE PERITRANSPLANT PERIOD WITH ADVERSE OUTCOMES IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTS

Mateusz Kubarek[1,2], Beata Piątkowska-Jakubas[2,3], Daria Zawirska[2], Marcin Sobociński[2,3], Tomasz Sacha[2,3], Piotr Pierzchalski[4], Patrycja Mensah-Glanowska[2,3]

[1]Jagiellonian University Medical Collage, Doctoral School of Medical and Health Sciences, Krakow, Poland, University Hospital in Krakow, Krakow, Poland, Jagiellonian University Medical College, Krakow, Poland, Jagiellonian University Medical College, Krakow, Poland

Background: Fluid overload (FO) is commonly observed in patients undergoing allogenic hemopoietic stem cell transplantation (alloHSCT). FO may be a consequence of different pathologies - conditioning regimen and other drugs toxicity, endothelial activation, and damage, proinflammatory immune response, and others. There are still scanty data on the impact of fluid overload in the peri-transplantation period on outcome in population of patients subjected to alloHSCT, particularly in those who do not meet the criteria for diagnosis of sinusoidal obstruction syndrome.

Methods: On purpose of the study 91 patients transplanted in 2 years period January 2018 to December 2019 at the BMT Unit of Hematology Department University Hospital in Krakow were retrospectively analyzed. Diagnostic criteria for fluid overload developed by Rondón et al. 2017 were adopted in the study, however FO grade O was added and defined by weight gain <2% of baseline weight and considered physiological variation. The primary endpoint of the study was overall survival, with the cut-off at 36 months after transplantation. To evaluate impact of conditioning regimen toxicity on FO – patients' data were analyzed using MAC, RIC or non-myeloablative categories and chemo- vs TBI-based regimen as well as modern assessment of transplant conditioning intensity -TCI score (Spyridonidis at al. 2019). Endothelial activation was assessed using EASIX score calculation. Additionally, relationship between FO and HCT-CI was analyzed. For statistical analysis Shapiro-Wilk, Spearman's rank order correlation, probability of Survival Kaplan-Meier's tests, were used.

Results: Results: Study group included 91 patients, median age 50 (range 19-69). All but 3 patients were diagnosed with hematological malignancies: AML/MDS 49, ALL 15, MDS-MPN/MPN 10, MF 8, NHL/HD 6. Two patients were subjected to alloHSCT because of aplastic anemia and one patient was transplanted because of CSF1R-related leukoencephalopathy. Almost 2/3 of study population were males 57/91. Among the analyzed patients, around half of them ($n = 46$) experienced fluid overload in the peri-transplantation period. Majority of patients experienced grade 1 FO, $n = 39$. The primary endpoint of 3-year OS was achieved by 58.2% of subjects: 71% with Grade 0 FO, 51% with Grade 1 FO, 40% with Grade 2 FO, 0% with Grade 3 FO.

In univariate analysis FO correlated with mortality ($R = 0.306747$, $p = 0.003103$), TRM ($R = -0.322729$, $p = 0.001808$), and 2-yr OS ($R = -0.277839$, $p = 0.007665$) as well as HCT-CI ($R = -0.228882$, $p = 0.029089$), preconditioning EASIX score ($R = 0.243934$, $p = 0.019799$), and TCI ($R = 0.342323$, $p = 0.0008896$) and TCI score code ($R = 0.249400$, $p = 0.018124$). Statistically significant correlations were not found between FO and age of patients, diagnosis, HLA compatibility, as well traditionally divided conditioning intensity (MAC, RIC and NMA). There were no FO differences between patients conditioned with chemo-based and TBI-based regimens.

Conclusions: The results of the study showed that FO in the peri-transplantation period impact on survival in alloHSCT patients. Using grading system - increase in FO may predict worse OS and higher TRM. Pre-transplant factors: HCT-CI, EASIX preconditioning, and TCI as those correlating with FO might be used to early identify high risk patients predisposed for FO enabling the implementation of preventive strategies.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P535

NUTRITIONAL ENERGY REQUIREMENTS IN PEDIATRIC PATIENTS UNDERGOING STEM CELL TRANSPLANTATION MEASURED BY INDIRECT CALORIMETRY

Louise Lindkvist Pedersen[1], Katrine Kielsen[1], Maria Ebbesen Sørum[1], Karin Kok[1], Tania Nicole Masmas[1], Marianne Rosenkrantz Ifversen[1], Christian Mølgaard[1,2], Klaus Gottlob Müller[1,3]

[1]Rigshospitalet, University Hospital, Copenhagen, Denmark, [2]Institute of Nutrition, Exercise and Sports, University of Copenhagen, Frederiksberg, Denmark, [3]Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Background: Nutritional therapy is considered an important part of the management of HSCT in children, but as numerous factors related to this treatment may alter nutritional requirements compared with healthy children the use of standard equations for calculation of the energy requirements may be misleading. A combination of high-dose chemotherapy and, in some cases, total body irradiation (TBI) before transplantation and acute GvHD is anticipated to increase energy requirements while immobilization

of the patients during the isolation regimen may reduce energy requirements.

The aim of this study was to compare resting energy expenditure (REE) measured by IC with REE estimated by use of the currently applied standard equations.

Methods: We included 12 children (9 males) undergoing allogenic HSCT for benign diseases (n = 9) or acute leukemia (n = 3) with a median age of 11 years (range: 8-18). Conditioning regimens were TBI-based (n = 2) or high-dose chemotherapy alone (n = 10).

REE was measured by IC before conditioning, at day 0, between day 7-14, between day 21-28 and at day +90. The REE measured by IC was compared with REE estimated by use of The Oxford Equation for healthy children based on the patients' weight at referral to transplant. The energy intake, both enteral and parenteral nutrition (PN) as well as iv fluids, was recorded in parallel to assess the degree of energy coverage.

Results: The measured REE decreased during the early phase of transplantation reaching a nadir at day 7-14. Generally, these levels were below the estimated needs according to The Oxford Equation and this was most pronounced on day 0 ($P = 0.04$) and day 7-14 ($P = 0.004$).

Next, we examined to what degree the measured REE are covered by energy intake. In all patients dietary intake was reduced at least at one assessment during the study period, being most pronounced in the very early phase. At day 0, before PN was initiated, the median intake was only 35% of the IC measured REE (range: 17-86%, $P \leq 0.001$) and, mainly covered by iv fluids containing glucose, with a median of 85 % of the supplied energy from carbohydrate (range: 58-100 E%). At day 7-14, 90% (11/12) of the patients received PN, the measured REE was met in 33% of the patients. At day 21-28, 50% of the patients remained on PN, however only 22% of the patients' REE was met, while on day 90, all patients were off PN, meeting a full coverage by enteral intake in 5/7 patients (71%).

Conclusions: Our findings suggest that the currently used equation for estimating the REE may lead to an overestimation when planning the nutritional support in pediatric HSCT patients. However, despite using the more conservation estimates based on IC, energy needs are not met sufficiently in a significant proportion of the patients, emphasizing the need for an increased focus on dietary support to enable reconstitution of the overall metabolic homeostasis.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P536

OUTCOMES FOLLOWING SECOND ALLOGENEIC STEM CELL TRANSPLANT FOR GRAFT FAILURE OR POOR GRAFT FUNCTION: A SINGLE CENTRE EXPERIENCE

Jowon L. Kim[1], Moss A. Bruton Joe[1], Shanee Chung[1,2], Donna L. Forrest[1,2], Kevin Hay[1,2,3], Florian Kuchenbauer[1,2], Stephen Nantel[1,2], Sujaatha Narayanan[1,2], Thomas J. Nevill[1,2], Maryse M. Power[1,2], Judith Rodrigo[1,2], David Sanford[1,2], Kevin W. Song[1,2], Ryan J. Stubbins[1], Heather J. Sutherland[1,2], Cynthia L. Toze[1,2], Jennifer White[1,2], Yasser Abou Mourad[1,2], Claudie Roy[1,2]

[1]University of British Columbia, Vancouver, Canada, [2]The Leukemia/ Bone Marrow Transplant Program of British Columbia, Vancouver, Canada, [3]Terry Fox Laboratory, BC Cancer Research Institute, Vancouver, Canada

Background: Graft failure is a rare but life-threatening complication following allogeneic hematopoietic stem cell transplantation (HSCT). We reviewed the outcomes of patients who underwent a second HSCT (HSCT2) for graft failure or poor graft function following an initial HSCT (HSCT1) in Vancouver, British Columbia.

Methods: We conducted a retrospective chart review on adult patients who received HSCT2 for graft failure or poor graft function between February 2001 and July 2021. Primary graft failure (PGF) was defined as failure to achieve ANC > $0.5x10^9$/L by day+30 with associated pancytopenia. Secondary graft failure (SGF) was defined as development of significant cytopenias after achieving initial engraftment. Poor graft function was defined as multilineage cytopenias requiring transfusion and/or growth factors in the presence of full donor chimerism (> 95%). Survival functions were estimated using Kaplan-Meier method (SPSS version 28).

Results: A total of 21 patients were identified; 10 with PGF and 11 with SGF. In those with SGF, the median time from engraftment after HSCT1 to SGF was 2.5 months (range:1-99). In the 14/21 patients in whom chimerism data was available, 10 had absent donor chimerism, 2 had mixed chimerism, and 2 had full donor chimerism. The median age at time of HSCT2 was 48 years (range:19-70). The median time between HSCT1 and HSCT2 for PGF was 51.5 days and between diagnosis of SGF and HSCT2 was 64 days. Matched unrelated donor was the most common donor type (33%) and the same donor was used in 23.8%. Peripheral blood was the most common stem cell source (85.7%). The most frequently used conditioning regimen was Cy-ATG +/−TBI(200cGy) (42.9%); the remainder received various reduced intensity regimens. All patients received calcineurin inhibitor-based GVHD prophylaxis with either methotrexate or MMF. The median follow-up for survivors was 118 months (range:6-167). Overall survival (OS) at 1 year was 51.9% with a median of 31.0 months. Death before day+30 occurred in 4 patients (19.0%). Of the 12 patients who died, the cause of death was infection in 8 patients, GVHD in 2, hepatic veno-occlusive disease in 1, and relapse in 1. Non-relapse mortality (NRM) was the major cause of treatment failure, with a 1-year NRM of 48.1%. Relapse occurred in 3 patients (14.3%). All patients who lived beyond day+30 successfully engrafted, with a median time to neutrophil recovery of 22 days (range:11-31). Two patients subsequently developed SGF and both underwent third allotransplant. The incidence of grade I-II acute GVHD was 52.9% in the 17 patients who survived beyond day+30, and incidence of chronic GVHD was 46.7% in the 15 patients who survived beyond day+100. There was a trend towards higher NRM and lower OS in patients with PGF compared to those with SGF, but this was not statistically significant.

Table 1. Selected characteristics for second transplants performed for graft failure or poor graft function following a first allogeneic stem cell transplantation

Stem cell source	
Peripheral blood	18 (85.7%)
Bone marrow	3 (14.3%)
Donor type	
Matched related	4 (19.0%)
Matched unrelated	7 (33.3%)
Mismatched unrelated	3 (14.3%)
Haploidentical	6 (28.6%)
Other	1 (4.8%)
Median number of CD34 x 10^6/kg infused	6.56 (range 3.5-20)
Conditioning regimen	
Cy-ATG +/− TBI(200 cGy)	9 (42.9%)
Flu-Treo/ATG	4 (19.0%)
Flu-Cy +/- TBI(200 cGy)/PT-Cy	4 (19.0%)
Flu-Cy	2 (9.5%)
Flu-Bu/Pt-Cy	2 (9.5%)
Other	1 (4.8%)

Stem cell source	
Conditioning intensity	
Myeloablative	9 (42.9%)
Reduced intensity	12 (57.1%)
GVHD prophylaxis	
CSA-MTX	10 (47.6%)
CSA-MMF	2 (9.5%)
Tac-MTX	1 (4.8%)
Tac-MMF	6 (28.6%)
MTX	2 (9.5%)

Conclusions: Similar to previously published literature, these data show that a second allotransplant for graft failure/poor graft function is associated with high NRM and early mortality. Nonetheless, there are long-term survivors and further studies should focus on improving NRM in these patients.

Disclosure: Kevin Hay: Research funding (Janssen), Advisory Boards (BMS, Janssen, Kite/Gilead, Novartis).

Shanee Chung: Honoraria from Takeda, Astellas, Novartis.

All other authors: Nothing to declare.

14 - Non-infectious Early Complications

P537

VARIATION IN EASIX SCORE AS A PREDICTOR OF SINUSOIDAL OBSTRUCTION SYNDROME AND OVERALL SURVIVAL

Guillermo Ramos Moreno[1], Esther Parra Virto[1], Adolfo Jesús Sáez Marín[1], Ana Jiménez Ubieto[1], Pilar Martínez Sánchez[1], Jose María Sánchez Pina[1], Paula Lázaro del Campo[1], Magdalena Corona de la Puerta[1], Tycho Stephan Baumann[1], Joaquín Martínez López[1], Alberto Blanco Sánchez[1], Rodrigo Gil Manso[1], Rafael Colmenares Gil[1], Daniel Gil Alós[1], Reyes Mas Babío[1], Lucía Medina de Alba[1], Andrea Tamayo Soto[1], María Calbacho Robles[1]

[1]Hospital Universitario 12 de Octubre, Madrid, Spain

Background: Allogenic stem cell transplantation (Allo-SCT) is a potentially curative treatment for malignant and non-malignant hemopathies, however, it is associated with significant morbimortality. In order to predict the risk of developing these complications, a variety of scores have been developed, such as HCT-CI, SCI, EBMT-Risk or EASIX.

The EASIX score, a simple marker of endothelial disfunction that was initially envisioned as a prognostic factor at the moment of diagnosis of aGVHD, has been able to predict NRM and the risk of other complications when applied before the start of conditioning for allo-SCT (EASIX-PRE). We hypothesized that the variation in EASIX score between the start of conditioning and at day 0 (Delta-EASIX) could be related to the development of sinusoidal obstruction syndrome (SOS) and with overall survival (OS).

Methods: Single-centre retrospective analysis. We included 84 patients who underwent allo-SCT at Hospital Universitario 12 de Octubre in Madrid, Spain, between January 2018 and March 2022. Each patient's EASIX score was calculated at admission for allo-SCT (EASIX-PRE) and at day 0 of transplant (EASIX day 0). We calculated an optimal cut-off point for prediction of SOS using a ROC curve, (corresponding with a value of EASIX variation of +0.72 points). We stratified patients in two groups, a high risk Delta-EASIX group (HR-D-EASIX, variation > 0.72 points) or standard risk Delta-EASIX group (SR-D-EASIX, variation ≤ 0.72 points).

Table 1: Patient Characteristics	
Gender	**n (%)**
Male/Female	47/37 (56/44)
Median age at transplant (range)	53.5 (17-67)
Previous diagnosis	**n (%)**
NHL/HL	8/9 (9.5/10.7)
AML/MDS	31/10 (36.4/11.9)
ALL	11 (13.1)
OTHER	15 (17)
Conditioning type	**n (%)**
RIC/ MAC	53/31 (63%/37%)
HLA status	**n (%)**
Haploidentical	48 (57.1)
MRD/MURD	24 /12 (28.6/14.3)
EASIX-PRE	
Mean (SD)	**Median (Range)**
1.81 (2.20)	1.12 (0.15-13.5)
DELTA-EASIX	
Mean (SD)	**Median (Range)**
1.32 (2.37)	0.65 (-2.97-13.47)

We then registered cases diagnosed of sinusoidal obstruction syndrome and measured overall survival in months in both groups, comparing overall survival with Kaplan-Meier analysis.

Results: Patient characteristics are summarized in Table 1

A total of 14 patients (16%) developed SOS, 8 of them (57%) very severe SOS (leading to death in all cases), 2 (15%) moderate SOS, and 4 (30%) mild SOS, as per EBMT 2016 criteria. Patients in the high risk Delta-EASIX group had a significantly higher proability of developing SOS (6% in the standard-risk group vs 26% in the high risk group, $p = 0.015$), In patients with very severe SOS, mean Delta-EASIX was significantly higher (0.95, $p = 0.03$).

Patients in the high risk Delta-EASIX group had a lower OS (Estimated mean 32 months vs 42 months, $p = 0.048$, median OS not reached in either group).

Conclusions: Our study suggests variation in EASIX score between the start of the conditioning chemotherapy and day 0 can be related with a higher risk of developing sinusoidal obstructive syndrome and of presenting a reduced overall survival. Limitations of this study include a small number of participants and the absence of multivariate analysis. We believe further studies with a larger number of participants may confirm this relationship and solidify the use of Delta-EASIX as a predictor of SOS.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P538

RETROSPECTIVE ANALYSIS AND COMPARISON OF SINUSOIDAL OBSTRUCTION SYNDROME DIAGNOSIS CRITERIA: CAN WE ANTICIPATE DIAGNOSIS?

Monica Cabrero[1,2], María Cortes[1,2], Estefania Perez-Lopez[1,2], Ana Africa Martin[1,2], Almudena Cabero[1,2], Monica Baile[1,2], Alejandro Avendaño[1,2], Ana Garcia-Bacelar[1,2], Cristina de Ramon[1,2], Marina Acera[2], Lourdes Vazquez[1,2], Fermin Sanchez-Guijo[1,2], Lucia Lopez-Corral[1,2]

[1]Salamanca University Hospital, Salamanca, Spain, [2]IBSAL, Salamanca, Spain

Background: Post-allogeneic transplant (AlloSCT) sinusoidal obstruction syndrome (SOS) can lead to high mortality. Early diagnosis and treatment improve outcome. Classic Seattle/ Baltimore criteria and EBMT criteria published in 2016 (EBMT16) can underestimate anicteric SOS/VOD and ultrasound (US) findings are only partially considered in EBMT16. In 2020, Cairo et al. suggested inclusion of platelets transfusion refractoriness (PlatTR) and ultrasounds (US) findings to early diagnose SOS cases lacking classical findings, but it has not been widely validated.

Methods: Retrospective analysis of all SOS diagnosed in our center after EBMT16 publication to compare different criteria and its impact on patients' diagnosis.

Results: We identified 21 SOS/VOD cases out of 527 AlloSCT (3.98%). Main characteristic are summarized in Table1.

Median time to SOS diagnosis was 17 days (3-125) and diagnosed was based on EBMT16 (n = 12; 57%), modified Seattle criteria (n = 8; 38%) or Cairo criteria (n = 1; 5%). Seven patients (33%) were diagnosed after day +21. Bilirubin was over 2mg/dL at some point in 17 patients (81%), with previous bilirubin over upper institutional limit (UNL) in 15 (71%). In 6 patients, bilirubin was below 2mg/dL at SOS diagnosis. Weight gain >5% and right upper quadrant pain were present in 16 patients (76%) and PlatTR in 12 (57%). Liver biopsy confirming diagnosis was available in 2 patients with late SOS.

When retrospectively reviewed, diagnosis based on Cairo criteria anticipates SOS diagnosis in 18 patients with a median of 4 days (1-16). This earlier diagnosis was based on evidence of PlatTR (n = 7; 33%), bilirubin USL (n = 15; 71%) or US finding (n = 7; 33%).

Regarding US, it was performed in the first 24 hours of SOS suspicion in 14 patients (67%); ascites (95%) and hepatomegaly (86%) were the most common findings. Diagnosis was based on US in 7 (33%), with hepatomegaly and ascites evidenced by US and not in physical examination in 13 (62%) and 14 (67%) cases. Gallbladder wall thickening was observed in 16 patients (76%). Reversal portal flow and high resistance in hepatic arteria were present in 4 (19%) and 5 (24%) respectively.

Severity was mild in 3 (14%), moderate in 3 (14%), severe in 6 (28%) and very severe in 9 (42%). Fourteen patients received Defibrotide for a median of 21 days whereas 7 were conservatively managed. SOS resolved in 14 patients after a median of 29 days (4-133) and 7 patients early died due to SOS in 5, progression disease in 1 and alveolar hemorrhage in 1. There were 3 late deaths due to progression disease, with no long-term complications due to SOS. Estimated overall survival at 12 months was 47% for the whole group and 75% for those who responded to treatment.

	Median (range) OR n (%)
Age	46 (22-70)
Diagnosis	Acute lymphoblastic leukemia 6 (28%) Acute myeloid leukemia 2 (9%) Non-Hodgkin lymphoma 3 (14%) Myelodysplastic syndrome 2 (9%) Hodgkin lymphoma 1 (5%) Multiple Myeloma 1 (5%) Chronic myeloid leukemia 1 (5%)
Donor	Haploidentical 11 (52%) Identical sibling 6 (29%) Matched Unrelated 4 (19%)
Conditioning regimen	Myeloablative 5 (24%) Reduced Intensity 16 (76%)
GVHD prophylaxis	Tacrolimus/postAlloSCT Cy 11 (53%) Tacrolimus/Sirolimus 7 (33%) Tacrolimus/MTX 3 (14%)
Number of risk factors for SOS/VOD	One 14 (67%); Two 5 (24%); 3 (14%)
Most common risk factors for SOS/ VOD	High ferritin level 6 (28%) 2nd AlloSCT 4 (19%) Previous Inotuzumab 3 (14%)
Median time to SOS/VOD diagnosis (days)	EBMT16 18 (6-125) Modified Seattle 16 (3-125) Cairo 14 (1-125)
Median time from Cairo to EBMT16 diagnosis	4 (1-16)
Ultrasound-based diagnosis	7 (33%)

Conclusions: Cairo criteria anticipates SOS in most patients. However, diagnosis based on PlatTR should be carefully considered given its high prevalence in the early post-AlloSCT.

Anicteric SOS remains a challenge when using EBMT16 criteria. Considering Bilirubin UNL could be a solution.

Based on our experience, US is a fundamental tool in SOS/VOD patients, and it should be mandatory in SOS clinical or analytical suspicion.

Disclosure: First author have received speaker honoraria from Jazz pharmaceuticals.

14 - Non-infectious Early Complications

P539

LOW DOSE DEFIBROTIDE WITH HIGH DOSE METHYLPREDNISOLONE IN MANAGEMENT OF SINUSOIDAL OBSTRUCTION SYNDROME IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Pranoti Kini[1], Rajesh Patil[1], Ratna Sharma[1], Amit Jain[1], Ashutosh Walawalkar[1], Santosh Khude[1], Poulami Das[1], Mamta Manglani[1]

[1]MCGM Comprehensive Thalassemia Care, Pediatric Hematology Oncology and BMT Centre, Mumbai, India

Background: Sinusoidal obstruction syndrome (SOS) is a life-threatening endothelial complication following hematopoietic stem cell transplantation (HSCT). Fluid restriction, diuresis and defibrotide are the standard of care. However, defibrotide is very expensive and not easily available. We present our data on use of low dose defibrotide in combination with high dose methylprednisolone (MPS) inchildren with SOS.

Aim: To evaluate the effectiveness of low dose defibrotide with high dose methylprednisolone for management of SOS in children undergoing HSCT.

Methods: We reviewed the charts of all pediatric HSCTs performed between June 2018 to October 2022. The new pediatric EBMT criteria were applied for diagnosis of SOS, identifying the risk factors and grading of severity. All patients received ursodeoxycholic acid as SOS prophylaxis. Fluid restriction and diuretics were the first line management for all patients who developed mild SOS, and all others received a combination of low dose defibrotide (400mg x 1 day followed by 200mg/day x 2 days followed by 100mg/day x 4 - 7 days in 4 divided doses) with high dose MPS (500 mg/m2 for 3 days f/b tapering over 7 days).

Results: A total of 241 children underwent 248 transplants (7 patients underwent second transplant). SOS was observed in 17 of them (6.8%). Six were autologous transplants (35.2%) and 11 were allogenic (64.7%). The median age of thecohort was 10 years (2-16 years) and male to female ratio of 3.25:1. The median weight of the cohort was 23 kg (8-53 kg). Severity of SOS was very severe in one patient (5.8%), severe in ten (58.8%), and mild and moderate in 3 (17.6%) patients each[rs1]. The median time of occurrence of SOS was 12 days after HSCT (3-41 days). 5 patients responded to fluid restriction and diuretics. Low dose defibrotide alone was given in 3 patients in view of suspected sepsis.

Low dose defibrotide with high dose MPS was given to 9/17 (52.9%) patients. Median time from the suspicion of SOS to start of MPS was one day(0-6 days) and to start of defibrotide was also one day (0-8 days). The median duration of defibrotide administration was 5.5 days (1-9 days). All patients had complete recovery with this strategy. The median time to complete recovery was 8 days (2-14 days). There were no significant adverse effects of defibrotide or MPS, or mortality due to SOS in our cohort.

Conclusions: Prompt identification of SOS and early intervention with low dose defibrotide with high dose methylprednisolone is a safe and cost-effective strategy to manage sinusoidal obstruction syndrome in pediatric HSCT.

Disclosure: No conflict of interest to disclose.

14 - Non-infectious Early Complications

P540

PURE RED CELL APLASIA IN MAJOR ABO INCOMPATIBLE ALLOGENEIC STEM CELL TRANSPLANT: RETOSPECTIVE ANALYSIS FROM A SINGLE CENTER EXPERIENCE

David Alonso Castronuño[1], Mónica Cabrero[1], Marta Fonseca[1], Elena Alejo[1], José María Navarro[1], Alberto Hernández[1], Borja Puertas[1], Sandra Patricia Gómez[1], Carlos Puerta[1], Evelyn Zapata[1], Pablo García[1], Ana África Martín[1], Miriam López-Parra[1], María Luisa Martín-Mateos[1], Estefanía Pérez-López[1], Mónica Baile[1], Almudena Cabero[1], Alejandro Avendaño[1], Cristina De Ramón[1], Ana García-Bacelar[1], Lourdes Vázquez[1], Fermín Sánchez-Guijo[1], Olga López-Villar[1], Lucía López-Corral[1]

[1]Salamanca University Hospital, Salamanca, Spain

Background: Although major ABO incompatibility (ABO-MM) is not a contraindication for allogeneic stem cell transplantation (alloHSCT), pure red cell aplasia (PRCA) can appear due to the persistence of anti-donor isohemagglutinins against bone marrow erythroid progenitors (BM-EP). Conditioning regimen and donor had been associated with PRCA in the small-sized studies. However, incidence, optimal management and prognosis of PRCA are still a field lacking enough evidence.

Methods: We retrospectively reviewed 454 receiving allo-HSCT in our center in the last 5 years and selected those with suspected PCRA. Inclusion criteria were: anemia <10g/dL with neutrophils and platelet recovery (>1500/uL, >50.000/uL), BM-EP aplasia/hypoplasia (<20%) at day +21/+56/+100, complete BM donor chimerism. Patients with deficiency anemia, relapse, severe infectious disease, >grade2 graft versus host disease (GVHD) or severe thrombotic microangiopathy or drug toxicity were excluded.

Results: Among 454 allo-HSCT, 192 had ABO-MM (42.2%). From them, 13 patients met inclusion PRCA criteria resulting in an incidence of 6.7% of ABO-MM allo-HSCT. Five of this thirteen patients had been initially considered multifactorial anemia.

Main characteristics are summarized in table1.

Incidence of PRCA in ABO-MM was 9.1%, 5.5%, and 7% for haploidentical, unrelated, and matched-related donor, respectively.

Median hemoglobin at day +21, +56 and +100 was 9.8g/dl (8.2-10.9), 9.1g/dl (8-12.3) and 9.6g/dl (7.2-12.1). Patients received a median of 8 packet red blood cells between day +21 and +100. Median ferritin level was 1349ng/ml, with 46.2% presenting with iron overload. Erythropoietin was below 500 U/L in 6 patients. In the inmunohematological study at PRCA diagnosis (available in 11 patients), serological and erythroid patient's ABO type persisted in 9 (81.1%).

All patients but 1 received treatment (92.3%) based on erythropoietin, intravenous inmunoglobulins, rituximab and daratumumab. First line of therapy was erythropoietin in 10 patients, Rituximab in 3 and inmunoglobulins in 2. Three patients needed more than one line of therapy. As second line, 1 patient received daratumumab, 1 inmunoglobulins and 1 inmunoglobulins combined with rituximab.

All but three patients (76.9%), achieved complete response (defined as Hb >10g/dl without transfusion) after a median of 62 days (6-119). One patient has not responded after two lines of therapy and is still under treatment at the moment of the analysis and two patients died before resolution of PCRA due to relapsed AML at day +100 (n = 1) and acute GVHD (n = 1). BM-EP improved over 20% in 38.5% and 54.5% of patients at day +56 and +100 respectively. After a median of 3 months of therapy, 66.7% and 41.7% of patients had donor's erythroid and serological ABO type respectively.

	ABO-MM allo-HSCT (*n* = 192)		**Allo-HSCT with PRCA (*n* = 13)**
Median age (range)	53 (17-71)		54 (17-68)
Sex (M/F)	111 (57,8%) / 81 (42,2%)		4 (30,8%)/9 (69,2%)
Hematological disease	-AML 98 (51%) -ALL 20 (10,4%) -MDS 26 (13,5%) -MPS 11 (5,7%) - Aplasia 1 (0,5%)	-LCL 5 (2,6%) -LNH 16 (8,3%) -LH 10 (5,2%) -MM 5 (2,6%)	-AML 9 (69,2%) -ALL 2 (15,4%) -MDS 1 (7,7%) -LNH 1 (7,7%)
Donor:			
-Identical sibling	86 (44,8%)		6 (46,2%)
-MUD 10/10	49 (25,5%)		3 (23,1%)
-MMUD 9/10	24 (12,5%)		1 (7,7%)
-Haplo	33 (17,2%)		3 (23,1%)
Source			
-Bone marrow	5 (2,6%)		-
-Peripheral Blood	186 (97,9%)		13 (100%)
-Cord Blood	1 (0,5%)		-
Conditioning regimen AMA/RIC	89 (46,4%)/103 (53,6%)		6 (46,2%)/7 (53,8%)
ABO Blood type			
-Receptor O	135 (70,3%): Donor A 102; B 32; AB 1		
-Receptor A	34 (17,7%): Donor B 20; AB 14		12 (92,3%): Donor A 10; B 2; AB 1
-Receptor B	23 (12%): Donor A 14; AB 9		-
Bidirectional ABO-MM	34 (17,7%)		0 (0%)

MUD matched inrelated donor; *MMUD* missmatched unrelated donor. *AMA* myeloablative conditioning; *RIC* reduced intensity conditioning.

Conclusions: Our results are in line with previously published, although variability in inclusion criteria leads to disparity of results. Moreover, we have demonstrated than PRCA can be under-diagnosed in some cases. The most used treatment was erythropoietin followed by Rituximab and intravenous inmunoglobulins, and the majority of patients achieved a satisfactory response although some of them needed more than 1 line of therapy.

Given the low incidence of this complication, multicentre studies are needed to better characterize PRCA and its risk factors.

Disclosure: "Nothing to declare".

14 - Non-infectious Early Complications

P541

MANAGEMENT OF DIARRHOEA IN HAEMATO-ONCOLOGY: CHANGING THE FLOW

Seda Cakmak[1], Jean Marc Pierre[1], Sabrina Munir[1], Joseph Taylor[1], Samir Agrawal[2], Jonathan Lambourne[1]

[1]St Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom, [2]Blizard Institute, London, United Kingdom

Background: Diarrhoea is one of the most debilitating and common acute toxicities of autologous stem cell transplant (ASCT). Current practice is to withhold antimotility agents until bacterial infection, including *Clostridium difficile* infection (CDI) is ruled out. Data supporting this approach is limited. We investigated the rates of bacterial gastroenteritis and CDI in patients undergoing ASCT.

Methods: Retrospective chart review was undertaken for patients undergoing ASCT between January 2021 and January 2022 at a haemato-oncology department in London, UK. Data collected included presence of diarrhoea, stool sample results, clinical features, presence of recognised risk factors for CDI and the use of antimotility agents. Stool samples were analysed using a multiplex PCR for bacterial causes of gastroenteritis, and CDI was investigated using a combination of GDH card, toxin EIA and toxin PCR assays.

Results: 76 patients underwent ASCT in the study period (48 myeloma, 26 lymphoma and 2 multiple sclerosis patients). 96% (73/76) had diarrhoea, with onset at a median of 4 days following start of induction chemotherapy. Stool samples were submitted from all patients with diarrhoea. The average time from diarrhoea onset to receipt of stool test results was 3 days. 59% (43/73) of patients received an antimotility agent. The mean time from diarrhoea onset to administration of antimotility agent was 4-5 days.

93% (70/73) of patients with diarrhoea had negative tests for bacterial pathogens and for CDI. *C. difficile* toxin and toxin gene were detected in one (1.4%) and two (2.7%) patients respectively. None of the three patients with positive CDI tests had any clinical or biochemical features of severe CDI infection, and all three had a contemporaneous serum C-reactive protein (CRP) concentration of <5mg/L. One of the three patients with positive CDI tests had received antibiotics in the preceding three months compared to 11 (15%) of the study population. No patients had a previous history of CDI. Campylobacter DNA and Shigella/E Coli DNA were detected in samples from one patient each. Neither patient with positive bacterial PCR testing had clinical features of colitis.

Conclusions: In conclusion, almost all patients undergoing ASCT suffered from diarrhoea. There was a delay of 4-5 days between diarrhoea onset and receipt of antimotility agents. The incidence of positive stool tests was low and no patients with positive tests had features of severe disease. We did not detect any risk factors or clinical features that allowed accurate prediction of positive stool test results.

Although it is common clinical practice to withhold antimotility agents in patients with positive tests for bacterial pathogens, including CDI, there is little data to support this practice. Emerging evidence suggests that using antimotility agents in patients with non-severe CDI does not worsen outcomes. Earlier use of antimotility agents should reduce the duration of diarrhoea and improve patient experience, nutritional status and recovery following ASCT.

Data presented here have lead to a change in local practice, to recommend that antimotility agents are started at the outset of diarrhoea, unless there is bloody diarrhoea, severe abdominal pain or cardiovascular instability.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P542

SINGLE-CYCLE PLASMAPHERESIS IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH MAJOR OR BIDIRECTIONAL ABO-INCOMPATIBILITY IS SAFE BUT INSUFFICIENT TO PREVENT PURE RED CELL APLASIA

Israel Henig[1], Amro Bashir[1], Dana Yehudai-Ofir[1,2], Eldad J. Dann[1,2], Tsofia Inbar[1], Lilach Bonstein[1,2], Hazim Khatib[1], Tsila Zuckerman[1,2]

[1]Rambam Health Care Campus, Haifa, Israel, [2]Ruth and Bruce Rappaport, Technion, Haifa, Israel

Background: About 40%-50% of allogeneic hematopoietic stem cell transplantations (HSCT) are from ABO-blood-group-incompatible donors. In over 30% of these cases, recipients will have isoagglutinins against the donor blood group (major or bidirectional ABO mismatch). This may lead to post-transplant hemolysis or pure red cell aplasia (PRCA) that occurs in 8%-26% of these patients. Given the lack of standard prophylaxis to prevent such complications, the current study evaluated the safety and efficacy of a single plasmapheresis (PE) cycle performed on day -3 in this setting.

Methods: In this single-center retrospective analysis, institutional electronic medical records were reviewed to retrieve demographic and clinical data on individuals receiving allograft from ABO-blood-group-incompatible donors. The identified patients were divided into three groups: Group 1: patients with a low anti-ABO antibody titer (≤ 1:8); Group 2: patients with a high titer (> 1:8) who received PE; Group 3: patients with a high titer (> 1:8) who did not receive PE. Baseline characteristics, transplant outcomes and complications caused by the anti-ABO antibodies were compared.

Results: One hundred and seventeen patients, who underwent HSCT between 2010-2019, were incorporated in the study. Group 1 comprised 48 patients, Group 2 included 41 individuals and Group 3 - 28 patients. The groups did not differ in terms of demographics (median age 55 years; females: 43.5%) or transplant characteristics (Table 1). At a median follow-up of 16.6 (range 0-102) months, no significant intergroup difference was observed in the incidence of acute or chronic graft-versus-host disease (GVHD), hematologic disease relapse or non-relapse mortality. A trend for improved median overall survival (OS) was observed in

Group 2 compared to Group 1 (36.6 months vs 11.8 months, respectively, p = 0.075). As for anti-ABO antibody-related complications, there was no significant difference in the hemoglobin level between the groups during the first day post-transplant. Surprisingly, on days +10 to +29, an average hemoglobin level was significantly lower (8.28 g/dL) in Group 2 compared to the other two groups (8.94 and 9.1 g/dL in Group 1 and Group 3, respectively). Accordingly, during this period, patients from Group 2 required transfusion of a median of one unit of packed red blood cells (PRBC) relative to zero units in the other two groups. A total of 7 PRCA cases were diagnosed during the follow-up, with 4 of them identified in Group 2. In a multivariate analysis, presence of anti-B type antibodies was found to be associated with increased risk for non-relapse mortality and decreased OS.

Table 1. Patient characteristics and outcomes

Patient group	Group 1 Titer ≤1:8 n = 48	Group 2 Titer >1:8, got PE n = 41	Group 3 Titer >1:8, no PE n = 28	P value
Myeloablative conditioning, n (%)	33 (68.8%)	31 (75.6%)	22 (78.6%)	0.60
Match unrelated donor	29 (60.4%)	26 (63.4%)	16 (57.2%)	0.84
Major ABO mismatch	39 (81.2%)	30 (73.2%)	23 (82.1%)	0.57
Bi-directional mismatch	9 (18.8%)	11 (26.8%)	15 (7.9%)	
Anti A antibody type	15 (31.3%)	30 (73.2%)	16 (57.1%)	<0.001
Anti B antibody type	3 (6.3%)	9 (22.0%)	12 (42.9%)	
Anti-ABO titer, median [range]	0 [0-8]	64 [16-512]	32 [16-128]	<0.001*
Neutrophil engraftment, day	14.9 ± 4.4	15.4 ± 3.3	13.4 ± 3.4	0.14%
Platelet engraftment, day	14.4 ± 4.8	14.2 ± 4.6	13.1 ± 3.9	0.49
Acute GvHD at 1 year, n (%)	21 (43.8%)	22 (53.7%)	16 (57.1%)	0.46
Chronic GvHD at 1 year, n (%)	14 (29.2)%	18 (43.9%)	8 (28.6%)	0.27
Non-relapse mortality rate at 1 year, n (%)	16 (33.3%)	12 (29.3%)	9 (32.1%)	0.92
Relapse at 1 year, n (%)	11 (22.9%)	1 (2.4%)	5 (17.9%)	0.02**
Overall survival at 1 year, n (%)	26 (54.2%)	29 (70.7%)	16 (57.1%)	0.26
Hemoglobin level at 24 hours, g/dL±SD	8.73 ± 1.4	8.61 ± 1.4	8.92 ± 1.9	0.73
Hemoglobin level on day 10-29, g/dL±SD	8.94 ± 0.92	8.28 ± 0.69	9.10 ± 0.97	***
Transfused PRBC units, days 10-29; median [25-75%]	0 [0-1]	1 [0-3]	0 [0-0]	****
PRCA, n (%)	1 (2%)	4 (8%)	2 (7.1%)	NA

*P-value significant between the control group (Group 1) and either Group 2 or Group 3. No significant difference between the two latter groups. ‡Anti-E antibodies. ¥Antibody titer is 0. **Group 1 vs Group 2, p = 0.005; Group 2 vs Group 3, p = 0.037; Group 1 vs Group 3, p = 0.77. ***Group 1 vs Group 2, p = 0.003; Group 3 vs. Group 2, p = 0.002. ****Group 2 vs Group 3, p = 0.002. NA: not applicable

Conclusions: The use of a single cycle of PE before HSCT in patients with anti-ABO antibodies against the donor blood type was safe and did not affect transplant-related outcomes. However, its efficacy was limited and not associated with a decrease in PRCA occurrence. The therapeutic approach proposed in this study needs to be further evaluated, preferably in a prospective randomized trial with planned anti-ABO antibody titer monitoring to guide additional apheresis cycles.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P543

EFFICACY AND SAFETY OF NETUPITANT/PALONOSETRON COMBINATION (NEPA) AND LOW DOSE OF DEXAMETHASONE IN PREVENTING NAUSEA AND VOMITING IN PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION

Alessandro Spina[1], Marina Aurora Urbano[1], Francesca Merchionne[1], Claudia Schifone[1], Pierluigi Masciopinto[1], Giovanni Quintana[1], Giuseppe Mele[1], Domenico Pastore[1]

[1]Hematology and Transplant Unit, Brindisi, Italy

Background: Chemotherapy-induced nausea and vomiting (CINV) can be associated with reduced quality of life and meaningful complications in allogeneic stem cell transplantation (AlloSCT). Currently, a three-drug combination containing a neurokinin-1 receptor antagonist (NK1-RA), a 5-hydroxytryptamine-3 (5-HT3)-RA, and corticosteroids in recommended as CINV prophylaxis regimen. Netupitant-palonosetron (NEPA) has been approved for highly and moderately emetogenic chemotherapy, but experience in alloSCT setting is limited. Furthermore dexamethasone (12-20 mg daily) is recommended by the antiemetic guidelines but its administration may be associated with a wide range of side effects, including serious infections in patients undergoing alloSCT. We retrospectively analyzed the efficacy and safety of NEPA and low dose of dexamethasone in alloSCT.

Methods: We analyzed 70 adult patents (acute myeloid leukemia=33, acute lymphoblastic leukemia=17, myelodysplastic syndrome=3, non-Hodgkin lymphoma=13, Hodgkin lymphoma=1, Myelofibrosis=3) who underwent allo SCT from matched related donor (n = 31), matched unrelated donor(n = 8), and haploidentical (n = 31) donors. The median age was 49 years (median 19-67); the conditioning regimen was myeloablative (n = 42) or reduced intensity (n = 28). Stem cell source was peripheral blood stem cells in 95% of the patients. NEPA (300 mg of netupitant plus 0,5 mg of palonosetron) and low-dose of dexamethasone (4 mg) was administered every other day of conditioning regimen, starting from the first day of conditioning regimen, with a maximum of 4 total doses. The observation period started with initiation of conditioning regimen and continued for 48 h after the last dose of chemotherapy

Results: Responses rate were 82% (58/70) for complete response (no emesis, no rescue medication), 81% (57/70) for complete control (complete response an no more than mild nausea); moreover, the percentage of patients that did not suffer any emetic episodes were 91% (64/70), and of patients that did not require a rescue therapy for controlling CINV were 85%(60/70). Moderate and severe episodes of nausea were reported in 9 patients (12%). Regarding the safety profiles, one patient presented headache, one patient experienced grade 1 abdominal pain and two patient had grade 1 constipation

Conclusions: NEPA and low dose of dexamethasone, administered every other day, show to be very effective in preventing CINV in patients undergoing alloSCT with a good tolerability profile.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P544

TRIAL IN PROGRESS: AN OPEN-LABEL, MULTI-CENTER PHASE 2 STUDY EVALUATING EFFICACY AND SAFETY OF NARSOPLIMAB FOR THE TREATMENT OF PEDIATRIC HIGH-RISK HSCT-TMA

William Pullman[1], Mary Brough[1], Carolina Soto[1], Tze-Chiang Meng[1]

[1]Omeros Corporation, Seattle, United States

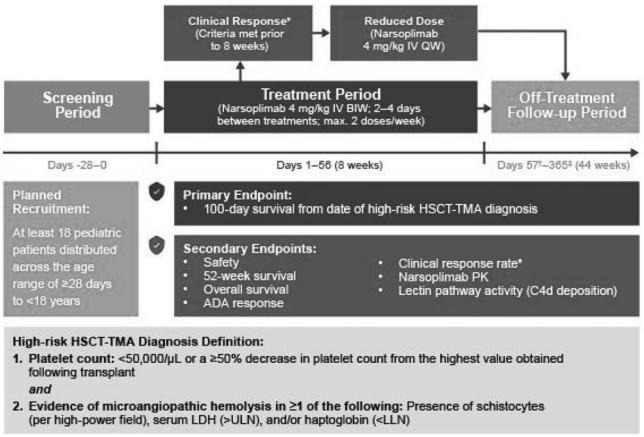
Background: Hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA; also known as TA-TMA) is associated with significant morbidity and mortality. HSCT-TMA incidence rates of up to 39% have been reported in both pediatric and adult allogeneic HSCT (alloHSCT) recipients. In the HSCT setting, toxic conditioning regimens, graft-versus-host disease, and infection can cause endothelial injury, which triggers activation of the lectin pathway of complement – and in turn the coagulation cascade – together leading to TMA. Narsoplimab (OMS721) is a fully human monoclonal antibody that inhibits mannan-binding lectin-associated serine protease-2 (MASP-2), the effector enzyme of the lectin pathway and an activator of the coagulation cascade. Narsoplimab was previously evaluated for efficacy and safety in adults with high-risk HSCT-TMA in an open-label pivotal trial (NCT02222545); narsoplimab treatment was well tolerated and resulted in clinical response and favorable overall survival (Khaled SK, et al. *J Clin Oncol*. 2022;40(22):2447). HSCT-TMA currently has no approved therapy, and therefore represents a significant unmet medical need. We describe the design of the first clinical trial evaluating efficacy and safety of narsoplimab in pediatric patients with HSCT-TMA.

Methods: This is an open-label, multi-center Phase 2 trial of narsoplimab in pediatric patients (Figure). Eligible patients are aged ≥28 days to <18 years, have received alloHSCT, and have been diagnosed with high-risk HSCT-TMA. Exclusion criteria include prior treatment with eculizumab, ravulizumab, or defibrotide within 3 months prior to screening, having Shiga toxin-producing *E. coli* hemolytic uremic syndrome (STEC-HUS), or ADAMTS13 activity <10%.

Patients will receive narsoplimab 4 mg/kg via intravenous (IV) infusion twice weekly during the 8-week treatment period (Days 1–56). If a patient meets all clinical response criteria prior to 8 weeks of treatment, dosing may be decreased to 4 mg/kg IV once weekly until the end of the treatment period. Narsoplimab can be used in conjunction with standard-of-care treatments. At the end of the treatment period, patients will enter a 44-week follow-up period (Days 57–365). The planned recruitment is at least 18 pediatric patients, distributed across the age range.

The primary endpoint is 100-day survival from date of HSCT-TMA diagnosis. Secondary endpoints include safety, survival at 52 weeks, overall survival from date of HSCT-TMA diagnosis, anti-drug antibody response, clinical response rate, narsoplimab pharmacokinetics, and measurement of lectin pathway activity via C4d deposition.

Figure: Trial Design



Results: N/A

Conclusions: Following the favorable results obtained in a pivotal Phase 2 study in adults with high-risk HSCT-TMA, further evaluation of narsoplimab efficacy and safety is warranted in pediatric patients.

Disclosure: William Pullman: personal financial interest (Omeros); Mary Brough: employment (Omeros), personal financial interest (Omeros); Carolina Soto: employment (Omeros), personal financial interest (Omeros); TC Meng: personal financial interest (Omeros).

14 - Non-infectious Early Complications

P545

PRE-TRANSPLANTATION VITAMIN D DEFICIENCY INCREASES ACUTE GRAFT-VERSUS-HOST DISEASE AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THALASSEMIA MAJOR PATIENTS

Vedat Uygun[1], Hayriye Daloğlu[2], Seda Öztürkmen[3], Koray Yalçin[4], Gülsün Karasu[5], Akif Yeşilipek[3]

[1]Istinye University, Medical Park Antalya Hospital, Antalya, Turkey, [2]Antalya Bilim University, Medical Park Antalya Hospital, Antalya, Turkey, [3]Medical Park Antalya Hospital, Antalya, Turkey, [4]Bahçeşehir University, Medical Park Göztepe Hospital, Istanbul, Turkey, [5]Medical Park Göztepe Hospital, Istanbul, Turkey

Background: Although there are many studies on the role of vitamin D deficiency (VDD) in hematopoetic stem cell transplantation (HSCT), outcomes have often reported conflicting results because of the heterogeneity of the patients in the studies.

Methods: We investigated the association between VDD prior to HSCT and outcomes after HSCT in a relatively homogenous group of patients with thalassemia major (TM) who received identical treatment for TM before transplantation, and the same conditioning regimen and GVHD prophylaxis during transplantation. All patients including the patients with normal vitamin D_3 levels received 400 to 800 IU per day of vitamin D in the first six months after HSCT.

Results: Data from 100 patients who were transplanted for thalassemia major from a full-matched donor were evaluated with regards to the level of vitamin D_3 which was collected within a month prior to HSCT. We have shown that pre-HSCT VDD increased the frequency of aGVHD after transplantation particularly in HSCTs performed with PBSC for the stem cell source. Pre-transplant low vitamin D_3 levels had no association with transplant

outcomes such as engraftment, viral infections, alloimmunization, chronic GvHD, total days of hospitalization, and success in terms of transfusion independence.

Conclusions: Low vitamin D_3 level before HSCT carries a significant risk for aGVHD. All patients with TM should be screened in terms of VDD before HSCT and every effort should be made in supplementation of vitamin D.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P546

OUTCOMES OF CD34-SELECTED STEM CELL BOOST OF CRYOPRESERVED PERIPHERAL BLOOD HEMATOPOIETIC CELLS FOR POOR ALLOGRAFT FUNCTION

Richard C. Godby[1], Dustin J. Strasburg[1], Margaret A. DiGuardo[1], William J. Hogan[1], Mark R. Litzow[1], Abhishek A. Mangaonkar[1], Mithun V. Shah[1], Eapen K. Jacob[1], Hassan B. Alkhateeb[1]

[1]Mayo Clinic, Rochester, United States

Background: Poor allograft function is a possible complication following hematopoietic cell transplantation (HCT). This can be addressed with a HC Boost (HCB), which may be enriched for CD34-positive cells in an attempt to minimize complications of graft-versus-host disease (GVHD). Since the pandemic, peripheral blood stem cell (PBSC) allografts have increasingly undergone cryopreservation prior to transplantation in order to ameliorate logistical challenges and facilitate safety. Little is known about the outcomes of CD34-selected HCB using previously cryopreserved PBSC.

Methods: We conducted a retrospective chart review on individuals at the Mayo Clinic (Rochester, MN) who received CD34-selected HCB without additional conditioning chemotherapy starting in 2020. CD34-selection was accomplished using CliniMACS technology utilizing previously cryopreserved PBSC allografts. Poor graft function was defined as achieving an ANC > 500 while remaining dependent on platelet and/or pRBC transfusions.

Results: Six patients were identified. The median age was 57.5 years (range: 29 – 70) and 50% were female with a median follow up time of 124.5 days (range: 29 – 240) from HCB. Other patient and transplant characteristics are described in Table 1. At the time of transplant, allografts contained a median of 5.81x10^6 CD34+ cells/kg and 1.77x10^8 CD3+ cells/kg. Neutrophil engraftment occurred in all allografts (median 20.5 days) while platelet engraftment only occurred in three patients (median 24 days) and the other three did not demonstrate platelet engraftment. All patients failed thrombopoietin receptor agonist. The median time from HCT to HCB was 161 days (range: 128 – 335). HCBs contained a median of 3.22x10^6 CD34+ cells/kg and 2.35x10^3 CD3+ cells/kg. The median time to neutrophil engraftment after the HCB was 12 days for the three patients who were not already engrafted (range: 3 – 12). Platelet engraftment occurred in all patients except one at a median of 14 days (range: 12 – 38). Pre-HCB, 4 patients had Grade I-II acute GVHD (aGVHD); all died post HCB of infection and/or multiorgan failure within a median of 120.5 days (range: 29 – 240 days). The two living patients, after HCB, have subsequently demonstrated 100% donor chimerism studies and achieved transfusion independence for more than three months. The four patients who died showed variable chimerisms before HCB (3: 100% donor, 1: 95% donor) and after HCB (1: not reported, 1: 100% donor, 2: 95% donor). Following HCB, half of the recipients were reported to have moderate to severe chronic GVHD (cGVHD), which subsequently improved or stabilized with systemic steroid therapy and immunosuppression. Post HCB, none of the patients experienced aGVHD or other immediate adverse events.

Conclusions: In the era of allograft cryopreservation, CD34-selected HCB utilizing a previously cryopreserved PBSC allograft is feasible and effective in patients with poor graft function who failed thrombopoietin receptor agonists. There were no immediate safety concerns directly related to the HCB, however, those with antecedent aGVHD were at higher risk of lethal infectious complications post HCB and had worse clinical outcomes. Further studies are warranted to better understand the clinical implications of CD34-selected HCBs.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P547

DRUG-INDUCED LUNG INJURY IN PATIENTS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

Valeria Rustamovna Ianbukhtina[1], Ivan Sergeevich Moiseev[1], Egor Alexandrovich Kulagin[1], Ilya Yurievich Nikolaev[1], Vlasova Julia Jurievna[1], Elena Vladislavovna Morozova[1], Anna Gennadievna Smirnova[1], Ludmila Stepanovna Zybarovskaya[1], Vasiliy Ivanovich Trofimov[2]

[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation, [2]Pavlov University, St. Petersburg, Russian Federation

Background: Drug-induced lung injury is relatively rare in patients undergoing hematopoietic stem cell transplantation (HSCT) with chemotherapy-based conditioning. There is no standard algorithm to diagnose such condition. Thus we conducted a retrospective analysis to determine the incidence and the clinical course of this complication.

Methods: We have retrospectively analyzed histories of 2661 patients after autologous (autoHSCT, n = 932) and allogeneic (alloHSCT, n = 1729) hematopoietic stem cell transplantation at RM Gorbacheva Research Institute from 2012 to 2022. We identified 5 patients who developed toxic pneumonitis in different terms after autoHSCT and 6 patients after alloHSCT. The diagnosis was based on lung biopsy. The underlying diagnosis spectrum was following: lymphomas (1 patient in autoHSCT and 2 patients in alloHSCT), acute myelogenous leukemia (1 patient in autoHSCT and 2 patients in alloHSCT), multiple myeloma (3 patients in autoHSCT), acute lymphoblastic leukemia (1 patent in alloHSCT) and chronic lymphocytic leukemia (1 patient in alloHSCT). Median age in auto group was 49 (20-68) years, in allo group – 30 (7-68) years. Conditioning regimens included BeEAM, FLAMSA, and melphalan in auto patients; fludarabine (with bendamustine, melfalan, cyclophospane or busulfan) and high dose cytarabine in allo patients.

Results: The incidence of toxic lung injury was 0,4% in general (0,5% in auto and 0,3% in allo). Only two patients from autoHSCT group received other pneumotoxic drugs before compared to 5 of 6 patients from alloHSCT group. Median drug-induced lung injury development period after autoHSCT was 3 days (from 1 to 19) and 13 days after alloHSCT (from 1 to 148). Clinical manifestation was present in 10 patients (5 in autoHSCT and 5 in alloHSCT), while 1 patient was asymptomatic. Most common clinical features were dyspnea (4 of 5 and 3 of 6) and cough (3 of 5 and 3 of 6), 2 patients of alloHSCT group had chest pain. Half of patients had pulmonary hypertension. Most common radiological pattern was ground glass opacities (3 of 5 autoHSCT patients and 6 of 6 alloHSCT patients, Figure 1A). We have also found reticular

changes (1 auto and 3 allo), nodes (1 patient in both groups), infiltrates (2 auto and 1 allo), bronchi changes (1 patient in both groups) and effusion (2 allo) (Figure 1B, 1C). Key laboratory alterations included elevation of LDH level (mean for all patients – 1252,5 U/L) and CRP level (mean – 61 g/l). Mean creatinine level was 0,088 mmol/l; mean SGPT level was 44,3 mmol/l. Mean white blood cell count was $6,9*10^9$. Key features on histopathological examination included nonspecific or lymphoid interstitial infiltration, granulomatosis and needle-shaped formations (Figure 1C).

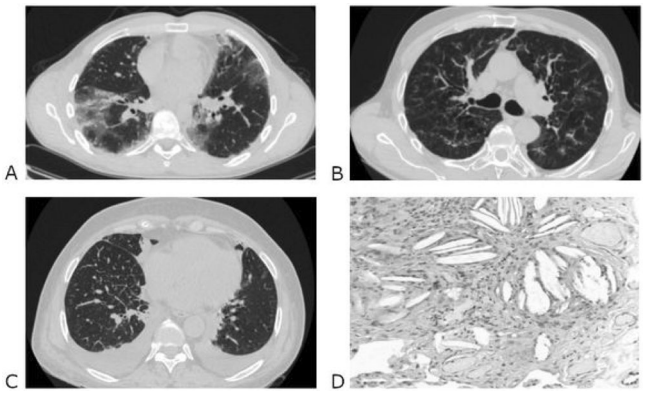


Figure 1. Radiological findings (A – ground glass opacities, B – reticular and brochi changes, C – pulmonary effusion) and histopathological pattern (giant cell granulomas and needle-shaped formations).

Conclusions: Toxic pneumonitis is a very rare event observed after chemotherapy-based conditioning before HSCT, slightly more common after autoHSCT. Key features that allow to clinically differentiate this condition are respiratory complaints (first of all – dyspnea), ground glass opacities and reticular changes on CT and abnormalities of systemic markers such as LDH and CRP. Histopathology is an important component of proper diagnosis.

Disclosure: Authors have nothing to declare.

14 - Non-infectious Early Complications

P548

NUTRITIONAL STATUS EVALUATION VIA BIOIMPEDANCE AND INDIRECT CALORIMETRY IN ADULT PATIENTS WITH ALLOGENEIC HSCT

Maxim Kucher[1], Natalya Saltykova[1], Alisa Volkova[1], Alexander Shcherbakov[1], Alexander Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint-Petersburg, Russian Federation

Background: Side effects of the conditioning regimen and allogeneic HSCT complications often have a negative impact on the nutritional status, which poor state can reduce the effectiveness of treatment, and require nutrition support (NS) initiation. At the same time, the implementation of sufficient and safe enteral and parenteral nutrition is a challenge as a result of the unstable patient's energy and nutrient reqiurements, their impaired metabolism against the background of organ failure, endotheliopathy and the risk of infectious complications.

Methods: In order to improve the evaluation of nutritional status, since February 2022, 41 adult allogeneic HSCT recipients with acute leukemia (n = 26), multiple myeloma (n = 4), lymphomas (n = 4) and other malignant diseases (n = 7) have been enrolled to the study. In addition to routine anthropometric and

Table 1.

Age	Tx Indication	Donor	Sex	Conditioning	GVHD PPX	Recipient blood type	Donor blood type	Graft CD34 (x10^6/kg)	Graft CD3 (x10^8/kg)	N Engraft (d)	Plt Engraft (d)	Boost (d)	Boost CD34 (x10^6/kg)	Boost CD3 (x10^3/kg)	Boost N Engraft (d)	Boost Plt Engraft (d)	Status
58	Ph+ B-ALL	MUD	F	Flu/Mel	PTCy, Tacro, MMF	B neg	B pos	6.00	1.12	16	24	132	2.46	5.32	12	No engraftment	Dead
57	AMML	MSD	F	Cy/TBI	Tacro/MTX	A pos	A neg	5.92	1.53	36	No engraftment	148	4.72	8.77	0	12	Dead
66	t-AML	MUD	F	Flu/Mel	Tacro/MTX	A pos	O pos	5.00	8.30	20	74	209	3.00	1.53	0	13	Dead
70	PH-neg B-ALL	MSD	M	Flu/Mel/TBI	Tacro/MTX	O neg	O neg	5.54	2.01	16	15	335	3.44	1.40	0	14	Dead
50	CMML-0	Haplo	M	Flu/Mel	PTCy, Tacro, MMF	A neg	A neg	6.76	1.41	28	No engraftment	128	5.13	3.17	3	38	Alive
29	U2AF1 mutant MPN	MSD	M	Flu/Mel	PTCy, Tacro, MMF	O pos	O pos	5.70	2.07	21	No engraftment	174	1.84	1.17	12	30	Alive

biochemical parameters, bioimpedance (analyzer BC-418, Tanita, Japan) and indirect calorimetry (metabolic system Fitmate Med, Cosmed, Italy) were performed. Instrumental studies were done at three control points – before the start of the conditioning regimen (D-7), at D + 7 and D + 28. Indirect calorimetry was performed in the morning time with the duration of 15 minutes, on an empty stomach, without previous physical activity, in a supine position. In case of clinical necessity, patients underwent pain control management, NS using a combination of sipping and parenteral nutrition.

Results: Dynamics of resting metabolic rate D-7, D + 7, D + 28.

The obtained data shows that the patients had have a decrease in anthropometric parameters – body weight by 6.9% (73.8 kg – 68.7 kg), $p = 0.04$, body mass index from 25.3 to 23.4, $p = 0.04$. According to bioimpedance analysis, a change in body composition proportional to weight was noted: lean muscle mass decreased by 8.7% (51.8 kg – 47.3 kg), fat by 3.6% (19.6 kg – 18.9 kg), total body water by 7.3% (39.7 kg – 36.8 kg). According to indirect calorimetry, initially 15 patients had an accelerated metabolism relative to the Schofield equation (115-137%), within the normal range – in 21 (90-114%), reduced – in 3 (67-85%). The metabolic rate did not correlate with the severity of weight loss and body composition, $p < 0.05$. The analysis revealed a clinically insignificant decrease in basal metabolism, as in men: D-7, median – 2034 kcal/day, D + 7, median – 1822 kcal/day, D + 28, median 1825 kcal/day, $p = 0.23$; so in women: D-7, median – 1539 kcal/day, D + 7, median – 1464 kcal/day, D + 28, median – 1478 kcal/day, $p = 0.065$, respectively. But resting metabolic rate had remained unchanged when recalculating energy needs per 1 kg of patient's body weight: in men, the median was 26,4 – 25,1 – 25,9 kcal/kg, $p = 0.53$; in women: 23 – 22,5 – 24,5 kcal/kg, $p = 0.56$. At the same time, the actual energy consumption correlates with the recommended EBMT values of 25-30 kcal/kg (EBMT Handbook, chapter 24, 2019).

Conclusions: Allogeneic HSCT have a negative impact on nutritional status despite adequate NS and supportive care. The energy consumption is not of significant changes in early posttransplant period in patients without severe complications, which makes it possible to use both worldwide accepted equations and values recommended by hematology societies when providing NS.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P549

SYSTEMATIC SCREENING FOR VENOUS OCCLUSIVE DISEASE/ SINUSOIDAL OBSTRUCTIVE SYNDROME (VOD/SOS)IS ASSOCIATED WITH EARLIER DIAGNOSIS AND PROMPT INSTITUTION OF DEFIBROTIDE TREATMENT AND ENABLES DIAGNOSIS OF LATE-ONSET VOD/SOS

Daniele Avenoso[1], Michelle Kenyon[1], Pramila Krishnamurthy[1], Varun Mehra[1], Shreyans Gandhi[1], Austin Kulasekararaj[1], Francesco Dazzi[1], Ye Ting Leung[1], Sandra Anteh[1], Maria Cuadrado[1], Mili Naresh Shah[1], Hayat Ullah[1], Styliani Bouziana[1], Christianne Bourlon[1], Oana Diana Dragoi[1], Antonio Pagliuca[1], Victoria Potter[1]

[1]King's College Hospital NHS Foundation Trust, London, United Kingdom

Background: The sinusoidal obstructive syndrome (SOS), also known as hepatic veno-occlusive disease (VOD), is a potentially life-threatening complication following haemopoietic stem-cell transplantation (HSCT).

The availability of reduced intensity conditioning regimens and new drugs for malignant haematological conditions allowed more patients to be eligible for HSCT and transplant patients will have most likely other risk factors.

Based on these considerations, we have undertaken a dedicated weekly VOD/SOS ward round which aims to identify patients at risk and facilitate early diagnosis of VOD/SOS and offers careful evaluation of the differential diagnoses.

Methods: This is an extra evaluation from the ward attending team and it performed by a consultant haematologist and consultant nurse in transplantation. The aim of an independent and multidisciplinary team is to offer a focused approach for this complication and a better differential diagnosis process following the discussion of the cases with the ward attending team.

The dedicated ward round approach is a regular evaluation and has documentation (at least once a week) from D + 7 relating to this complication in the patient's electronic notes. In case of re-admission the VOD/SOS-team starts again the weekly evaluations.

Results: Herein, we present the results of our VOD-ward round: between September 2020 and September 2022, 151 consecutive patients were evaluated.

147 out of 151 patients underwent HSCT with at least one known risk factor for developing VOD/SOS. The median number of risk factors present in the VOD/SOS group and non-VOD/SOS group was 5(range 3 – 6) and 3 (range 0 – 7), respectively. Late-onset VOD/SOS was diagnosed in 31% of our patients that developed this complication.

Since September 2020, the median number of VOD/SOS ward round clinical note entries per patient is 3 (range 1 – 25); these multiple entries are a consequence of long admission or readmissions. Furthermore, this weekly evaluation and documentation has prompted discussion of the findings at our multidisciplinary meeting and at the handover meeting before the weekends and bank holidays and is incorporated within forward planning of patient care.

The impact of the ward round extends beyond the weekly event, whereby the round provides a teaching moment for doctors and nurses and leads to increased awareness and confidence within the wider team.

In our experience, the focused assessment of risk factors and regular evaluations has shown that our transplant population has multiple risk factors for VOD/SOS.

Conclusions: In conclusion, the identification of patients with multiple risk factors for VOD/SOS and a consistent and independent approach allowed the diagnosis of the complication before the onset of multiorgan failure, decreasing the median time to treatment by 48 hours. A formal VOD/SOS ward round has been fundamental to document all the risk factors and has demonstrated educational value for the health care professionals within the BMT/HSCT service.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P550

EVALUATION OF TOLERANCE AND NUTRITIONAL IMPACT OF PRODUCTS ENRICHED WITH FERULIC-ACID IN HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS

Monica Cabrero[1,2], Estefania Perez-Lopez[1,2], Silvia Preciado[1,2], Juana Frias[3], Ana Africa Martin[1,2], Monica Baile[1,2], Almudena Cabero[1,2], Alejandro Avendaño[1,2], Elena Peñas[3], Daniel Rico[4],

Lucia Lopez-Corral[1,2], Ana Belen Martin-Diana[4], Cristina Martin-Villaluenga[3], Fermin Sanchez-Guijo[1,2]

[1]Salamanca University Hospital, Salamanca, Spain, [2]IBSAL, Salamanca, Spain, [3]Institute of Food Science, Technology and Nutrition (ICTAN), Valladolid, Spain, [4]Agricultural and Technical Institute of Castile and Leon (ITACyL), Valladolid, Spain

Background: Hematopoietic stem cell transplantation (HSCT) remains as the better treatment for many malignant and non-malignant hematological diseases. This procedure is associated with high toxicity due to conditioning regimen and, in the particular case of allogeneic stem cell transplant, related with graft-versus-host disease (GVHD). Gastrointestinal complications are among the most prevalent after HSCT, with reduced oral intake, malnutrition and parenteral nutrition requirements. That is why development of food products in this setting is highly relevant. Ferulic acid (FA) has demonstrated anti-inflammatory, immunomodulatory and antioxidants effects, so food products enriched with easy absorption FA could have a beneficial role in HSCT patients.

Methods: We designed a prospective randomized study to evaluate tolerance and nutritional impact of food products (mousse and bread) enriched with FA elaborated from hydrolysate or wheat bran in patients undergoing HSCT.

Inclusion criteria: patients over 18 years of age receiving autologous or allogeneic HSCT at our center. We excluded those patients with previous reduced oral intake due to any cause.

Results: Nineteen patients receiving autologous (4) or allogeneic (15) HSCT were included. Patients were randomized based on the chronological order of hospital admission to received FA enriched product (FAP) (n = 10) or placebo (n = 9). They received study product (mousse in 10, bread in 5 and both in 4) from the conditioning regimen to day +21 or hospital discharge. Median days of product administration was 21 days (7-28) and 11 patients completed planned duration of the study. Eight patients early stopped due to own decision (n = 3), impaired oral intake (n = 3) or oral intolerance (n = 2).

Weight loss was observed in 100% of patients, with a median of 2.95 kg at day +7, 4.85kg at day +14 and 5.5 kg at day +21, without significant differences between FAP and placebo. None of patients included in the study had decreased albumin levels below 3g/dL. Median albumin was 3.9 g/dl at the beginning, 3.7 at day +14 and 3.9 at day +21, without significant differences between FAP and placebo.

Parenteral nutrition was administered in 26% of patients for a median of 4 days (2-10), without significant differences between FAP and placebo. Only 4 patients had null oral intake for a median of 5 days.

Product were well tolerated in 100% of patients, with no adverse events related with them. They qualified products with e median of 4 points (scale from 1-5), with lower qualification for the item "flavor" in the mousse (3 points). Many patients also did negative comments about mousse package due to flavor transference to the product.

Conclusions: Food products enriched with FA are well tolerated by HSCT patients. This nutritional support could help to maintain oral intake in these patients given the low number of days they had zero-diet.

Due to low number of patients included, we could not find significant differences between FAP and placebo. Bigger studies including a higher population should be done to better define FA role as a protective factor for gastrointestinal complications in HSCT patients.

Disclosure: Authors declare no COI.

14 - Non-infectious Early Complications

P551

CLINICAL RESPONSE TO NOMACOPAN IN THE PAEDIATRIC HSCT-TMA SETTING

Claire Horgan[1], Roisin Borrill[1], Omima Mustafa[1], Srividhya Senthil[1], Ramya Nataraj[1], Madeleine Powys[1], Denise Bonney[1], Yenting Ngai[2], Joe Datt[2], Robert Wynn[1]

[1]Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust, Manchester, United Kingdom, [2]Akari Therapeutics, London, United Kingdom

Background: HSCT-TMA (haematopoietic stem cell transplant associated- transplant microangiopathy) is a rare but devastating complication of HSCT, with a survival rate of around 20% in severely affected individuals. It is characterised by endothelial damage and complement activation resulting in microvascular thrombi, haemolytic anaemia, platelet consumption, hypertension, and organ dysfunction. Nomacopan, a novel bispecific inhibitor of complement C5 and the pro-inflammatory mediator leukotriene B4, has been proposed as a potential treatment. We report clinical and biochemical response to nomacopan in a paediatric HSCT-TMA patient in the ongoing AK901 open-label clinical trial.

Methods: Patient X, a 6-year-old male underwent a 6/8 HLA-mismatched unrelated cord blood (CB) HSCT conditioned with fludarabine, treosulfan and thiotepa, for relapsed refractory AML in January 2021 post CB HSCT in April 2020. The patient received 7 granulocyte infusions peri-transplant as part of an experimental protocol to augment the graft-versus-leukaemia effect. His immediate post-transplant course was complicated by engraftment syndrome, acute gastrointestinal GVHD grade 3 and CMV viraemia.

At day +66 (post-transplant) the patient developed features suggestive of TMA in the form of crampy abdominal pain with blood in stool, raised urine protein creatinine ratio, hypertension, schistocytes in the peripheral blood and elevated sC5b9. He was enrolled into AK901 and started treatment with nomacopan on day +74. A single age and weight based ablating dose was followed by maintenance twice daily dosing for 21 days.

Results: After initial pharmacodynamic analysis at day 14 of treatment, the patient was found to have predose terminal complement activity (TCA) slightly higher (value 14.4) than the LLOQ (CH50 > 10 U Eq/ml). Although his TCA had been reduced by 95% from an unusually high baseline CH50 of 299.6U Eq/ml and sC5b9 had normalised, dose was increased in line with the protocol. A few days later the patient developed neurological symptoms following a period of hypertension and was diagnosed with posterior reversible encephalopathy syndrome (PRES). Nomacopan was stopped for 3 days and restarted after the diagnosis was deemed to be unrelated to nomacopan treatment. Treatment continued for a further 46 days until the primary end point of the study was met with correction of the patients' urine protein creatinine ratio for ≥28 days. Gut pathology and thrombocytopenia resolved, and the patient remains well and in remission. No adverse events related to nomacopan were experienced during the 72-day treatment period.

Conclusions: The pathophysiology of HSCT-TMA is complex and multifactorial. It is important to be vigilant for clinical signs and symptoms of TMA and screen appropriately when suspicion arises so patients can receive prompt management and complement inhibition considered early. These data show that nomacopan had a favourable safety profile and controlled complement activity in this patient with severe HSCT-TMA.

Clinical Trial Registry: NCT 04784455
https://clinicaltrials.gov/ct2/show/NCT04784455

Disclosure: Akari developed nomacopan and sponsor the clinical trial.

14 - Non-infectious Early Complications

P552

ULCERATIVE COLITIS POST HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH FEATURES OF ISOLATED INTESTINAL THROMBOTIC MICROANGIOPATHY PROVOKED BY COVID19 – A PEDIATRIC CASE REPORT

Peter Svec[1], Jaroslava Adamcakova[1], Julia Horakova[1], Dominika Doczyova[1], Iveta Cierna[1], Pavel Babal[2], Zoltan Prohaszka[3], Sonata Jodele[4], Ivana Bodova[1], Maria Fussiova[1], Tomas Sykora[1], Miroslava Pozdechova[1], Santia Vargova[1], Alexandra Kolenova[1]

[1]National Institute of Children's Diseases and Comenius University, Bratislava, Slovakia, [2]Comenius University, School of Medicine, Dept. of Pathology, Bratislava, Slovakia, [3]Semmelweis University, Dept. of Internal Medicine and Hematology, Budapest, Hungary, [4]Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, United States

Background: Features of thrombotic microangiopathy (TMA) affecting isolated organs without systemic complement activation are rarely reported after HSCT and remain a debated entity. We describe a well-documented isolated intestinal transplantation-associated (TA-) TMA re-triggered in a child by COVID19 infection and clinically presenting as ulcerative colitis.

Methods: Detailed clinical, endoscopic, laboratory findings and independent histopathologic evaluations were used to provide a pediatric case report of an inflammatory bowel disease post HSCT with dominant TMA features, distinct from known GvHD definitions.

Results: 3-year-old boy 13 months after HLA 9/10 unrelated donor HSCT for AML in CR1 manifested clinical and endoscopic picture of ulcerative colitis 2 weeks after his COVID19 infection. He presented with weight loss, abdominal pain, diarrhea with fresh blood and clots and systemic inflammation (elevated C-reactive protein), intestinal inflammation (elevated calprotectin), hypoalbuminemia. No infectious agent was detected. This was his second episode of colitis – first developed at 7 months post HSCT short after an urinary tract E.coli infection. At both occasions the histopathology of colonic biopsies did support a non-specific colitis and did not meet criteria for GvHD. At recurrence of colitis after COVID19 numerous vessels with intraluminal thrombi of detached endothelial cells were noted in colonic biopsies and significant complement depositions (C3, C1q) were found. On the contrary, no signs of systemic TA-TMA were identified (repeated monitoring of hemoglobin, platelets, lactate dehydrogenase, schistocytes, blood pressure, renal functions, proteinuria, detailed complement activation profile). A non-specific ulcerative colitis with isolated intestinal thrombotic microangiopathy was concluded. Therapeutic measures: Before biopsies were finalized and consulted, steroids were administered but only mild improvement was documented. Two doses of mesenchymal stromal cells were given with no clear response. Then cyclosporin A was decreased and discontinued, steroids tapered. Complement blockade was not administered as clinical improvement occurred and no systemic TA-TMA was present. However, due to intestinal and systemic inflammation persisting despite clinical improvement ruxolitinib was initiated and later vedolizumab started.

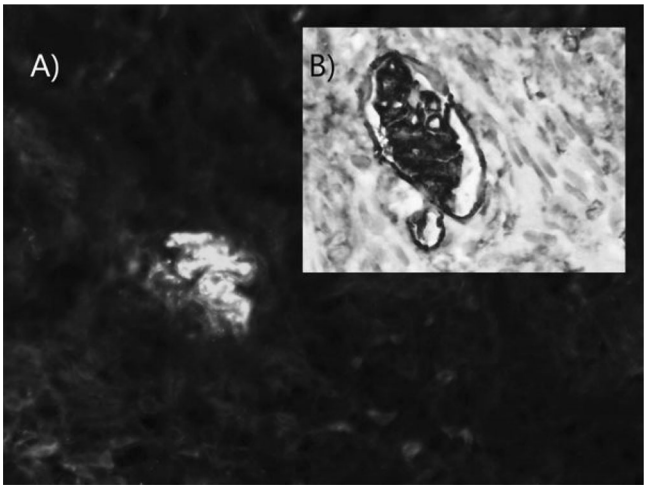


Figure 1: Colonic endoscopic biopsy with endothelial thrombi and complement deposition. A) C3 complement deposits in a vessel lumen. B) CD31 staining for endothelial cells in an intraluminal thrombus filling a mucosal vessel.

Conclusions: Isolated intestinal thrombotic microangiopathy may be triggered by COVID19 infection post HSCT. Specific histopathologic features and complement staining may drive the proper diagnosis. The colonic inflammation and vessel damage appear steroid refractory and a trial of calcineurin inhibitor substitution by JAK2 inhibition and gut-selective anti-inflammatory (anti-integrin) therapy may be beneficial.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P553

IMMUNE-MEDIATED INFLAMMATORY SYNDROMES OTHER THAN GRAFT-VERSUS-HOST DISEASE (GVHD) AND TRANSPLANTATION WITH CRYOPRESERVED HAEMATOPOIETIC STEM CELLS: A POSSIBLE CORRELATION

Anita Betulla[1], Samanta Bonato[1], Giulia Perali[1], Francesca Carobolante[1], Giulia De Fusco[1], Francesca Polese[1], Barbara Sapino[1], Michela Pivetta[1], Gianluca Gessoni[1], Renato Bassan[1], Cristina Skert[1]

[1]Ospedale dell'Angelo Mestre, Venezia, Italy

Background: Microangiopathic syndromes, i.e. thrombotic thrombocytopenic purpura (TTP) and veno-occlusive disease (VOD) together with macrophage activation syndrome (MAS) are complications of allogeneic stem cell transplantation (allo-SCT) with a variable incidence, likely due to the investigation of heterogeneous populations and the adoption of different diagnostic criteria (TTP: 8-39%; VOD 10-15%; MAS 4-8 %). However, they have in common high mortality rate (>75%) and inflammatory mechanisms, which involve donor and host immune systems, and especially their innate component. This retrospective study aimed at evaluating incidence, risk factors, and influence on survival of these complications in a population of 86 patients, which underwent allo-SCT at our Centre between 2018 and 2022.

Methods: Patient's and transplant characteristics were analysed in relation to TTP, VOD, and MAS. Chi-squared test and Mann-Whitney U test were used to compare percentages and continuous variables, respectively. Overall survival (OS) was estimated by the Kaplan-Meier method. The cumulative incidence

procedure was used to estimate transplant related mortality (TRM) and incidence of acute GVHD.

Median age at transplant was 53 years (range, 20-68), 50% of patients were male, and acute leukaemia was the main diagnosis (75%).

Results: The incidence of TTP, VOD, and MAS was 10%, 11% and 9%, respectively. Overall, these complications affected the transplant related mortality (1year-TRM C.I. 46 vs 15%; $p = 0.01$) and survival (2year-OS 38 vs 62%; $p = 0.04$). The incidence of grade III-IV acute GVHD was higher in patients with microangiopathic syndromes and MAS (TTP 47 vs 6%, $p = 0.0003$; VOD 38 vs 9% $p = 0.04$; VOD/TTP/MAS 32 vs 6% $p = 0.009$).

Among patient's and transplant variables, the ones which correlated with TTP and VOD were high/very high disease risk index ($p = 0.04$), and HHV-6 and BKP-virus reactivation ($p < 0.05$). The elapsed time from harvest to cryopreservation of SC correlated positively with MAS (33 vs 18 hours; $p = 0.04$) and all the immune-mediated syndromes (25 vs 18 hours; $p = 0.01$). Reduced CD34 viability was associated with MAS (88 vs 96%; $p = 0.04$).

Conclusions: Our study confirmed the negative influence on survival of microangiopathic syndromes and MAS by increasing TRM, and likely by interplaying with severe acute GVHD. Cryopreservation with reduced CD34 viability and graft travelling time correlated with all these syndromes, and thus with a poor transplant outcome. Cryopreservation and graft travelling time may also affect the vitality and the function of not only CD34+ cells, but of lymphocyte subsets as well. Furthermore, the variable composition of apoptotic cells in the graft may trigger pro-inflammatory responses in an unpredictable way. Our findings, if confirmed by further studies, suggest a careful approach to cryopreserved graft, especially by limiting the travelling time. Furthermore, the role of graft composition should be further investigated, not only in term of viable and functioning cell subtypes, but also in term of apoptotic cell subtypes.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P554

INCIDENCE OF GRAFT FAILURE AND DELAYED ENGRAFTMENT AFTER ASCT IN SPANISH HOSPITAL: SUCCESSFUL OUTCOME WITH THE USE OF CYCLOSPORINE

Maria Poza[1], Irene Zamanillo[1], Rodrigo Iñiguez[1], María Calbacho[1], Jose Maria Sánchez-Pina[1], Sandra Gómez-Rojas[1], Pilar Martínez[1], Adolfo Sáez[1], Paula Lázaro[1], Joaquin Martinez-Lopez[1], Ana Jiménez-Ubieto[1]

[1]Hospital Universitario 12 de Octubre, Madrid, Spain

Background: Graft failure (GF) is a rare but severe complication in patients undergoing autologous stem cell transplantation.

Methods: A cohort of 451 consecutive patients receiving autologous stem cell transplantation (ASCT) from January 2014 to May 2022 at a Spanish transplant center were reviewed. We collected main variables to analyze the median days to neutrophil and platelet engraftment and the incidence of graft failure. GF was defined as the failure of granulocyte counts to reach 0,5 x 109 /L by day 28. Delayed engraftment was defined as absolute neutropena at day 18.

We herein report a series of 5 cases with GF or delayed engraftment treated with cyclosporine.

Results:

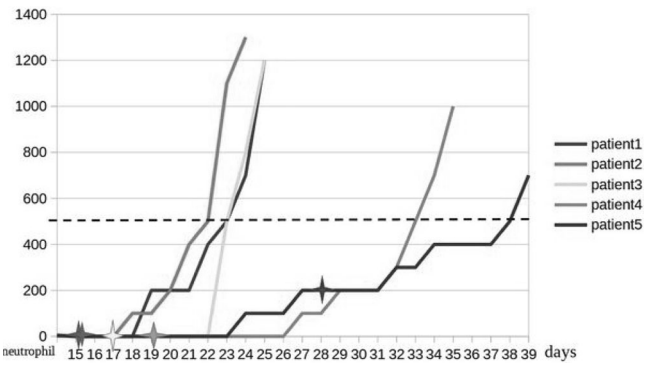
The median age to ASCT was 58 years (range 13-71) and 45% were female. The more frequent indications were 53% Multiple Myeloma (MM) and 25,7% Non-Hodgkin Lymphoma (NHL). Of the 410 patients with available laboratory data, the median number of days to neutrophil and platelet engraftment was 11 and 12, respectively. Only 2 patients (0,44%) did not reach neutrophil engraftment at day 28 and presented a graft failure. One was treated with cyclosporine and the other other was treated with prednisona and died of invasive aspergillosis. Moreover, only 16 (3,9%) patients presented neutrophil delayed engraftment. No clinical or analytical variable was prognostic of GF.

During these years, 1 patient with GF and 4 patients with delayed engraftment were treated with cyclosporine. The diagnoses were 3 MM and 2 NHL. The conditioning regimen used was BUMEL, MEL200, BEAM, and TT-BCNU. The median CD34+ infused dose was 2.74x10^6/kg (range from 2.19 to 3.36). All patients received 300 mcg granulocyte colony-stimulating factor QD since day +5 after cell infusion, with dose escalation after day +14.

Immunosuppressive treatment with cyclosporine was started a median between days 18 and 29 after stem cell infusion. The ideal therapeutic plasma level of cyclosporine was established between 150 and 300ng/ml, by analogy with immune-related cytopenias. Bone marrow biopsy was performed in three cases, resulting in severe hypoplasia and no fibrosis. Three patients also received a stem cell booster infusion. 3 patients could stop cyclosporine after 30 days of treatment due to stable neutrophil and platelet count and 2 patients required more prolonged treatment.

In terms of security two of the patients developed mild renal failure, managed by dose adjustment. No other adverse events were reported.

Today, all the patients remain with good neutrophil and platelet engraftment.



Conclusions: GF in ASCT is a very rare complication, barely described in the literature. In our center a very low GF rate was reported, but with significant mortality (50%). The pathophysiological mechanism is not very well described and, beyond the infused dose of CD34+, no other predictors of GF have been consistently proven. Due to the possibility of an underlying immune mechanism, cyclosporine was used in 5 patients with GF or delayed engraftment, with successful results in all of them, without significant adverse effects. We strongly support postponing allogenic stem cell transplantations in the GF algorithm and promptly use cyclosporine.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P555

OUTCOMES OF OUTPATIENT AUTO-HSCT

Juan Carlos Caballero Hernáez[1], Amalia Domingo González[1], Jose L. López Lorenzo[1], Javier Cornago Navascués[1], Laura Pardo

Gambarte[1], Alberto López García[1], Raquel Capellán García[1], Jesús Ignacio Merlo Luis[1], Alberto Sánchez Donaire[1], Ana Rodríguez Calvo[1], Carmen López Álvarez[1], Pilar Llamas Sillero[1], Laura Solán Blanco[1]

[1]Fundación Jiménez Díaz University Hospital, Madrid, Spain

Background: While high-dose chemotherapy followed by hematopoietic stem cell transplantation (HSTC) continues to be one of the standard treatments for patients with multiple myeloma (MM) and lymphoma, the development of outpatient (OP) transplantation programs has become increasingly common(1,2). The purpose of this study is to evaluate the outcomes between patients undergoing HSCT in the hospital and patients introduced into the home transplantation program in a tertiary hospital since March 2021.

Methods: We performed a retrospective analysis of 72 adults with MM and lymphoma diagnosis undergoing autologous HSCT between March 2021 and December 2022 at Fundación Jiménez Díaz University Hospital. Patients undergoing OP transplant program were discharged on day 1 after stem cell infusion. Furthermore, these performed anti-infectious prophylaxis with levofloxacin, ceftriaxone and fluconazole. Unlike inpatients (IP) transplant program, they also used intermediate doses of corticosteroids for 6 days to avoid engraftment syndrome and did not use G-CSF. SPSS 25.0 software was used for statistical analysis.

Results: Baseline patient characteristics are described in Table 1.

Median number of infused CD34+ cells was the same in both cohorts, $3.4x10^6$/kg IP (range 2.06-6.30) and $3.4x10^6$/kg OP (range 2.4-9.6).

Median time to engraftment was significantly shorter in hospitalized patients: 11 days (10-16) *vs*. 14 days (12-25) for neutrophils >500/µl and 11 days (10-40) *vs*. 21 days (12-32) for neutrophils >1000/µl ($p < 0.001$). This could be justified because OP did not receive G-CSF, and they were blood-tested less frequently.

Despite de above, we observed significantly less febrile episodes in OP; 33% *vs*. 87% (HR 16; $p < 0.001$). Of these fevers, 36.5% had an infectious cause for IP and none for OP ($p = 0.13$).

We found no differences in time to platelet engraftment (>20.000/µl); 18 days IP (range 11-43) *vs*. 21 days OP (range 12-32) ($p = 0.8$).

Furthermore, we found significantly less mucositis development OP rather than IP: 25% *vs*. 87% (HR 21; $p < 0.001$), (Figure 1).

None of OP received parenteral nutrition compared to 78% of IP ($p < 0.001$). None of OP received morphine infusion compared to 10% IP ($p = 0.24$).

We found no significant differences in diarrhea rates 36.7% OP *vs*. 27.3% IP ($p = 0.09$) although there is tendency toward significance.

Engraftment syndrome tends to be more common in hospitalized patients (55% *vs*. 33.3%; $p = 0.17$).

Table 1. Patient characteristics

	Inpatients	Outpatientes	*p value*
Patients, n	60	12	
Age, median (range)	58 (39-72)	54 (46-68)	0.28
Sex			
Man / Female	32/28	6/6	0.8
Personal history, n (%)			0.49
HIV	3 (5)	1 (8)	
Cardiovascular disease	9 (15)	1 (8)	
Cancer history	4 (6)	0 (0)	
Age-adjusted HCT-CI, n (%)			0.45
<3	33 (55)	8 (66)	
≥3	27 (45)	4 (33)	
Primary disease, n (%)			0.8
MM/AL	41 (68)	9 (75)	
Lymphoma	19 (31)	3(25)	
Response before HCT, n (%)			0.7
Complete remission	35 (28)	6 (50)	
Not complete remission	25 (42)	6 (50)	

HIV human inmunodeficiency virus; *MM* multiple myeloma; *AL* amyloid light-chain amyloidosis; *HCT* hematopoietic cell transplantation.

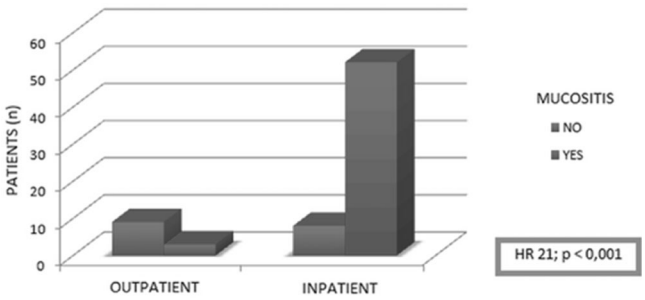


Figure 1. Mucositis in patients with autologous HCT

Conclusions: Outpatient auto-HSCT is a safe and accessible alternative with significant benefits for patients. Despite the small size of our series, a lower rate of digestive complications, especially mucositis, and fewer febrile events are confirmed.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P556

ENERGY INTAKE, LEVEL OF NUTRITION SUPPORT AND SYMPTOMS FOLLOWING STEM CELL TRANSPLANTATION. A RETROSPECTIVE, OBSERVATIONAL STUDY

Victoria Mace[1], Sarah Biglin[1], Simon Hallam[1], Edward Truelove[1], Hortensia Gimeno[1,2]

[1]Barts Health NHS Trust, London, United Kingdom, [2]Wolfson Institute for Population Health, Queen Mary University, London, United Kingdom

Background: Malnutrition, defined as consuming less than 50% nutritional requirements for more than seven days, is common in patients undergoing stem cell transplant (SCT) due to the toxicity of conditioning chemotherapy. Malnutrition is associated with an increased risk of complications, such as infection, longer hospital admission, poorer tolerance of treatment, muscle wasting and reduced quality of life. This study describes energy intake, nutrition support and side effects which reduce oral intake (nutrition impact symptoms) in the 28 days post SCT, specifically in relation to conditioning regimen.

Methods: Retrospective single-centre analysis on all patients following SCT at St Bartholomew's Hospital between June and November 2021. Data were collected on patient characteristics, conditioning regimen, estimated energy requirements, estimated energy intake, nutrition impact symptoms, route of

nutrition support and days to neutrophil engraftment. Energy intake was based on 24 hour dietary recall or food record charts. Data are included here on regimens received by 10 or more patients.

Results: Data from a total of 53 patients, 25 (47%) female and 28 (53%) male were included in the study. There were 6 (11%) of Asian, Asian-British, Asian-Bangladeshi or Asian-Pakistani ethnicity, 6 (11%) Black, Black British-Caribbean or Black British-African and 41 (77%) were White British or White non-British. The median age was 60, the youngest patient was 34 and the eldest 74.

Of the conditioning regimens, 29 (55%) received myeloablative Melphalan, 12 (23%) received myeloablative LEAM (Lomustine, Etoposide, Ara-C, Melphalan) and 12 (23%) received Flu/Cy (Fludarabine, Cyclophosphamide) reduced intensity SCT.

Criteria for artificial nutrition support (ANS) were met in 27 (51%) of the cohort. ANS was recommended to 22 of this group however, 18 (82%) declined. The remaining 5 were not recommended ANS, according to the patient records.

Energy intake did not immediately improve post neutrophil recovery, with 15 (37%) having inadequate energy intake for more than 12 days. See table 1 for more detailed results.

Table 1: Energy intake, nutrition support and symptoms related to conditioning regimen.

	Conditioning Regimen		
	Melphalan N = 29	**LEAM N = 12**	**Flu/Cy N = 12**
Days with < 50% estimated energy requirements			
Median (range)	8 (0-28) days	12.5 (5-23) days	0.5 (0-18) days
>7 days (%)	16 (55)	9 (75)	2 (17)
>12 days (%)	9 (31)	6 (50)	2 (17)
Highest level of nutrition support (%)			
Food First	0	1 (8)	3 (25)
Oral nutritional supplements	25 (86)	9 (75)	7 (58)
Naso-gastric tube	4 (14)	0	2 (16)
Total parenteral nutrition	0	2 (16)	0
Nutrition impact symptoms (%)			
Reduced appetite	26 (90)	12 (100)	5 (42)
Taste changes	26 (90)	11 (92)	4 (33)
Diarrhoea	24 (83)	12 (100)	5 (42)
Nausea	25 (26)	9 (75)	5 (42)
Vomiting	15 (52)	6 (50)	1 (7)
Oral mucositis	12 (41)	9 (75)	3 (25)
Days to neutrophil engraftment (>0.5 x $10^{9/L}$)			
Median (range)	10 (7-15) days	11 (9-17) days	16.5 (12-33) days

Conclusions: This study shows the majority of patients who receive myeloablative autologous SCT are malnourished. Reduced appetite, taste changes, diarrhoea, nausea, vomiting and mucositis are common and impact oral intake.

European and American guidelines recommend enteral nutrition (e.g. naso-gastric tube) if a patient is likely to have less than 50% of their nutritional requirements for more than seven days. This study shows uptake of this is low, resulting in increased incidence of malnutrition. This presents an opportunity to understand barriers to enteral nutrition in this patient group.

Patients who have a reduced intensity allogeneic SCT have a longer hospital admission due to a lengthier time to neutrophil engraftment. However, as nutrition impact symptoms were less common in this group, fewer of these patients were malnourished.

For patients who are malnourished post SCT, our current practice of oral nutritional supplements is inadequate for patients to meet nutritional requirements. An alternative approach, such as earlier promotion of ANS, consideration of prophylactic enteral nutrition and improved management of nutrition impact symptoms, warrants further research.

Clinical Trial Registry: n/a

Disclosure: No conflict of interest.

14 - Non-infectious Early Complications

P557

EFFICACY AND ADVERSE EFFECTS OF ABO MISMATCH TRANSFUSIONS IN PATIENTS WITH HIGH-TITER MAJOR AB0 MISMATCH BEFORE ALLOGENEIC STEM CELL TRANSPLANTATION

Emma Oberbach[1], Mascha Binder[1], Lutz P. Müller[1], Judith Schaffrath[1]

[1]Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

Background: In allogeneic stem cell transplantation (alloSCT), an AB0 major mismatch between stem cell recipient and donor is associated with increased risks during and after alloSCT and an increased need for blood transfusions, particularly in case of a high antibody titer against the donor's blood group. A commonly used method to reduce this high antibody titer is AB0 mismatch red blood cell transfusion with the donor's blood group.

Methods: In our exploratory retrospective unicentric study, we investigated 132 patients aged 20 to 75 years with AB0 major mismatch, who received a first or second alloSCT from a 9/10 or 10/10 matched related or unrelated donor for various hematologic diseases between 2005 and 2022. According to local standards, AB0 mismatch transfusions were applied to patients with an antibody titer > 1:8. We compared antibody titers before and after mismatch transfusions and investigated the frequencies of adverse events related to the transfusion. In the entire cohort of patients with major AB0 mismatch we compared post-SCT transfusion requirements as well as other mismatch related adverse events in patients who received mismatch transfusions compared to those who did not.

Results: In our cohort of 132 patients with major AB0 mismatch, 43 patients received a median of two mismatch transfusions prior to alloSCT. The median donor-blood group directed antibody titer was reduced from 1:32 before mismatch transfusions to 1:8 afterwards ($p = 0.001$), but remained at a higher level than in patients who did not require mismatch transfusions (median 1:4, $p = 0.003$).

During mismatch transfusion 51.2% of patients developed adverse events, 18.2% CTC°II or higher. Fever was the most common (27.9%), followed by hypertension (18.6%) and tachycardia (18.6%). 9.5% of patients required additional medication during mismatch transfusion, most frequently paracetamol (30.2%). One patient had to be transferred to the intensive care unit due to hypotension possibly related to the transfusion.

There were no differences between the two groups regarding adverse events and medication requirements during alloSCT as well as regarding the time to engraftment (thrombocytes $p = 0.799$, neutrophils $p = 0.202$). No difference in the number of red blood cell transfusions within the first 100 days after alloSCT was observed ($p = 0.133$).

There was no difference in overall and progression free survival between the two groups.

Conclusions: Our study comprises the largest analysis of mismatch transfusions in patients with major AB0 mismatch prior to alloSCT so far. Although our study was limited by its retrospective design and the lack of an actual control group, we conclude that AB0 mismatch transfusions are a procedure with tolerable adverse events. While they fail to completely eliminate the high antibody titer pre-alloSCT, no difference in overall and progression free survival as well as transfusion requirements was observed. This suggests a protective effect against adverse events related to high-titer major AB0 mismatch SCT.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P558

ACUTE KIDNEY INJURY IN PATIENTS UNDERGOING HSCT: A RETROSPECTIVE COHORT STUDY

Pastora Duarte[1], Isabella Duarte[2], João Vitor Duarte[2], Beatrice Duarte[2], Fernando Duarte[1]

[1]Universidade Federal do Ceará, Fortaleza, Brazil, [2]Christus University, Fortaleza, Brazil

Background: Hematopoietic Stem Cell Transplantation (HSCT) is a procedure widely performed in patients with hematological autoimmune diseases and metabolic disorders which involves the administration of healthy hematopoietic stem cells, which increases the overall survival. Despite this, Acute Kidney Injury(AKI) remains a frequent complication, affecting 10-70% of patients, contributing to an expressive mortality. Objectives: To analyze the occurrence of AKI in patients undergoing HSCT, correlate the sociodemographic and clinical profile and variables related to HSCT with the onset and evolution of AKI.

Methods: Retrospective cohort study, with descriptive and analytical approach, including all patients undergoing HSCT between Jan/2014 and Dec/2019 at Hospital Universitário Walter Cantídio(HUWC). Data were collected from multidisciplinary medical records and Master platform for laboratory tests and were tabulated in Microsoft Excel® 2016. For identification and stratification of AKI, the KDIGO method was used. Serum, creatinine was used as a marker of glomerular filtration rate (GFR) at time Zero, d30, d60 and d100 after HSCT, the CKD-EPI formula was used for estimation.

Results: 391 patients were included in the analysis, the most prevalent underlying disease was Multiple Myeloma (35.04%), followed by leukemia (31.20%). We had 264 autologous (67.52%) and 127 allogeneic (32.48%) HSCT. AKI was diagnosed in 129 patients (32.99%). In multivariate analysis, by logistic regression, the variables independently associated with AKI were: Allogeneic transplantation, diagnosis of leukemia and germ cell tumor, need for transfusion of packed red blood cells, use of three or more classes of antimicrobials, use of amphotericin B, polymyxin B, amikacin, voriconazole and teicoplanin, grafting time, BuFlu conditioning protocols, CyATG, FluCyATG, FluMel 140 and FluMel180, sepsis/ septic shock, sinusoidal obstruction syndrome, cytomegalovirus infection, grade III mucositis and use of calcineurin inhibitors. The test post hoc showed that basal and early creatinines were different and higher than intermediate and late and that GFR in patients with AKI were lower than in those without AKI in all periods, except for baseline. The survival time of the group without AKI was higher than the group with AKI, and in these groups, the need to use renal replacement therapy (RRT) determined a higher risk of death. Among those who underwent conservative treatment, we found greater survival in those who recovered their kidney function.

Conclusions: The incidence of AKI in patients undergoing HSCT at the HUWC was high, with classical association variables confirming its importance and impact on patient survival.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P559

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME FOLLOWING PEDIATRIC ALLOGENEIC BONE MARROW TRANSPLANTATION: A CASE SERIES OF SINGLE CENTER EXPERIENCE

Hatice Ilgen Sasmaz[1,2], Bulent Antmen[1], Utku Aygunes[1], Barbaros Sahin Karagun[1], Duygu Turksoy[1]

[1]Acibadem Adana Hospital, Adana, Turkey, [2]Cukurova University, Adana, Turkey

Background: Posterior reversible encephalopathy syndrome (PRES) is an neuro-radiological syndrome characterized by headache, seizures, visual disturbance, and altered mental function associated with reversible white matter edema affecting the posterior parietal and occipital lobes of brain. PRES has been reported to occur in association with numerous co-morbidities, including hypertensive encephalopathy, pre-eclampsia, eclampsia, infections, electrolyte imbalance, immunosuppressive drugs, allogeneic bone marrow transplantation (BMT), solid organ transplantation, autoimmune diseases, and high-dose cancer chemotherapy. We report 31 patients who developed PRES during the treatments with Cyclosporine A (CsA), tacrolimus and metilprednisolone, utilized for graft versus host disease (GVHD) prophylaxis and treatment after pediatric allogeneic BMT.

Methods: Between 2013 and 2022, 502 patients received an allogeneic BMT at Acıbadem Adana Hospital Pediatric Bone Marrow Transplant Unit. Thirty one cases of PRES were observed in this period. Medical records and magnetic resonance images (MRIs) were evaluated retrospectively.

Results: We presented 35 patients with PRES, age ranging from 3 years to 19 years with a average of 10.4 years. There were 14 patients with thalassemia major, 9 patients with acute leukemia, 4 patients with sickle cell disease and 1 patient with myelodysplastic syndrome, one patient with immune deficiency, four patients with fanconi aplastic anemia, one patient with diamond blackfan Anemia, one patient with congenital dyserythropoietic anemia. Fourteen patients were males, 17 were females. All patients were treated with CsA or tacrolimus and metilprednisolone for the prophylasix of GVHD. PRES occurred at a median of 75 days (range 4-625). Clinical findings at onset of leukoencephalopathy were hypertension, headache, seizures, visual disturbance, and altered mental function. MRI showed abnormalities in all patients including patchy bilateral cortical and subcortical lesions, especially in parieto-occipital lobes.

Conclusions: BMT is ascociated with several neurological complications that may be underlying diseases, BMT procedure, and severe immunosupression. One of these condition that PRES is not an uncommon and serious complication after BMT. In this retrospective analysis of 35 cases of PRES who received allogeneic BMT, we reported our experiences, conclusions and that to emphasize the importance of early recognition and institution of appropriate management of PRES following BMT of early 100 days.

Disclosure: No disclosure.

14 - Non-infectious Early Complications

P560

PERCUTANEOUS GASTROSTOMY IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Maxim Kucher[1], Alexander Shvetcov[1], Nina Gurgenidze[1], Natalya Saltykova[1], Maxim Kondrashov[1], Alexander Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation

Background: In some cases, the most optimal option for providing long-term nutritional support in allogeneic hematopoietic stem cell transplantation (allo-HSCT) is gastrostomy. Currently, this surgical technology is being improved and represents a minimally invasive endoscopic manipulation. However, the using experience in allo-HSCT is extremely limited due to the risk of hemorrhagic and infectious complications.

Methods: Since 2016, in RM Gorbacheva Research Institute of Pediatric Oncology, Hematology and Transplantation 25 percutaneous endoscopic gastrostomies (PEG) have been installed for allo-HSCT recipients from 7 months to 45 years old with acute leukemia – 19, neuroblastoma – 2, multiple myeloma – 1, X-linked adrenoleukodystrophy – 1, Wiskott-Aldrich syndrome – 1, primary immunodeficiency – 1. In 76% of patients (n = 19), low-profile silicone radiopaque MIC-KEY tubes were used according to age, in 24% – standard MIC tubes (Avanos, USA). The installation was performed via "push" technology with the T-shaped gastrointestinal Saf-T-Pexy fixative introducers and with endotracheal anesthesia for the aspiration prevention and better gastrostomy positioning. The main criteria for predicting a low risk of complications were the absence of cytopenia, coagulopathy, platelet count of more than $50x10^9$/l, which in the study ranged from 20 to $424x10^9$/l, average – $156x10^9$/l. In the case of thrombocypenia, the preventive transfusion of platelet concentrate was performed. It was mandatory to teach the patient and/or accompanying persons the exploitation rules of gastrostomy care.

Results: Indications for gastrostomy were anorexia (n = 9), cachexia as the outcome of the intestinal graft-versus-host disease (GvHD) (n = 5), malabsorption syndrome on the background of mixed etiology enterocolitis (intestinal GvHD, colonization with pan-resistant strains of *Klebsiella pneumonie*, cytomegalovirus infection, Epstein-Barr virus) (n = 5), malabsorption syndrome as a result of GvHD (n = 3) and cerebral insufficiency (n = 3). The terms of gastrostomy installation after allo-HSCT ranged from 7 to 1336 days, the average – 321 days. In one patient, gastrostomy was performed preventively before allo-HSCT. Nutritional status at the time of manipulation was: cachexia (n = 9), grade III hypotrophy (n = 7), grade II hypotrophy (n = 5), grade I hypotrophy (n = 4). The duration of gastrostomy exploitation ranged from 8 to 775 days, the average was 201 days, while one patient included in the study continues dynamic follow-up. By the time of the gastrostomy removing, the nutritional status remained unchanged in 14 patients, improved in 10 and with no cases of negative anthropometric dynamics. The gastrostomy was removed due to the restoration of sufficient self-feeding (n = 13), provocation of vomiting (n = 1), malabsorption syndrome escalation (n = 1). In 9 cases, gastrostomy was used until the moment of death, which was not associated with the manipulation: septic shock (n = 5), disease progression (n = 3), gastrointestinal bleeding (n = 1). During the installation and gastrostomy usage, major complications were noted: gastric bleeding (n = 1); minor – peristomal pain syndrome (n = 3), skin maceration (n = 1), urge to vomit with bolus injection of fluids and enteral formulas (n = 1).

Conclusions: The obtained data demonstrate the relative safety of PEG in allo-HSCT patients and sufficient clinical efficacy to maintain and improve nutritional status on the background of severe digestive system dysfunction. It is necessary to define accurate criteria for the gastrostomy installation in this cohort of patients in order to avoid untimely, as a rule, belated decision-making.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P561

CLINICAL EFFICACY AND SAFETY OF NARSOPLIMAB IN A PATIENT WITH WORSENING HSCT-TMA FOLLOWING DISCONTINUATION OF CALCINEURIN INHIBITORS

Felix Mensah[1]

[1]Indiana Blood and Marrow Transplantation, Franciscan Health Alliance, Indianapolis, United States

Background: Hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA) is a serious complication of HSCT, arising from endothelial injury associated with conditioning or graft-versus-host disease (GVHD). Endothelial injury activates the lectin pathway of complement; narsoplimab inhibits MASP-2, the effector enzyme of the lectin pathway. In a pivotal clinical trial, narsoplimab showed 61% response rate in patients with HSCT-TMA.

Methods: In this case report of a patient with worsening HSCT-TMA following withdrawal of calcineurin inhibitors (CNIs), HSCT-TMA resolved upon treatment with narsoplimab via a compassionate use program.

Results: A 40-year-old female was diagnosed with Stage 4 diffuse large B-cell lymphoma. She received autologous HSCT after first complete remission but later relapsed. She underwent CAR-T therapy and subsequent imaging showed no evidence of disease. She relapsed once again and was treated with radiation therapy and salvage chemotherapy. End of treatment PET/CT showed no evidence of disease.

She subsequently underwent matched unrelated allogeneic HSCT after reduced-intensity conditioning with FluCy/TBI, with post-transplant cyclophosphamide. Post-HSCT immunosuppression involved mycophenolate mofetil and cyclosporin. She engrafted on Day +16. Post-transplant, she developed biopsy-proven Grade 3 aGVHD involving the GI tract. She was initially treated with steroids, ruxolitinib, and photopheresis. However, ruxolitinib was discontinued due to cytopenia; she remained on photopheresis, steroids, and cyclosporin for GVHD. The patient was weaned off prednisone but had a recurrence of GVHD and was deemed steroid-dependent. She was admitted and received tocilizumab for GVHD.

Subsequently, the patient was diagnosed with HSCT-TMA three months post-transplant due to hemolytic anemia, lactate dehydrogenase (LDH; peak of 3,313 U/L), and proteinuria. ADAMTS13 activity was 61%, indicating absence of thrombotic thrombocytopenic purpura. Complement levels including C3, C4, and CH50 were normal. Cyclosporin was discontinued and she received 1 dose of eculizumab and plasma exchange, with no improvement. Three weeks later, she started on narsoplimab and received 9 doses, 370 mg twice weekly for 4 weeks.

Narsoplimab treatment led to clinical resolution of HSCT-TMA. During treatment, laboratory values improved from: 18 to 43 $x10^9$

L (platelets); 558 to 253 U/L (LDH); 6.8 to 8.9 g/dL (hemoglobin); and <30 to 198 mg/dL (haptoglobin). Patient monitoring continued and lab values remain normal.

Conclusions: Following withdrawal of CNIs, the patient's HSCT-TMA continued to worsen. After 4 weeks of narsoplimab, HSCT-TMA resolved and in 10 months since last dose, there has been no relapse of HSCT-TMA. Narsoplimab was well tolerated with no adverse events.

Disclosure: Felix Mensah: funding (CTI Bio, Eli Lilly); honoraria (Omeros, Targeted Oncology).

14 - Non-infectious Early Complications

P562

OVERLAP OF TA-TMA VS ACUTE GVHD IN THE GASTROINTESTINAL TRACT: TWO CHALLENGING CASE REPORTS

Sara Tarantino[1], Paola Perfetti[1], Alessia Ripamonti[1], Beatrice Manghisi[1], Marilena Fedele[1], Elisabetta Terruzzi[1], Andrea Aroldi[1], Carlo Gambacorti Passerini[1], Matteo Parma[1]

[1]Ospedale San Gerardo, Monza, Italy

Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is a complication of allogeneic hematopoietic stem cell transplant (HSCT). The triad of endothelial cell activation, complement dysregulation, and microvascular haemolytic anaemia can cause organ dysfunction with high mortality rate. Involvement of gastrointestinal (GI) tract is frequent in TA-TMA and clinical manifestations are similar to GI acute Graft versus Host Disease (GVHD), representing an important diagnostic and therapeutic challenge. Here we present two cases of TA-TMA involving GI tract.

Methods: Case 1: a 19 yo patient (MUD-HSCT for AML) developed at day +31 severe GI symptoms compatible with aGvHD, refractory to steroid treatment. Endoscopic examination and micro-bioptic analysis revealed severe mucosal damage of whole GI tract, so the immune-suppressive (IS) treatment was increased with the introduction of Ruxolitinib, oral Budesonide, Extracorporeal Photopheresis, Mycophenolate-Mofetile (MMF) and Mesenchymal Stem Cells (MSC), without significant clinical improvement.

At day +78 an important bleeding appeared due to ulcerative lesions from the last portion of ileus requiring two surgical resections for a total of 80 cm. Histologic exam showed microthrombi in the terminal arterial vessels. In the previous days LDH level, platelets count and schistocytes were only minimally abnormal and do not satisfy serologic criteria for TA-TMA. Immediately Cyclosporin-A (CyA) was suspended, then patient progressively improved. Actually, 11 months after HSCT, he is waiting for recanalization, free of IS treatment.

Case 2: a 43-yo patient (Haploidentical-HSCT for T-ALL), developed at day +20 severe GI symptoms (grade IV, Magic Criteria). Biopsies from endoscopy revealed severe damage to the intestinal and stomach mucosa compatible with severe a-GVHD. Steroid treatment and oral Budesonide were started in addition to CyA and MMF followed by Ruxolitinib and MSC for failure of response. After an initial improvement there was a clinical worsening with bowel bleeding, renal failure, jaundice, hypertension, serositis. High LDH level, proteinuria, schistocytes, sC5b-9 levels and decrease of C3 levels were compatible with TA-TMA. CyA was stopped and Eculizumab was administered. At day +55 rectal bleeding increased so that the patient underwent right colectomy. The histologic exam showed persistent severe a-GvHD as well as damage to vessels associated with endoluminal thrombi consistent with TA-TMA. Unfortunately, patient died of massive bleeding after surgery.

Results: These two cases showed the overlap of TA-TMA and GvHD in GI tract. Clinical features are the same in GI TA-TMA and GvHD. Endoscopic micro-bioptic analysis cannot always reveal vessel typical damage. Unfortunately, TA-TMA is often related to calcineurin inhibitors which are difficult to suspend in patients affected by GvHD. Biochemical parameters (LDH level, platelet counts, schistocytes) and clinical criteria (severe hypertension) of TA-TMA can lack in GI form and only histologic analysis, can provide a sure diagnosis of TA-TMA, as shown in our cases.

Conclusions: These two cases outlined that TA-TMA diagnosis is extremely difficult in some settings such as GI involvement, when the clinical features are the same of GvHD and laboratory criteria are not satisfied. When TA-TMA is suspected, calcineurin inhibitors should be promptly suspended.

Disclosure: Nothing to disclose.

14 - Non-infectious Early Complications

P563

EVALUATING THE INCIDENCE, RISK FACTORS AND OUTCOME OF ACUTE KIDNEY INJURY AMONG PEDIATRIC PATIENTS RECEIVING HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Bibi Shahin Shamsian[1], Atbin Latifi[1], Nader Momtazmanesh[1], Zahra Khafafpour[1], Masoumeh Mohkam[1], Armin Shirvani[1], Mahnaz Jamee[1]

[1]Shahid Beheshti University of Medical Sciences, Tehran, Iran, Islamic Republic of

Background: Acute kidney injury (AKI) is a common adverse event after hematopoietic stem cell transplantation (HSCT) which can lead to chronic kidney disease (CKD) and mortality. AKI may cause many limitations in the correct management of HSCT-related complications including the administration of therapeutic components. Due to its clinical impact and the scarcity of studies about AKI in pediatric HSCT, this study may be helpful for optimizing the treatment and management of patients.

Methods: This retrospective study was performed on patients receiving HSCT at the pediatric transplantation ward of Mofid Children's Hospital, Tehran, from 2016 to 2021. The demographic, clinical, and laboratory data of enrolled patients were investigated from medical records at the time of admission and the latest outpatient follow-up at the post-transplantation clinic. AKI was defined and staged according to the KDIGO criteria. In order to classify the AKI stages, the serum creatinine level of the patients was measured at the baseline and then on the first, third, and seventh days and the second to fourteenth weeks after HSCT.

Results: This study included 110 transplanted patients (68 [61.8%] male and 42 [38.2%] female) at a mean (±SD) age of 6.4 (±4.1) years. Sixty-four (58.1%) patients had malignant and 46 (41.9%) had non-malignant underlying disorders. Most patients (84, 76.3%) received allogeneic HSCT with the source of peripheral blood (66, 78.5%), bone marrow (10, 11.9%), and cord blood (8, 9.6%). The other 26 (23.7%) patients underwent autologous HSCT. The majority of patients (77, 70%) received myeloablative conditioning (MAC) regimens with busulfan, melphalan, fludarabine, ATG, cyclophosphamide, carboplatin, and etoposide. Other patients (33, 30%) received reduced intensity conditioning (RIC) with ATG, melphalan, and fludarabine. AKI was developed in 53 (48%) patients within the first 100 days post-transplant. The

incidence of stage 1, 2, and 3 AKI was 38%, 40%, and 22%, respectively. The incidence of AKI in allogenic HSCT was more than in autologous HSCT ($p = 0.023$). Patients with younger age ($p = 0.033$) and non-malignant underlying disorder ($p = 0.033$) had higher risks of developing AKI. Patients' gender, source of HSCT, type of conditioning regimen and GvHD prophylaxis, and thrombotic events (veno-occlusive disease (VOD) and transplant-associated thrombotic microangiopathy (TA-TMA)) were not significantly correlated with AKI manifestation. At the end of the survey, 77 patients (70%) were alive and 33 patients (30%) were deceased. There was a statistically significant positive correlation between AKI stages with mortality ($p = 0.004$).

Conclusions: This study showed a high prevalence of AKI among transplanted patients, particularly in those with allogenic HSCT, low age at the time of transplantation, and non-malignant disorder. The post-transplant renal monitoring at regular intervals may improve patients' survival.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P564

INVESTIGATION OF THE FREQUENCY AND RISK FACTORS OF CARDIAC COMPLICATIONS AFTER INITIAL ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Ryu Yanagisawa[1], Hideyuki Nakazawa[2], Mikiko Harada[2], Hitoshi Sakai[2], Sayaka Nishina[2], Toru Kawakami[2], Fumihiro Kawakami[2], Shin-ichiro Fujiwara[3], Hirohiko Motoki[2], Toshiro Ito[4]

[1]Shinshu University Hospital, Matsumoto, Japan, [2]Shinshu University School of Medicine, Matsumoto, Japan, [3]Jichi Medical University, Shimotsuke, Japan, [4]National Hospital Organization Matsumoto Medical Center, Matsumoto, Japan

Background: Cardiac complications after hematopoietic cell transplantation (HCT) are rare but can sometimes lead to serious outcomes. Thus, further clarification of the incidence and risk factors of cardiac complications is desirable. We aimed to determine the frequency of cardiac complications after HCT and the risk factors involved.

Methods: We analyzed 308 adult patients who underwent first allogeneic HCT at Shinshu University Hospital between 2005 and 2022, and used the patient background data available before HCT. Patients who required additional chemotherapy or HCT due to recurrence or failure of engraftment were censored at that time.

Results: Cardiac complications occurred in total 38 patients, with an incidence of 11.3% (95% confidence interval [CI]: 7.9–15.3) at 5 years after HCT. Cardiac complications included heart failure, pericarditis/myocarditis/pericardial effusion, and arrhythmia/coronary artery disease, with incidence rates of 4.7% (95% CI: 2.7–7.6), 3.7% (95% CI: 1.9–6.5), and 2.8% (95% CI: 1.3–5.3), respectively. For heart failure, there were multiple candidate risk factors, but multivariate analysis identified left ventricular ejection fraction before HCT of <60% (hazard ratio [HR] 4.238, 95% CI: 1.571–11.930; $p = 0.005$) and cumulative anthracycline dose before HCT of ≥250mg/m^2 (calculated as doxorubicin equivalent doses) (HR 3.456, 95% CI: 1.148–10.400; $p = 0.027$) as risk factors. For other cardiac complications, no risk factors were identified in the patient background before HCT.

Conclusions: Some patient background characteristics at the time of HCT may be related to the risk of developing heart failure. Therefore, screening prior to HCT may help predict the onset of heart failure. On the other hand, the risk of other cardiac complications may be influenced to a large extent by lifestyle and patient background characteristics after HCT.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P565

INTENSIVE CARE OUTCOMES IN ADULT HEMATOPOIETIC STEM CELL TRANSPLANTATION PATIENTS AT A SINGLE CENTER

Jose Luis Lopez Lorenzo[1], Laura Pardo Gambarte[1], Javier Cornago Navascues[1], Sergio Ramos Cillan[1], Alberto Lazaro Garcia[1], Juan Carlos Caballero Hernaez[1], Edwin Uriel Suarez Merchan[1], Raquel Capellan Garcia[1], Alicia de las Heras Moreno[1], Gonzalo Castellanos Arias[1], Laura Solan Blanco[1], Teresa Arquero Portero[1], Begoña Perez de Camino Gaisse[1], Isabel Iturrate Basaran[1], Jose Maria Milicua Muñoz[1], Natividad Arias Martinez[1], Alberto Lopez Garcia[1], Gala Vega Achabal[1], Lara Colino Gomez[1], Elena Prieto Pareja[1], Cesar Perez Calvo[1], Pilar Llamas Sillero[1]

[1]Hospital Fundacion Jimenez Diaz, Madrid, Spain

Background: Intensive care unit (ICU) admission following hematopoietic stem cell transplantation (HSCT) is an threatening event. Our objective was to determine the probability of ICU admission by type of HSCT, reason and short and long term outcome.

Methods: We review 435 HSCT performed at our center between January/2013 and September/2022, that were admitted to ICU for any reason during the first 60 days at our hospital.

Results: Twenty-four (5.5%) (13 males and 11 females) of all HSCT were admitted to the ICU in this period. 139 allogenic HSCT, 17 (10 males and 7 females) were admitted at ICU. The median age was 53 years. The main reason was respiratory failure followed by septic shock. The diagnosis were 6 AML, 4 high risk MDS, 2 Myelofibrosis, 2 advanced Mycoses fungoides, 1 T ALL, 1 NOS peripheral T NHL and 1 advanced Hodgkin Lymphoma. The HSCT type was always peripheral stem cells and there were 5 family identical donors, 8 haploidentical donors and 4 non-related donors. 11 (65%) of patients died during ICU stay. 3 more during prolonged hospitalization. Median days stay in ICU was 5 (1-69). There were no survivors after intubation. Most patients were in multiorgan failure at some point. 3 long term survivors relapsed (1 ALL,1 mycoses and 1 HL). 2 patients survived longer than 2 years, 1 AML with well controlled chronic GVHD and 1 HL that needed additional therapy for relapse. Between 296 autologous HSCT, 7(3 males and 4 females) were admitted to ICU.the median age was 54 years(40-67). Also the main reason was respiratory failure followed by septic shock The diagnosis were 4 myeloma and 3 NHL. There were 2 pneumonia (influenza and unknow germ), 1 hearth failure, 1 convulsion because CNL lymphoma progression, 1 septic shock, 1 progressive myeloma and 1 renal failure. 4 patients survived long term, all relapsed after some time, and need additional therapy. The overall probability of developing complications requiring ICU admission was 12% for allogeneic transplantation and 2% for patients receiving autologous grafts.

Conclusions: The probability of admission to ICU for allogenic and autologous HSCT is very different. Less autologous HSCT are admitted, and if admitted to ICU have a higher probability of recovery. Long term survival for allogenic HSCT is still very poor. Endotraqueal intubation is a very bad sign. We need to do better, but intensive care support can be life-saving.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P566

EVALUATION OF IMPACT OF AUTOLOGOUS HEMATOPOIETIC STEM CELL MOBILIZATION ON LEFT HEART FUNCTION AND SIZES

Audrone Vaitiekiene[1], Monika Bieseviciene[1], Benas Kireilis[2], Migle Kulboke[3], Justinas Zemaitis[1], Antanas Jankauskas[4], Rolandas Gerbutavicius[3], Milda Rudzianskiene[3], Ruta Dambrauskiene[3], Elona Juozaityte[3], Jolanta Justina Vaskelyte[1], Domas Vaitiekus[3], Gintare Sakalyte[1]

Lithuanian University of Health Sciences, Kaunas, Lithuania, [2]Lithuanian University of Health Sciences, Medical Academy, Kaunas, Lithuania, Lithuanian University of Health Sciences, Kaunas, Lithuania, Lithuanian University of Health Sciences, Kaunas, Lithuania

Background: Hematopoietic stem cell transplantation (HSCT) process is known to cause cardiac toxicity of different grade. Recently published guidelines of cardio-oncology developed by European Society of Cardiology (ESC) classified patients' risk according to the type of HSCT (allogeinic versus autologous), cardiovascular risk factors, preexisting cardiovalscular morbidities, cardiotoxic anticancer treatment effects. To our knowlende there is no published data of cardiovascular impact of different parts of HSCT proccess. In this paper we aimed to evaluate the impact of mobilization procedure for autologous HSCT proccess on left ventricular function and size of left ventricle and atrium.

Methods: Data of 24 patients undergoing autologous HSCT at the Department of Oncology and Hematology in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics from October 2021 till November 2022 were analysed. Bioethics approvement for prospective study was obtained (No BE-2-96). All patients underwent hematopoietic stem cell mobilization with chemotherapy and filgrastim 10ųg/kg/d. Echocardiography was performed two times: before enrolling to the transplantation process and after mobilization before the transplantation procedure. Echocardiography was performed and evaluated by one experienced cardiologist using Phillips Epiq 7 ultrasound machine. Left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (EF), left ventricular global longitudinal strain (GLS), left atrium (LA) diameter from parasternal axis view and LA volume and their changes were evaluated. SPSS statistics 20 was used for statistical analysis. Qualitative data is presented as absolute value (N) and percentage (%), quantitative parameters are given as average (m ± standard deviation). We used paired-samples T test to compare quantitative parameters. Statistically significant difference was considered, when $p < 0.05$.

Results: Out of 24 patients there were 13 men (54.2%) and 11 women (45.8%). Mean age was 55.75 ± 15.167 years, ranging from 18 to 73. 17 (70,8%) patients had multiple myeloma, 6 (25,0%) Hodgkin and non-Hodgkin lymphoma, and 1 (4,2%) Ewing's sarcoma. Mean LVEDD before mobilization was 47.00 ± 2.813 mm, after 47,58 ± 4.010 mm, no statistically significant difference was observed ($p = 0.493$). Mean EF before mobilization was 61.11 ± 7.465 %, after 60.95 ± 7.089 %, ($p = 0.935$). Mean GLS before mobilization was -16.85 ± 3.235%, after -17.85 ± 4.148% ($p = 0.138$). LA diameter before mobilization was 38.41 ± 5.672mm, after 38.21 ± 6.833 (p 0.802), LA volume before mobilization was 59.67 ± 15.893 ml, after 58.96 ± 23.673 ml (p 0.829). No statistically significant change in evaluated parameters was observed.

Conclusions: Mobilization procedure does not have a short term negative impact on the function of left ventricle and sizes of left ventricle and left atrium.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P567

EVALUATION OF EFFICACY IN FOLINIC ACID PREVENTING ORAL MUCOSITIS AFTER METHOTREXATE CONTAINED GVHD PROPHLAXIS FOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Bahar Sevgili[1], Ajda Güneş[1], Denis Sabriye Bozer[1], Nur Soyer[1], Mahmut Töbü[1], Fahri Şahin[1], Güray Saydam[1], Filiz Vural[1]

[1]Ege University, Izmir, Turkey

Background: Mucositis is challenging early complication of allogeneic hematopoietic stem cell transplantation (AlloHSCT). Methotrexate (MTX) for graft versus host disease (GVHD) prophylaxis has been widely used though its well-known mucosal toxicity. Effect of folinic acid (FA) rescue after low dose MTX as prophylaxis is still controversial with little knowledge based on small studies. We aimed to evaluate the effect of FA after MTX on mucositis following posttransplant 30 days.

Methods: We retrospectively analyzed patients who had undergone alloHSCT and had received MTX for GVHD prophylaxis between January 2021- December 2022 in Ege University Adult Stem Cell Transplantation Center; after exclusion of patients who had inadequate information in their records. Age, sex, HSCT comorbidity index (HSCT-CI), previous diagnosis, conditioning regimens and its intensity, previous oropharyngeal pathologies such as mucositis, dental implant, or denture history. All the patients received MTX on D1 15 mg/m2 and 10 mg on D3,6,11. FA was administered 4x5 mg/m2 24 hours later of MTX use. All the patients received supportive treatment such as antiseptic mouthwash, glutamine and oral cryotherapy if needed. Patients' mucositis incidence, grade (according to CTCAE version 5.0), duration of resolution, opiate need, use of parenteral nutrition (PE) posttransplant first 30 days.

Results: Twelve patients received FA and 10 patients FA naive were included to our study. All the patients received MTX based GVHD regimen (20 of patients received with cyclosporin, 1 with tacrolimus and 1 with cyclosporin combined with posttransplant cyclophosphamide) and FA dose with no delay or dose reduction. Patient's gender, HSCT-CI, conditioning regimens' intensity, previous oropharyngeal pathology incidence was found similar in both groups. Mucositis incidence (3 in FA group and 6 in FA-naïve group, p: 0,13) and severe (grade 3-4) mucositis incidence was lower in FA group but not statistically significant (FA/ FA naïve: 2/3, P: 0,288). Mean duration of resolving mucositis was 9 days to 20 days (p: 0,073) Opiate need or total parenteral nutrition use due to mucositis were also lower in FA group though not statistically significant. Gastroenteritis was reported 4 in FA group whereas 3 in FA naïve group. (Table 1)

Table 1: previous history of of alloHSCT patients and Comparative outcomes of patiens posttransplant 30 days.

PARAMETER	FA received	FA naive	Total/ overall evaluation	P value
Age, median (year)	31 (19-59)	37 (20-66)	33	0,07
Female/male	3/9	7/3	12/10	0,084
HSCT-CI (0-1 / 2-3)	10/2	8/2	12/10	0,381
Diagnosis				

PARAMETER	FA received	FA naive	Total/ overall evaluation	P value
Acute myeloid leukemia	4	0	4	
Acute lymphoblastic leukemia	3	0	3	
Myelodysplastic syndrome	0	1	1	
Aplastic anemia	2	2	4	
Lymphoma	3	2	2	
Other	3	1	4	
Conditioning intensity (MAC/RIC)	6/6	4/6	10/12	0,658
Previous oropharyngeal pathology (no/yes)	7/5	8/2	15/7	0,3
OUTCOMES				
Mucositis	3	6	9	0,13
Grade 3-4 mucositis	2	3	5	0,288
Opiate need	1	4	5	0,078
Total parenteral nutrition	1	3	4	0,190
Gastroenteritis	4	3	7	0,867
Mucositis resolution (mean day)	9 (5-14)	20 (3-43)	15	0,06

Conclusions: Results about FA use after MTX for GVHD prophylaxis is not yet satisfactory. In our study, we found lower incidence of mucositis and shorter duration of resolution though not statistically significant. More prospective clinical trials with larger groups are needed to improve our knowledge.

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

P568

MANAGEMENT OF PEDIATRIC SINUSOIDAL OBSTRUCTION SYNDROME/VENO-OCCLUSIVE DISEASE IN A RESOURCE-LIMITED SETTING: A CASE REPORT

Sara M Makkeyah[1], Nayera HK El-Sherif[1], Fatma SE Ebeid[1], Salwa M AbdelKader[1], Marwa W Tolba[1], Safa M Sayed[1]

[1]Pediatric Hematology/Oncology & BMT Unit, Ain Shams University, Cairo, Egypt

Background: Sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is a serious and potentially life-threatening condition. Access to therapy represents a major obstacle to timely appropriate management in resource-limited countries.

Methods: We herein report a case of SOS/VOD successfully managed in the absence of the standard of care treatment.

Results: A nine-year-old girl was admitted to receive her matched sibling donor peripheral blood SCT for transfusion-dependent beta-thalassemia. Her conditioning regimen was Bu/Cy (busulfan and cyclophosphamide) and she received antithymocyte globulin, cyclosporin, and methotrexate (ATG/CSA/MTX) for graft-versus-host disease (GVHD) prophylaxis. We used ursodeoxycholic acid as SOS/VOD prophylaxis together with low dose low molecular weight heparin (LMWH). On the fifteenth day post stem cell infusion, she showed a rise in serum bilirubin 2.6 mg/dl, ALT 24 IU/L, AST 38 IU/L, and LDH 201 IU/L, followed one day later by severe epigastric and right hypochondrial pain. Physical examination revealed a weight gain of more than 2% (31.2 Kg from 30 Kg), and a painful hepatomegaly (11 cm below costal margin). A pelviabdominal ultrasound revealed normal portal flow, mild ascites, and mild pleural effusion. Over the previous week, she suffered mild blood-tinged vomiting and subconjunctival hemorrhage for which LMWH was stopped and she received multiple platelet transfusions with a poor platelet increment. We initiated IV furosemide and oral spironolactone together with fluid restriction. Two days later, the patient had multiple episodes of melena together, progressive abdominal enlargement, and elevated kidney function tests creatinine 1.2 mg/dl from a baseline of 0.3 mg/dl, BUN 20 mg/dl, serum bilirubin 2.5 mg/dl, ALT 34 IU/L, AST 53 IU/L, and LDH 232 IU/L. As there was no access to defibrotide treatment at that time and based on the diagnosis of severe SOS/VOD according to the new EBMT criteria, we initiated furosemide infusion and fresh frozen plasma (FFP) transfusion to correct the ongoing coagulopathy. Concurrently, methylprednisolone was started at a dose of 500 mg twice daily for 6 doses followed by 2 mg/k/d for 3 days then gradually weaned off. Over the following ten days, the patient showed gradual improvement with the resolution of her abdominal pain, regression of her weight, and decrease in hepatomegaly. She had normalized liver and kidney function tests, and resolution of the pleural effusion and the ascites.

Conclusions: Supportive therapy and methylprednisolone may be an acceptable alternative if defibrotide cannot be used in patients with severe SOS/VOD.

Clinical Trial Registry:

Disclosure: All authors declare no conflict of interest.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P569

HCT FRAILTY SCALE FOR YOUNGER AND OLDER ADULTS UNDERGOING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Maria Queralt Salas[1,2], Eshetu Atenafu[2], Ivan Pasic[2], Oral Bascom[2], Leeann Wilson[2], Carol Chen[2], Wilson Lam[2], Arjun Datt Law[2], Igor Novitzky-Basso[2], Dennis Dong Hwan Kim[2], Armin Gerbitz[2], Auro Viswabandya[2], Fotios V Michelis[2], Jeffrey Howard Lipton[2], Jonas Mattsson[2], Shabbir Alibhai[2], Rajat Kumar[2]

[1]Hospital Clinic de Barcelona, Barcelona, Spain, [2]Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

Background: In 2018, a frailty assessment composed of the Clinical Frailty Scale, Instrumental Activities of Daily Living Test, Timed-up and Go and Grip Strength tests, Self-Health Rated Questionnaire, falls question, and albumin and C-reactive protein levels was implemented at our Institution for all adult candidates for allo-HCT, using existing resources. Consecutively, with these measurements, a HCT Frailty Scale was designed to classify patients into fit, pre-frail, and frail groups.

This study compares the characteristics and risk factors of fit, pre-frail and frail patients, and explores the clinical relevance of frailty in allo-HCT in two ways: Evaluating the power of the frailty classification to predict OS and NRM of transplants; and assessing whether the predictive power was similar in younger and in older patients.

Methods: 298 adults undergoing allo-HCT between 2018 and 2020 were prospectively included. With the application of the scoring and cut-off values, patients evaluated in all components of the frailty scale were classified into fit, pre-frail, and frail groups.

Results: Overall, the median age was 58; 102 (34.2%) adults underwent MAC allo-HCT, and 70 (26.2%) received alternative donor grafts. At the first consultation, 103 (34.6%) patients were classified as fit, 148 (49.7%) as pre-frail, and 47 (15.8%) as frail, with comparable age medians and sex. There were significantly more frail patients than Fit/Pre-Frail patients with HCT-CI score > 3 (34% vs. 16.2%, P = 0.0047) and with KPS < 90% (48.9% vs. 13.4%, P < 0.001).

The 2-year OS and NRM of frail, pre-frail, and fit patients were 48.3%, 67.4%, and 82.9% (P < 0.001) and 37.7%, 19.5% and 5.4% (P < 0.001), respectively. The multivariable analysis controlling for HCT-CI and KPS, confirmed that pre-frail and frail patients had higher HR for OS (Pre-frail: HR 2.10, P = 0.021 / Frail: HR 4.51, P < 0.001) and higher NRM (Pre-frail: HR 4.22, P = 0.006 / Frail: HR 9.40, P < 0.001) than fit patients; age was not an independent risk factor for OS and NRM **(Table 1)**.

Univariate Regression Analysis	Overall Survival HR (95% CI)	P value	Non-Relapse Mortality HR (95% CI)	P value
HCT Frailty Scale				
Fit	Ref.	-	Ref.	-
Pre-Frail	2.00 (1.09-3.69)	0.026	1.56 (0.95-2.55)	0.078
Frail	4.39 (2.26-8.55)	<0.001	2.88 (1.64-5.08)	<0.001
Multivariate Regression Analysis	**Overall Survival HR (95% CI)**	**P value**	**Non-Relapse Mortality HR (95% CI)**	**P value**
HCT Frailty Scale				
Fit	Ref.	-	Ref	-
Pre-Frail	2.10 (1.12-3.94)	0.021	4.22 (1.51-11.83)	0.006
Frail	4.51 (2.18-9.33)	<0.001	9.40 (3.02-29.28)	<0.001
Age				
>60 years (vs. ≤60 years)	1.42 (0.78-2.56)	0.251	0.69 (0.29-1.61)	0.391
KPS				
70-80% (vs. 90-100%)	0.91 (0.50-1.65)	0.762	0.88 (0.40-1.90)	0.735
HCT-CI				
>3 (vs. 0-3)	1.67 (0.95-2.92)	0.074	2.27 (1.17-4.40)	0.015
Conditioning Intensity				
RIC (vs. MAC)	1.01 (0.52-1.97)	0.983	1.03 (0.40-2.61)	0.956
Donor type				
9/10 MMUD, haplo (MSD, MUD)	1.33 (0.65-2.71)	0.982	1.38 (0.58-3.25)	0.466
Grade 3-4 acute GVHD				
Time-dependent variable	5.94 (3.55-9.94)	<0.001	1.02 (0.98-1.06)	0.279

When separating the patients into younger (n = 174) and older (n = 124) than 60 years, the HCT Frailty Scale classified patients into the three frailty groups in comparable proportions in the two age groups (P = 0.984). The 2-year OS and NRM of frail, pre-frail, and fit in older adults were 41.4%, 63.8%, and 75.5% (P = 0.006), and 42.1%, 16.4%, and 4.9%, (P = 0.001). The 2-year OS and NRM for frail, pre-frail, and fit younger adults were 53.1%, 69.3%, and 88.4% (P = 0.002), and 34.8%, 22.8%, and 5.8% (P = 0.005). Lastly, controlling for HCT-CI and KPS, the HRs of OS of frail patients relative to the fit ones was statistically different in the older (HR 5.09, P = 0.002) and the younger (HR 5.02, P = 0.004) groups.

Conclusions: Frailty, diagnosed according to the HCT Frailty Scale, was an independent predictor of worse post-transplant outcomes. The probability of being classified as fit, pre-frail, and frail was similar in older and younger patients. The difference in the likelihood of OS between frail patients and the rest was the same in the two age groups.

Clinical Trial Registry: No applicable

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P570

TEN-YEAR FOLLOW UP STUDY OF CHILDREN WITH THALASSAEMIA MAJOR POST TRANSPLANTATION USING TREOSULFAN, THIOTEPA, FLUDARABINE BASED CONDITIONING REGIMEN AND ITS IMPACT ON GROWTH AND PUBERTY

Revathi Raj[1], Ramya Uppuluri[1], Venkateswaran Vellaichamy Swaminathan[1], Satishkumar Meena[1], Kavitha Ganesan[1], Sohini Chakraborty[1], Suresh Duraisamy[1], Soundaram Karthik[1]

[1]Apollo Cancer Hospitals, Chennai, India

Background: We present a uniform cohort of children with thalassaemia major who underwent treosulfan conditioning based HSCT and its impact on growth and puberty.

Methods: Our study is a retrospective analysis on children who underwent allogeneic HSCT for transfusion dependent thalassaemia major between 2010 to 2020 with a minimum follow up period of two years. All children were classified as per Lucarelli Class 1, 2 and 3 based on the iron overload status and received conditioning chemotherapy with treosulfan, thiotepa and fludarabine with ATG for MUD And ATG and 2 Gy total body radiotherapy for haploidentical HSCT. Data collection focussed on the presence of graft versus host disease both acute and chronic, and the need for steroid use for over 4 weeks. We documented the height and weight and Tanner stage if applicable at the time of HSCT and the current height, weight and Tanner stage and the need for growth hormone replacement. The study has been approved by our hospital Ethics Committee.

Results: Of 202 children in our study 59% were males and 41% females and 110/202 (54%) had a matched family donor (MFD), 62/202 (31%) haploidentical and 30/202 (15%) matched unrelated donor (MUD). 73 (36%) were in <5 years of age at HSCT, 90 (45%) between 5 to 10 years and 39 (19%) over 10 years of age. The mean height SDS at HSCT was -0.574 and at current assessment the mean height SDS was -0.669 (p = 0.391). There was no major reduction in growth potential. 29 (14.4%) were short at the time of HSCT (height SDS < -2) and at current assessment only 6 (20.7%) were still short and 23 (79.3%) had catch up growth and moved to height SDS > = -2. The mean height SDS during HSCT in Class1 thalassemia was -0.216, -0.478 in Class 2 and -0.898 in Class 3 respectively (p = 0.026). The current height SDS in these classes are -0.115, -0.710 and -0.929 respectively, confirming that children in Class 1 are able to catch up on their growth but the Class 2 and 3 patients failed to catch up growth after HSCT (p = 0.010). In children with acute GVHD there was no difference in contrast to a statistically significant difference in mean current height SDS in chronic GVHD group (-0.468 against -0.920, p = 0.020).

In the children currently above 10 years group, 17 (43.6%) were in Tanner stage 5 at HSCT and of the 83 female children, 45 (54.2%) attained spontaneous menarche. Their mean age during HSCT was 8 years and their current mean age is 14.8 years. 14 (6.9%) children are on growth hormone GH.

Conclusions: Our study clearly demonstrates that treosulfan does not have a negative impact on growth and puberty in children with thalassaemia major. Only 6.9 % children required growth hormone supplementation and there was no impact on puberty in both boys and girls with menarche at a median age of 14.8 years Despite the higher cost of treosulfan the reduced late side effects justifies its use in all children undergoing HSCT for thalassaemia major.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P571

IMPACT OF HYDROXYUREA AND VASO-OCCLUSIVE CRISIS ON OVARIAN FOLLICLE DENSITY IN GIRLS AND YOUNG FEMALES WITH SICKLE CELL DISEASE

Tamara Diesch-Furlanetto[1], Catherine Poirot[2], Carlos Sanchez[3], Andrew Atkinson[3], Corinne Pondarré[4], Nathalie Dhedin[2], Bénédicte Neven[5], France Pirenne[6], Gilles Lenaour[7], Isabelle Brocheriou[7], Benoit Terris[8], Francoise Bernaudin[4], Jean-Hugues Dalle[9]

University Children's Hospital, Basel, Switzerland, AYA Unit, Saint Louis Hospital, Paris, France, [3]Pediatric Research Center, University Children's Hospital, Basel, Switzerland, [4]French Referral Center for Sickle Cell Disease, Centre Hospitalier Intercommunal Créteil, Université Paris XII, Créteil, France, [5]Pediatric Immunology, Hematology and Rheumatology Unit, Necker Enfants Malades Hospital, Paris, France, [6]Etablissement Francais Sang Ile de France, Henri Mondor Hospital, Créteil, France, [7]Groupe Hospitalier Pitié-Salpetrière, Paris, France, [8]Cochin-Port Royal Hospital, Paris, France, [9]Hematology & Immunology Pediatric Unit, Robet Debré Hospital, Paris, France

Background: One of the major advances in care for sickle cell disease (SCD) is the introduction of hydroxyurea (HU) in the middle of the 1980s to prevent vaso-occlusive crisis. Despite the proven benefit of HU, there are concerns about side effects. In male mice application of HU impacts spermatogenesis resulting in a hypogonadism. In young boys, it is been shown that HU didn't affect the spermatogonial pool. In adult men a reduction of sperm count was observed. Little is known about gonadotoxicity of HU in women with SCD. The purpose of the study was to assess the impact of HU exposure and vaso-occlusive crisis on ovarian follicle density in young females with SCD who had an ovarian tissue cryopreservation (OTC) before hematological stem cell transplantation (HSCT), as fertility preservation measure.

Methods: In this retrospective multicenter cohort study females with SCD who underwent an OTC before HSCT were included. OTC was performed between April 1998 and November 2020 at one institution. After written informed consent from patient or their parents at time-point of OTC, a fragment of ovarian tissue was evaluated histologically. Each histological slide was revised from two independent investigators with a digital system (Hewell, Paris, France). All follicles were counted and classified according to their growing stage. Surface of each fragment was measured. The follicular density was calculated as number of primordial follicles divided by the surface of the sample and expressed in mm^2. For the comparison of the follicle density values non-paired Wilcoxon Rank-sum test was performed and for the concordance test between the two investigators, the Cronbach's alpha was used. Medical data concerning complications, HU treatment and pubertal development were extracted from medical records. This study was approved by ethical committee of Avicenne Hospital, France (CLEA-2021-195).

Results: In totally, 88 sickle cell females with HbSS were enrolled Their median age at OTC was 10.9 years [IQR 7.5, 14.7]. Fifty-six (64%) were prepubertal at time point of OTC. Forty patients (45%) were under HU treatment at the time of OTC with a median daily dosage of 23.0 mg/kg [IQR 20.0, 25.0] and a median exposure time of 43.5 months [IQR 21.0, 54.7]. VOC were reported in 78% (69/88) of the cohort, 49% (34/69) were under HU treatment. Blood transfusion were administered in 94% (83/88). The median applied units were 22.0 [IQR 11.5, 47.5]. Concordance test showed an accordance of 98% between the two investigators for histological evaluation. Follicle density was similar in the HU group compared to those without HU exposure (median 6.0 follicle/mm^2 [IQR 1.6, 12.8] versus 5.6 follicle/mm2 [IQR 1.2, 13.7], $p = 0.614$). Follicle density was significantly higher in patients without VOC (median 12.3 [IQR 7.4, 21.9])) compared to those with VOC (median 5.0 [IQR 1.5, 12.0]; $p = 0.015$). There was no correlation between applied transfusion units and follicle density ($p = 0.45$).

Conclusions: Hydroxyurea exposure does not appear to reduce ovarian follicle density in females with SCD. For the first time our study could show an influence of VOC on ovarian follicle density.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P572

METABOLIC SYNDROME AFTER PEDIATRIC ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR NONMALIGNANT DISEASES

Joëll E. Bense[1], Erik G. J. von Asmuth[1], Sophie E.H. van Rees-Vellinga[1], Arjan C. Lankester[1], Hester Vlaardingerbroek[1], Anne P.J. de Pagter[1]

[1]Leiden University Medical Center, Leiden, Netherlands

Background: Metabolic syndrome (MetS) has not yet been evaluated in patients after pediatric allogenic hematopoietic stem cell transplantation (HSCT) for nonmalignant diseases, but knowledge is essential for long-term comprehensive care programs, where prompt screening on MetS could contribute to reduce the risk of cardiovascular disease, diabetes, and premature mortality.

Methods: This single center retrospective study evaluated MetS and MetS components among patients ≥2 years after pediatric HSCT for nonmalignant diseases who participated to our long-term follow-up comprehensive care program. Due to the lack of international consensus, and due to data availability, a modified definition of MetS was used. MetS can only be diagnosed in patients above 10 years of age and was defined as at least 3 components present simultaneously. Patients below 10 years of age were assessed for the individual MetS components. Point prevalence was calculated at set timepoints (2, 5, 10 and 20 years post-HSCT). Additionally, to take transient MetS components into account multistate analysis was performed, which included patients with ages above and below 10 years.

Table 1. Modified definition MetS

Age	BMI	Triglycerides	Total cholesterol	Blood pressure	Random glucose levels
< 10 years	Z-score > 2	>2.2 mmol/L Males > 3.1 mmol/L Females	> 4.8 mmol/L Males > 5.1 mmol/L Females	Z-score > 95th percentile *or* use of antihypertensive drugs	> 11.1 mmol/L *or* use of antidiabetic drugs
10-16 years	Z-score > 2	≥ 1.7 mmol/L	> 5.2 mmol/L Males > 5.3 mmol/L Females	Z-score > 95th percentile *or* use of antihypertensive drugs	> 11.1 mmol/L *or* use of antidiabetic drugs
> 16 years	Z-score > 2	≥ 1.7 mmol/L	> 5.0 mmol/L	Z-score > 95th percentile *or* use of antihypertensive drugs	> 11.1 mmol/L *or* use of antidiabetic drugs

Results: This study included 137 patients, of whom 83 were male (61%). Median age at HSCT was 5.4 years (IQR 1.8-11.3 years) and median follow-up was 8.4 years (IQR 4.6-14.8 years). Underlying diseases were inborn errors of immunity (N = 52), hemoglobinopathies (N = 39), and bone marrow failure syndromes (N = 46). At HSCT, 9 patients (7%) had a BMI Z-score >2.

At 2 years post-HSCT, 46 patients were above the age of 10, of whom 1 had MetS (2%), and 33 had 1-2 MetS components (37%). At this timepoint, 65 patients were aged below 10, of whom 33 had 1-2 MetS components (51%). At 5 years post-HSCT, 38 patients were above the age of 10, of whom 3 had MetS (8%), and 12 had 1-2 MetS components (32%). At this timepoint, 41 patients were aged below 10, of whom 20 had 1-2 MetS components (49%). Of the MetS components hypertension was most common, especially in patients below 10 years of age (32%).

Using multistate analysis to model progression of MetS components, starting at 2 years post-HSCT with 1% of the patients having MetS and 45% having 1-2 MetS components (as established by a cross-section at that timepoint). MetS occurrence increased to 4.2% at 5 years post-HSCT, with 40% of the patients having 1-2 MetS components. Subsequently, MetS occurrence decreased to 3.4% at 10 year post-HSCT, with 35% of the patients having 1-2 MetS components.

Conclusions: This was the first study to evaluate MetS in patients after pediatric HSCT for nonmalignant diseases and the first to take the transient nature of individual MetS components into account. MetS occurred in 8% of the patients at 5 years post-HSCT. Presence of 1-2 MetS components was common, specifically in patients below 10 years of age, and ranged from 27-51% across the set timepoints. These results indicate the need for adequate screening strategies in a structured comprehensive care program and early intervention to prevent MetS in HSCT patients.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P573

GERIATRIC ASSESSMENT AND OUTCOMES OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN OLDER PATIENTS

Parastoo B. Dahi[1], Armin Shahrokni[1], Jessica Flynn[1], Sean M. Devlin[1], Stephanie A. Chinapen[1], Jennifer Ayala[1], Soni Brown[1], Sarah Bugen[1], Christina Cho[1], Boglarka Gyurkocza[1], Soo Jung Kim[1], Richard Lin[1], Esperanza B. Papadopoulos[1], Miguel-Angel Perales[1], Ioannis Politikos[1], Doris M. Ponce[1], Brian C. Shaffer[1], Gunjan Shah[1], Roni Tamari[1], James W. Young[1], Sergio A. Giralt[1], Ann A. Jakubowski[1]

[1]Memorial Sloan Kettering Cancer Center, New York, United States

Background: Allogeneic hematopoietic cell transplantation (allo-HCT) candidacy in older patients is not well defined.

Methods: We incorporated a self-reported, electronic rapid fitness assessment (eRFA) tool to evaluate patient's physical and cognitive function over 12 domains, including Timed Up and Go (TUG) and Mini-Cog. An accumulated geriatric deficit score is the composite of the number of impairments (0-12).

Results: The allo-HCT outcomes of 327 consecutive recipients ≥65 years between 2015-2021 were studied. 131 patients provided eRFAs, of which 75 completed all domains. The 95% cumulative incidences (CI) of neutrophil and platelet engraftment at day +30 were 99% and 75% respectively. The CI of grades III/IV acute graft-versus-host disease (GvHD) at day +100 was 17%, and chronic GvHD at 1-year was 2.2%. The CI of relapse was 30% at 1- and 35% at 2-years respectively. The CI of non-relapse mortality was 4% at 100 days and 13% at 1-year, respectively. 151 patients died: disease relapse or progression (n = 84, 25%), GvHD (n = 29; 19%), infection (n = 20, 13%), organ failure (n = 10, 3%), second malignancy (n = 2, 1.3%), graft failure (n = 1), others (n = 5, 1.5%). The 2-year progression-free (PFS) and overall survivals (OS) were 48% and 59%, respectively. We identified high levels of impairments in activity (71%) and depression (62%). In univariate analysis, higher eRFA score was significantly associated with lower PFS and OS.

Conclusions: Tools like eRFA can provide complementary information to the traditional age, performance status, and HCT-CI on the patient's overall risk for HCT and may further enable interventions for identified impairments.

Clinical Trial Registry: n/a

Disclosure: Nothing to declare relevant to this study.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P574

EFFECT OF BUSULFAN AND TREOSULFAN ON GONADAL FUNCTION AFTER ALLOGENEIC STEM CELL TRANSPLANTATION IN CHILDREN AND ADOLESCENTS WITH NONMALIGNANT DISEASES IS NOT EXPOSURE-DEPENDENT

Mey Yin Eileen Christina van der Stoep[1], Joëll E Bense[1], Liselotte C de Kloet[1], Erik G J von Asmuth[1], Anne P J de Pagter[1], Sabine E Hannema[1,2], Henk-Jan Guchelaar[1], Juliette Zwaveling[1], Arjan C Lankester[1]

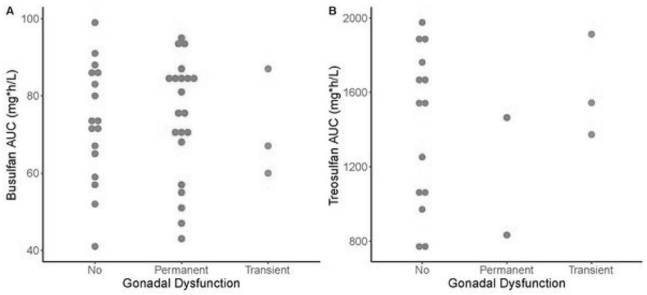
[1]Leiden University Medical Center, Leiden, Netherlands, [2]Amsterdam UMC, Vrije Universiteit, Amsterdam, Netherlands

Background: With an increasing number of young patients surviving into adulthood after hematopoietic stem cell transplantation (HSCT), gonadal dysfunction becomes an important late effect with significant impact on quality of life. To date, it is unknown if drug exposure is of influence on the prevalence of endocrine complications.

Methods: In this retrospective single-center study, we evaluated the exposure of busulfan (BU) and treosulfan (TREO) in relation to gonadal function in pediatric patients transplanted for a nonmalignant disease between 1997 and 2018. All patients underwent a clinical and laboratory endocrine evaluation prior to HSCT. At annual follow-up visits after HSCT, pubertal stage was evaluated and laboratory investigations including FSH, LH, testosterone and estradiol, were performed. Gonadal dysfunction was defined as gonadotropins above the reference range, i.e. FSH ≥ 21.5 U/L and/or LH ≥ 60 U/L for females and FSH ≥ 12.5 U/L and/or LH ≥ 9.0 U/L for men. If elevated gonadotropins had normalized at subsequent visits gonadal dysfunction was classified as transient; if they remained elevated at last visit it was classified as permanent. BU and TREO exposure was divided in 2 exposure groups; low (< 70 mg*h/L for BU and < 1750 mg*h/L for TREO) and high (≥ 70 mg*h/L for BU and ≥ 1750 mg*h/L for TREO).

Results: A total of 157 patients were included, 90 were conditioned with BU and 67 with TREO. Of the 90 patients in the BU cohort, 56 patients were eligible for analysis; 27 patients were still prepubertal and data of 7 patients were incomplete or were excluded from the analysis because of gonadal dysfunction prior to HSCT. Of the 67 patients in the TREO cohort, 32 patients were eligible for analysis; 34 patients were still prepubertal and data of 1 patient was incomplete. In the BU cohort gonadal dysfunction occurred in 35 (63%) patients. Lower BU exposure

(< 70 mg*h/L) was not associated with a reduced risk of gonadal dysfunction (OR 0.92 95% CI 0.25-3.49, p = 0.90). In the TREO cohort gonadal insufficiency occurred in 9 patients (28%). Lower TREO exposure (AUC < 1750 mg*h/L on day 1) was not associated with a reduced risk of gonadal dysfunction (OR 1.6 95%CI 0.16-36.6, p = 0.71) (Figure 1).



Conclusions: Our data do not support the premise that reduced intensity BU-based conditioning lowers the risk for gonadal toxicity and it is unlikely that TDM-based reduced treosulfan exposure will further reduce the risk for gonadal dysfunction.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P575

IDENTIFYING HEALTH MEASURES DIRECTLY INFLUENCING PATIENT REPORTED OUTCOME MEASURES (PROMS) TO DIRECT PATIENT CENTRED LONG TERM FOLLOW UP CARE AFTER ALLOGENEIC HAEMOPOIETIC STEM CELL TRANSPLANTATION

Tricia Wright[1,2], Sharon Avery[1], Yvonne Panek-Hudson[3,4], Daniela Klarica[1], Bianca Cirone[1], Wood Erica[2], David Ritchie[4,3], Andrew Spencer[1,2]

[1]Alfred Health, Melbourne, Australia, [2]Monash University, Melbourne, Australia, [3]The Royal Melbourne Hospital, Parkville, Australia, [4]Peter MacCallum Cancer Centre, Melbourne, Australia

Background: This study examines the impact of chronic health conditions after allogeneic haemopoietic stem cell transplantation (alloHSCT) on health-related quality of life (HRQOL).

Patient reported outcome measures (PROMs) have been identified as critical to the delivery of quality patient centred health care.

Understanding the influences to variations in HRQOL can assist health professionals to deliver patient centred quality long term follow up care.

Methods: Individuals attending Long Term Follow Up (LTFU) clinics after alloHSCT at two tertiary health services in Melbourne Australia were enrolled in the Victorian alloHSCT Survivorship Study (VaHSS).

At each annual LTFU clinic attendance prospective measures of number of chronic diseases, chronic graft versus host disease (cGVHD) status and time since alloHSCT were collected and the Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire completed.

Number of health conditions was divided into 3 cohorts: 1: <3 chronic health conditions; 2: 3-5 chronic health conditions and 3: ≥ 6 chronic health conditions. Chronic graft versus host disease categories (never (1), not active(2), active(3)).

Multiple linear regression was used to test which predictor variables influenced FACT-G scores

Stata/IC 16.1 for Windows was used to develop the fitted regression model.

PROM = β0 + β1*number of post alloHSCT chronic diseases + β2*status of cgvhd + β3*time since alloHSCT to clinical attendance + β0*gender.

Results: Data was analysed from 591 individuals, 321(54%) males, attending the most recent LTFU clinic enrolled in the VaHSS between May 2008 and February 2019.

CGVHD was recorded in 64.3% of participants, half with active disease requiring immunosuppressive therapy.

For males and females there is a trend for a step wise decrease in FACT-G scores with increasing numbers of CHC. For males and females, lower FACT-G scores are associated with active cgvhd

Compared to individuals with 0-2 chronic health conditions, those with

- 3-5 health conditions had a significant reduction in FACT-General HRQOL of an average of 5.7 points (95% CI -9.39, -2.00, p = 0.003
- ≥ 6 chronic health conditions had a significant reduction in FACT-General HRQOL scores of an average of 9.9 points (95% CI -14.4, -5.4), P < 0.0001).

Compared to individuals with no history of cgvhd, those with active cgvhd had a significant average reduction of 5.2 points on the FACT-General HRQOL measure (95% CI -8.91, -1.4, p = 0.007).

There was no difference between individuals with a history of cgvhd and no cgvhd. There was no significant difference between HRQOL FACT-general scores by gender or time since alloHSCT to clinic visit.

Conclusions: Individuals with six or more chronic health conditions compared to one to five chronic health conditions and active cGVHD compared to either a positive history or no cGVHD, identified individuals with poorer HRQOL.

Predictors of poorer HRQOL collected from PROMs provide important information to inform patient centered long term follow up care after alloHSCT.

Disclosure: no conflict of interest.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P576

PREVALENCE, CAUSES AND SURVIVAL IMPACT OF CHRONIC KIDNEY DISEASE IN 1564 RECIPIENTS OF ALLOGENIC HEMATOPOIETIC CELL TRANSPLANTATION

Alexandra Kutilina[1], Jürgen Finke[1], Robert Zeiser[1], Ralph Wäsch[1], Ihorst Gabriele[2], Hartmut Bertz[1], Johanna Schneider[1], Claudia Wehr[1]

[1]Freiburg University Hospital, Freiburg, Germany, [2]Freiburg University, Freiburg, Germany

Background: Deterioration of kidney function is a common complication after allogeneic hematopoietic cell transplantation (allo-HCT). Chronic kidney disease (CKD) has a major effect on global health, both as a direct cause of global morbidity and mortality and as an important risk factor for cardiovascular disease. This study investigates the prevalence and risk factors of CKD at one year after allo-HCT. Also the impact of preexisting and newly diagnosed CKD on post-allo-HCT mortality is assessed.

Methods: In this single-center retrospective study adult patients who had undergone 1st allo-HCT between January 2001 and March 2020 at our center were included. Multivariate analysis, adjusting a logistic regression model, was performed to determine

the independent predictors of CKD-development (CKD as defined by KDIGO: GFR<60ml/min present for >3 months) at one year after allo-HCT. To examine associations between CKD at one year after allo-HCT and overall and relapse-free survival Cox regression was used and the cohort was restricted to survivors at one year.

Results: We identified 1564 patients with median age at allo-HCT of 56 years (IQR 45-64). Among those 170 (10.8 %) had a pre-existing renal insufficiency (KDIGO GFR categories G3a–G5; with two patients having a histologic confirmed CAST-nephropathy). Acute kidney injury developed in 1183 patients (75.68%) within 100 days after transplantation. De novo CKD at one year post-transplant occurred in 196 (12.5%) patients with a median GFR (CKD-EPI) of 48.8 ml/min (IQR 40-54) compared to 85.2 ml/min (IQR 72-98) before allo-HCT. From all de novo CKD patients 159 (81.1%) had AKI in the early post-transplant phase. Significant risk factors associated with a decline in GFR < 60 ml/min at one year after allo-HCT were age > 50 years, occurrence of acute graft versus host disease (GvHD) grade III-IV, moderate and severe chronic GvHD, and acute kidney injury grade 3 within first 100 days after allo-HCT ($p < 0.05$). In cases with nephrological assessment of de novo CKD cases renal GvHD and post-transplant thrombotic microangiopathy (incl. in the context of GvHD) were identified in $n = 7$ and $n = 12$ patients, respectively.

The survivors at one year with CKD had a five-year-mortality rate of 48.9% (46.9% in patients without CKD). However, patients with GFR < 45 ml/min at one year after allo-HCT showed an increased five-year-mortality rate of 58.4%. In the CKD group the main causes of mortality were infections (38.1%), relapsed/refractory disease (32.2%), secondary malignancy (13.5%) and severe graft versus host disease (5%).

Conclusions: CKD was newly diagnosed in 12.5% of all allo-HCT recipients at one year after transplantation. Age, severe acute and chronic GvHD and severe acute kidney injury after allo-HCT were significantly connected to CKD.

Disclosure: Novartis, Incyte, Sanofi, MNK, Takeda.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P577

NEUROLOGIC COMPLICATIONS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH CALCINEURIN-FREE GRAFT-VERSUS-HOST DISEASE PROPHYLAXIS

Aitana Balaguer Roselló[1,2], Sara García Gil-Perotín[1,2], Juan Montoro[1], Marta Villalba[1,2], Ana Facal[1,2], Manuel Guerreiro[1,2], Pedro Chorão[1,2], Alberto Louro[2], Pablo Granados[1], Javier De La Rubia[1], Jaime Sanz[1]

[1]Hospital Universitari i Politecnic la Fe, Valencia, Spain, [2]Instituto Investigación Sanitaria La Fe, Valencia, Spain

Background: Calcineurin inhibitors (CNI) are frequently implicated in a variety of neurologic complications (NCs). The aim of this study is to compare the incidence and characteristics of NCs in two cohorts of adult patients undergoing allo-HSCT, one CNI-based cohort and one CNI-free cohort.

Methods: We evaluated 894 consecutive adult patients with hematologic malignancies who underwent MSD, MUD or haploidentical SCT at our institution using CNI-containing GVHD prophylaxis in the period 2000 to 2016 (CNI-based cohort) and PTCy-Sir-MMF in the subsequent period 2017 to June 2022 (CNI-free cohort).

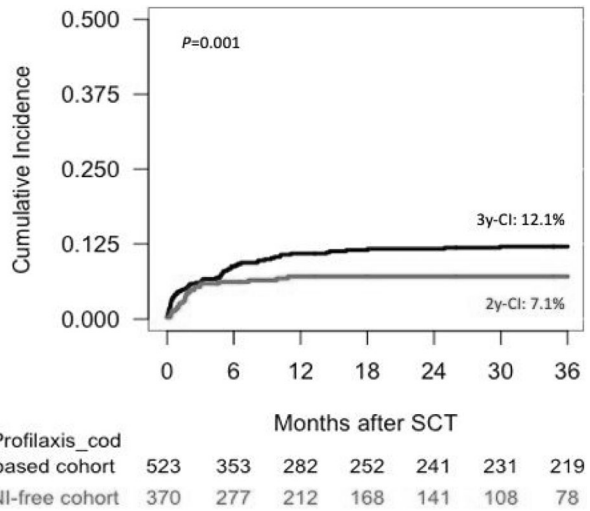
NC was defined as any neurological event that occurred after starting the conditioning regimen and before relapse.

Results: The current series comprised 894 allo-HSCT, of whom 523 received CNI-based GVHD prophylaxis and the remaining 371 received CNI-free regimen. Overall, 585 (65%) patients received MSD transplant, 167 (19%) matched unrelated donor SCT and 142 (16%) an haploidentical SCT. Patients receiving a CNI-free GVHD prophylaxis were older and received more RIC regimens. ($P < 0.001$). A higher proportion of MSD transplants was observed in the CNI-based GVHD prophylaxis (83% versus 41% in the CNI-free cohort). Rest of characteristics were similar in both groups. Median follow-up of surviving patients was 52 months (range, 3–269).

Overall, 96 episodes of NCs were documented, 70 (13.4%) in the CNI-based cohort and 26 (7%) in the CNI-free cohort. The most frequent NC was encephalopathy in both cohorts (27%). The distribution of the rest of noninfectious NC was different in both groups ($P = 0.02$). In the CNI-based cohort the second NC was headache followed by peripheral neuropathy. In the CNI-free cohort, the second most frequent NC was neuropathy followed by cerebrovascular events. Clinical and radiological findings of encephalopathies were different in both groups. Distribution of CNS infections was the same in both groups (10%). Median time to NC was 97 days in the CNI-group and 50 days in the CNI-free cohort.

The cumulative incidence risk of developing at least 1 episode of NC at 6 months and 2 years were 7.7% and 9.9%, respectively. The 2-years cumulative incidence of NC was 12% in the CNI-based GVHD prophylaxis cohort and 7% in the CNI-free GVHD cohort ($P = 0.001$). There were no differences in the cumulative incidence of NCs according to the donor source or conditioning regimen.

The 5-years overall survival was 37% for patients who developed NCs and 54% for the rest ($P < 0.0001$).



Neurologic Complications	Overall (894), n (%)	CNI-based GVHD prophylaxis (573), n (%)	CNI-free GVHD prophylaxis (371), n (%)	P value
TOTAL	96 (11)	70 (13.4)	26 (7)	0.002
CNS	52 (54)	39 (55)	13 (50)	0.02
Stroke	10 (10)	7 (10)	3 (12)	
PRES	1 (1)	1 (1)	0	
Encephalopathy	26 (27)	18 (26)	8 (31)	
Isolated seizures	2 (2)	1 (1)	1 (4)	
Headache	11 (11)	10 (14)	1 (4)	
Myelopathy	2 (2)	2 (3)	0	
PNS	25 (26)	17 (24)	8 (31)	0.01
Neuropathy	16 (17)	9 (13)	7 (27)	
Myopathy	9 (9)	8 (11)	1 (11)	
CNS infections	14 (15)	10 (14)	4 (15)	0.2
CNS-VEB associated PTLD	2 (2)	2 (3)	0	NA

Conclusions: NCs are common and diverse after allo-HSCT. Using a CNI-free GVHD prophylaxis is associated with less non-infectious NCs. Frequency of the different types of NCs is also different according to the use of CNI in GVHD prophylaxis, with less CNS complications using a CNI-free schedule. NC are associated with poor OS.

Clinical Trial Registry: NA

Disclosure: No disclosure.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P578

PREVALENCE OF ENDOCRINE DYSFUNCTION IN RECIPIENTS OF ALLOGENIC HSCT AFTER TOTAL BODY IRRADIATION (TBI) – CYCLOPHOSPHAMIDE BASED CONDITIONING, FOR MALIGNANT HAEMATOLOGICAL CONDITIONS: AN 11-YEAR SINGLE-CENTRE FOLLOW-UP

Subramaniam Ramanathan[1,2], Gaurav Kharya[3], Debbie Matthews[4], Roderick Skinner[1,2,5]

Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, [3]Centre for Bone Marrow Transplant and Cellular Therapy, Indraprastha Apollo Hospital, New Delhi, India, Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, [5]Translational and Clinical Research institute, Newcastle University Centre for Cancer, Newcastle upon Tyne, United Kingdom

Background: This single centre evaluation documented the prevalence of endocrine dysfunction in 35 consecutively transplanted children with malignant haematological conditions uniformly conditioned with cyclophosphamide and TBI (Cy-TBI).

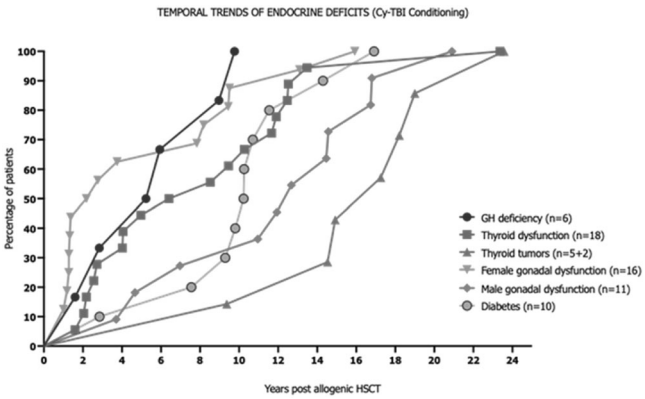
Methods: Retrospective evaluation of patients who were at least 11 years post-HSCT. Assessment of endocrine function was performed at yearly intervals and as clinically indicated based on the patients' endocrine status. Standard reference ranges were used to define the nature of the endocrine deficit.

Results: A total of 35 patients (19 males, 16 females) were eligible for the evaluation with a median age at diagnosis of 7.4 years (range: 0.8 – 17). The most common diagnoses were acute lymphoblastic leukemia in 15 (44%) patients followed by acute myeloid leukemia (n = 8; 22%) and chronic myeloid leukemia (n = 6; 16%). The stem cell source was bone marrow in 32 patients (matched sibling donor (MSD) = 12; matched unrelated donor (MUD) = 17; mismatched donor = 3), peripheral blood stem cells in 2 (both MUDs) and cord blood in 1 (matched sibling). The median age at the time of allogenic HSCT was 9.8 years (range: 2.1 – 19.3). The median age at last follow-up was 28.2 years (18.8 – 36.7) and the median time from HSCT until last follow-up was 18.5 years (11.4 – 24.6). Thirty-four patients received Cy-TBI conditioning (IV Cyclophosphamide (60 mg/kg day –6 and –5) and TBI: 14.4 Gy in 8 fractions (180 cGy BD on days –3, -2, -1, and 0)) and one patient received fludarabine in addition to Cy-TBI. Acute GVHD was seen in 24 patients and chronic GVHD in 5 patients. Systemic steroids for GVHD were used in 20 (57%) patients. Of these, 9 patients (45%) received systemic steroids for >6 months. Thirty-two patients were alive at last follow-up. The most common endocrine abnormality noted was primary hypothyroidism (52%), followed by diabetes (28.5%) and growth hormone deficiency (17%). Thyroid tumors (n = 5 (14%)) and silent nodules (n = 2 (6%)) were noted at a latency of 14.9 years (range: 9.4 - 18.2) and 21.3 years (range: 19 - 23.6) respectively. At last follow-up, amongst the patients without GH insufficiency (n = 19), the mean final height was 162.66 ± 14.03 cm against a mean mid-parental height (MPH) of 172.56 ± 8.70 cm ($p < 0.01$). While all females developed signs of primary ovarian insufficiency at a median period of 2.5 years (range: 1 – 15.9), 3 patients showed evidence of ovarian recovery, allowing withdrawal of hormone treatment. A total of 6 pregnancies (in 3 patients) were recorded, which resulted in 2 offsprings. Amongst males, a total of 11 patients were diagnosed to have testosterone insufficiency at a median latency of 12.7 years (range: 3.7 – 20.9). The temporal trend of the deficits is summarised in Figure 1.

TABLE 1. FREQUENCY OF ENDOCRINE DEFICITS

	Male	Female	Total
Thyroid status			
Hypothyroidism	4 (21%)	5 (31%)	9 (26%)
Subclinical hypothyroidism	5 (26%)	4 (24%)	9 (26%)
Silent thyroid nodules	1 (5%)	1 (6%)	2 (6%)
Thyroid tumors	2 (11%)	3 (19%)	5^ (14%)
Growth Hormone status			
GH insufficiency	4 (21%)	2 (12.5%)	6 (17.1%)
Gonadal Function			
Patients on hormone supplementation# at last follow-up	10 (52.6%)	12 (75%)	22 (63%)
Patients needing hormone for pubertal induction	4 (21%)	8 (50%)	12 (34%)
Puberty status at time of HSCT			
Pre-pubertal	13 (68%)	10 (63%)	23 (66%)
Mid-puberty	3 (16%)	2 (13%)	5 (14%)
Completed puberty	3 (16%)	4 (24%)	7 (20%)
Diabetes			
Type I DM	1 (5%)	1 (6%)	2 (6%)
Type II DM	4 (21%)	4 (24%)	8 (22%)

^Thyroid adenoma in 1; Follicular carcinoma in 1; Papillary carcinoma in 3.



Conclusions: Patients after HSCT require lifelong surveillance for the detection of endocrine and metabolic disorders. A worrying trend is the increase in frequency of the endocrine deficits, including thyroid tumours with a longer follow-up. Alternative conditioning regimens without TBI should be explored to obviate morbidity from long term endocrine dysfunction.

Disclosure: The authors have nothing to disclose regarding the contents of the manuscript.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P579

AVASCULAR BONE NECROSIS: HIGH MORBIDITY AND IMPACT ON QUALITY OF LIFE IN PEDIATRIC ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION SURVIVORS

Maria Luz Uria Oficialdegui[1], Melissa Panesso[1], Laia Martinez[1], M.Isabel Benitez-Carabante[1], Daniel Pacha[1], Luis Riera[1], Laura Alonso[1], Ariadna Campos[1], Pablo Velasco[1], Anna Llort[1], Sara Marsal Barril[1], Mireia Lopez-Corbeto[1], Cristina Diaz-de-Heredia[1]

[1]Hospital Universitari Vall d'Hebron, Barcelona, Spain

Background: Avascular bone necrosis (ABN) after allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is poorly studied in pediatrics, with an unfavorable impact on the patient's life quality. The main objective of this study was to describe the incidence and magnitude of the problem in patients who survived >1year post-Allo HSCT and to identify risk factors (RF). The high incidence detected prompted the design of a prospective study whose main objective is prevention, early diagnosis, and explore potential therapeutic options.

Methods: Retrospective study in <18 years diagnosed with ABN post-Allo HSCT who survived >1year post-Allo HSCT between January 2015-2021. Diagnosis was made by imaging tests (X-ray/MR). The characteristics of the patients, of the Allo-HSCT and the RF were studied.

Results: Among 169 patients whose indication for Allo-HSCT was malignant disease in 73 and non-malignant in 96, 37 of them (22%) were diagnosed with ABN, with no significant difference between genders. The median age at Allo-HSCT was 13.5 years (3.6-17.8) and the main indication was malignant disease (n = 23), mostly ALL/LL (n = 18). All had RF: age >8 years (n = 32), Tanner stage >2 (n = 22), pre (n = 21) and post-Allo HSCT (n = 35) steroid treatment, calcineurin-inhibitors treatment (n = 37), HLA-mismatch (n = 15), myeloablative-conditioning (n = 28), TBI 12Gy (n = 19), aGVHD II-IV (n = 31), cGVHD (n = 12) and chronic kidney disease stage >II (n = 6). 65% (n = 24) had >5 concomitant RFs. The median time from Allo-HSCT to ABN diagnosis was 13.5 months (3-53) and the median age at diagnosis was 15 years (4-18). In 91% (n = 34) the bone involvement was multifocal. 56% (n = 21) presented low bone mineral density (BMD) (BMD as defined by Z-score-2) and 21% (n = 8) suffered pathological fractures (vertebral/long bones). 43% (n = 16) had insufficient 25-hydroxycholecalciferol levels (< 30ng/dl). 27% (n = 10) required orthopedic surgery. Due to these findings, a prospective study was designed in patients aged 0 to 18 years, consisting of a **first stage of**: **clinical assessment** (anamnesis/physical exam/Tanner-stage/BMI), **laboratory test** (calcium-phosphate metabolism/Mg),**genetic polymorphisms (SNP) and proteomics studies** in all patients. In addition, **imaging tests** (BMD/thoracolumbar and wrist X-rays/whole-body MR) and **hormonal profile** are performed in the group aged 4-18 years. Evaluations are done pre-HSCT, 6, 12, 24 and 36 months post-Allo HSCT.

Throughout the study, medical and nutritional interventions, an intensive physical rehabilitation program, and hormone replacement therapy are performed. In a second stage: randomization for treatment with bisphosphonates.

Conclusions: ABN represents a serious complication in long-term Allo-HSCT survivors. Underlying disease (ALL), age group with rapid bone growth, myeloablative conditioning (TBI), low bone mineral density, and steroid therapy (cumulative dose/duration) are important RFs. It is essential to design prevention, early diagnosis, and treatment protocols in pediatric patients.

Disclosure: None.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P580

LONG TERM FOLLOW UP CLINIC AFTER ALLOGENEIC HAEMOPOIETIC STEM CELL TRANSPLANT, THE PATIENT EXPERIENCE

Tricia Wright[1,2], Bianca Cirone[1], Daniela Klarica[1], Andrew Spencer[2,1], Erica Wood[2]

[1]Alfred Health, Melbourne, Australia, [2]Monash University, Melbourne, Australia

Background: Stakeholder engagement and feedback is considered a critical component to quality health care.

This qualitative study examines the patient experience of attending a Long Term Follow Up (LTFU) clinic for individuals after allogeneic haemopoietic stem cell transplant (alloHSCT).

Methods: Individuals attending a LTFU clinic for individuals surviving at least 2 years after alloHSCT at a health service in Melbourne Australia were enrolled in the study.

Each participant was asked the following interview questions,

- Is the clinic attendance a positive experience for you
- What do you think about
  1. the late effects clinic care plan?
  2. blood tests and clinic investigations?
  3. patient reported outcome measures (PROMS) completed for the clinic (specific documents were indicated)?
- Do you have a primary care physician (PCP)? What is your opinion about components of the clinic being transferred back to your PCP?
- What is the optimal clinic structure going forward for you?

Clinic responses were recorded in individual interview documents stored with the clinic care plans.

Following each clinic, the interviewers met and analysed the responses, agreed on themes, and informative patient response were identified representing these themes.

Results: Interviews were conducted with 81 individuals, 47 (54%) males, attending an annual LTFU clinic between February and September 2022. The median age at the interview was 54 years. The average number of chronic health conditions was four (range 1-12). Thirty four (42%) of participants had a diagnosis of Chronic graft versus host disease (cGHVD) of which 11 were receiving active treatment.

The table provides examples participant responses to interview questions in positive and negative themes.

The majority of participants 75 (92.5%) reported a positive response to the LTFU clinic attendance experience.

Almost one quarter of participants identified reassurance for checking all possible health complications with a complete set of investigations conducted through the clinic 19(23.5%). The remaining participants considered the level of testing overwhelming and / or a duplication of their primary care health management. Sixty two (76.5%) indicated they would prefer a full blood examination only in the LTFU clinic.

The majority of participants stated they received no benefit from completing the PROMS 73(90%) or receiving a detailed care plan 66(81%).

Most participants 72 (89%) had a PCP and 68 (84%) described confidence in their PCP care in particular regarding chronic health conditions not related to specialist haematology care.

The most common response for the optimal focus of the clinic was an annual health checklist identified by 78 (96%) participants.

Table: Examples of participant survey responses by negative and positive themes for clinic attendance, clinic investigations and GP participation in care following alloHSCT

Topic	Positive themes		Negative themes	
Clinic attendance	Engagement and annual check Overall participants valued the clinic attendance particularly remaining engaged with the health service that performed their alloHSCT and also an opportunity for an annual health check		Most of the negative responses to the clinic related to the burden of health care appointments and / or anxiety due to re-exposure to the hospital where they were very unwell	
	Belonging	"you.. (health service) are my family and this clinic allows me to visit properly and tell everyone how grateful I am"	Health burden	I have so many health problems and clinic appointments are it's a full time job. I have a haematologist that I see regularly, if I don't need another clinic I would prefer not to attend.
	Opportunity for information / annual reminder	"hub of information. It's not just about surviving it's about thriving. Check in with each area of health and specialist advice of self-care screening process and strategies to optimise health is critical. You can't get that from a GP for our situation." "I really appreciate the time to discuss my illness and treatment in a holistic way, I feel the further away from transplant my questions change" "The most important part of the clinic is a reminder every year about the health checks I need to do, like go to the dentist"	Exposure anxiety	"I don't mind coming to the clinic but when I attend the hospital I have severe anxiety, like a panic attack remembering where I was sick
PROMS	There were no responses coded as positive directly related to PROMS. Participants were however very aware of contributing to health service research where they received treatment		Most participants found the surveys unhelpful and not relevant to their long-term care after alloHSCT in particular the longer health quality of life survey	
	Benevolence	I am so grateful to ... (health service I am very happy to participate in any research that will help others"	Irrelevant	"Most of the questions are irrelevant to me or don't change. I feel like I could photocopy my results and send the same survey in each year" "My mental health is fine, I have no issues. I don't want to fill in this form – here give it to my husband to fill in its more relevant to him and his suffering as a carer.
Pre clinic investigations	Participants described reassurance with the annual tests. Most reported at some time post-transplant the fear of recurrence of the disease was relieved by the annual test. In particular participants cited a full blood examination reviewed by a haematology service		Several participants noted the burden of blood tests and wondered at their relevance. Many also identified double up of investigations performed by their GP	
	Health reassurance / anxiety fear of recurrence	"I am reassured that once a year I will get a complete health check from the clinic – my GP rarely does blood tests"	Imposter syndrome	"I had my transplant so long ago and I was young so I don't remember. I feel really well now and these tests. Make me feel like a sick person
PCP for follow up care	For individuals engaged with their GP the relevance to their optimal health was clear		A common theme related to GPs knowledge of alloHSCT and how that impacted their optimal healthcare	
	Favourable relationship with GP	"First few years, late effects was a lifeline for me. Now several years out, currently all primary health with a GP and this is not a problem for me" "Very happy for my GP to manage me on a regular basis, but happy to stay in touch with the hospital. Staying in touch is more the critical point for me"	Concern about GP knowledge of care after alloHSCT	"I like the full check with a tertiary system given my history and the potential for long term complications. My GP wouldn't know what they were" "I went to my GP and said I'm not feeling well and because of my extensive history she doesn't know what to do with me"

Conclusions: The range of participant feedback highlights the variable experience and needs of individuals after alloHSCT.

A LTFU clinic after alloHSCT that is truly patient centred must respond to individual needs and ensure care delivered is appropriate with regard to clinical need, type of delivery and location of care.

Delivery of complex health care such as LTFU after alloHSCT should include a system for regular review and consumer feedback.

Disclosure: no conflict of interest.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P581

RISK FACTORS ASSOCIATED TO SECONDARY MALIGNANCIES IN HEMATOPOIETIC STEM CELL ALLO-TRANSPLANTED PATIENTS: THE EMERGENT ROLE OF POST-TRANSPLANTATION CYCLOPHOSPHAMIDE

Barbara Sarina[1], Flavio Pistolese[1,2], Jacopo Mariotti[1], Filippo Magri[3], Chiara De Philippis[1], Daniele Mannina[1], Daniela Taurino[1], Armando Santoro[1,2], Stefania Bramanti[1]

[1]IRCCS Humanitas Research Hospital, Milan, Italy, [2]Humanitas University, Milan, Italy, [3]IRCCS San Raffaele Scientific Institute, Milan, Italy

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is routinely administered as a treatment for both malignant and non-malignant life-threatening diseases.

In the last decades, advances in treatment and supportive care have resulted in increased long-term survival among allo-HSCT recipients. Particularly, the introduction of post-transplant cyclophosphamide (PTCy) has reduced the incidence of graft-versus-host disease (GVHD) and of non-relapse mortality (NRM) rates.

It has been demonstrated in several studies that survivors who underwent all-HSCT are at a significantly higher risk of developing secondary neoplasms than the matched general population, resulting in negative consequences for non-relapse morbidity. Following allogeneic stem cell transplantation, the cumulative incidence (CI) of solid cancers varies from 1.2 to 1.6% at 5 years, from 2.2 to 6.1% at 10 years, and from 3.8 to 14.9% at 15 years following transplantation.

The aim of this retrospective study was to determine the CI of secondary malignancies in patients who underwent bone marrow transplants and were followed for more than two years, as well as determine which factors could increase this risk, such as conditioning regimen, incidence of acute and chronic GVHD, donor type, and exposure to post-transplantation cyclophosphamide (PTCy).

Methods: From 1/2009 to 12/2020, 410 patients underwent bone marrow transplant at our Institution and 217 were evaluable for analysis. Screening for late effects started one year after transplantation and included dermatology, otorhinolaryngology, cardiology, and rheumatology assessment.

Results: Secondary neoplasms were reported in 31 out of 217 patients. The most frequent were neoplasms of the skin (19), oral cavity (3), cervix (1), breast (1), gastroenteric (1) and onco-haematological disease (3).

With a median follow-up since transplantation of 63 months, the 6-year CI of secondary malignancies was 15% (10-22%).

In univariate analysis no significant difference was detected based on conditioning regimen, acute and chronic GVHD and donor type.

The secondary cancer incidence was significantly higher in patients receiving PTCy than those not receiving PTCy. In addition, the median time between transplantation and diagnosis of the second cancer was shorter in the PTCy cohort (32 months *vs* 60 months). No difference in overall survival (OS) was observed between the two groups.

Conclusions: In our study, we confirmed that allo-HSCT is associated with an increased risk of developing secondary tumours, most frequently skin cancers. According to our results, GVHD prophylaxis seems to be the only major risk factor playing a significant role, with no impact on the OS. No difference has been seen according GVHD, type of conditioning regimen and donor selection. Due to the limited number of events in each sub-group, further sub-analyses were not possible.

These data should be confirmed in a multicentre study, nevertheless they suggest the need of enhanced screening for non-hematologic malignancies in allo-SCT recipients, taking into consideration the type of GVHD prophylaxis.

Disclosure: None.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P582

PREDICTIVE ROLE OF PRE-TRANSPLANT WELL-BEING PROFILES OF PATIENTS FOR THEIR LONG-TERM FUNCTIONING TRAJECTORIES FOLLOWING HCT

Malgorzata Sobczyk-Kruszelnicka[1], Marta Kijowska[2], Aleksandra Kroemeke[2]

[1]Maria Skłodowska-Curie National Research Institute of Oncology Gliwice Branch, Gliwice, Poland, Gliwice, Poland, [2]SWPS University of Social Sciences and Humanities, Warsaw, Poland, Warsow, Poland

Background: Hematopoietic cell transplantation (HCT) may have an impact on patients' short- and long-term well-being. Therefore, the study aimed to investigate (a) whether there were changes in patients' well-being (health-related quality of life (HRQoL); symptoms of anxiety and depression) 6 and 12 months following HCT, and (b) whether belonging to specific pre-transplant well-being profiles predicted short- and long-term changes in patients' well-being following HCT.

Methods: Symptoms of depression, anxiety, and HRQoL were assessed in 290 patients (mean age = 47.28 ± 13.79 yrs; 43% females, 57% males; mean time since diagnosis = 21.59 ± 25.86 months) a few days after admission to the first autologous (67%) or allogeneic (33%) HCT, and 6 months (N = 169) and 12 months later (N = 145).

Results: Four pre-transplant latent well-being profiles were identified: well-functioning (51%, patients with the highest well-being in all aspects), dysfunctional (10%, patients with the weakest functioning in all aspects), and two profiles of patients with moderate HRQoL and high (5.6%) or low (33.4%) anxiety and depressive symptoms. In the whole group, the longitudinal analysis showed a decrease in anxiety and depressive symptoms, an improvement in the functional subscale of HRQoL (cognitive-emotional-social functioning), and a decrease in global health assessment (HRQoL subscale) 6 months after HCT compared to the measurement before HCT. There were no further changes in well-being (12 months after HCT); somatic symptoms (HRQoL subscale) remained constant throughout the study period. Belonging to the specific pre-transplant well-being profiles predicted changes in the level of anxiety symptoms ($F[1,132] = 29.18$, $p < 0.001$, $\eta 2 = .40$), depressive symptoms ($F[1,131] = 35.76$, $p < 0.001$, $\eta 2 = .45$), global health assessment ($F[1,131] = 23.89$, $p < 0.001$, $\eta 2 = .35$), and cognitive-emotional-social functioning ($F[1,131] = 37.81$, $p < 0.001$, $\eta 2 = .46$) following HCT. Patients in the most disadvantaged groups had poorer well-being after HCT but improved over time.

Conclusions: The findings highlight the heterogeneity in pre- and post-transplant well-being and successful psychological adaptation after transplantation. The improvement in well-being takes place within the first 6 months after HCT. The results indicate the predictive role of pre-transplant well-being profiles of patients for their long-term patterns of functioning after HCT.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P583

A PROSPECTIVE COHORT STUDY TO EVALUATE MICROVASCULOPATHY AND ENDOTHELIAL DYSFUNCTION BY USING NON-INVASIVE TESTS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Table: Comparison of variables for the assessment of microvasculopathy and endothelial function in the study cohorts.

S. no	Variables	COHORT A Allo HSCT	COHORT B Auto HSCT	Healthy Controls	Comparison between Allo HSCT and Auto HSCT		Comparison between Allo HSCT and Healthy Controls		Comparison between Auto HSCT and Healthy Controls	
		(mean ± SD)	(mean ± SD)	(mean ± SD)	Mean difference (SE)	P value	Mean Difference (SE)	P value	Mean Difference (SE)	P value
1.	Median capillary density (capillaries/mm)	6.63 ± 1.03	8.34 ± 1.63	8.2 ± 0.96	-1.71 (0.303)	<0.001	-1.57 (0.294)	<0.001	0.14 (0.303)	1
2.	Median capillary diameter (micrometer)	20.56 ± 5.17	16.19 ± 3.31	14.66 ± 2.61	4.37(0.955)	<0.001	5.9 (0.925)	<0.001	1.52 (0.9555)	0.342
3.	Number of fingers with dilated capillary	3.06 ± 2.35	1.03 ± 1.75	0.76 ± 1.23	2.02 (0.459)	<0.001	2.29 (0.444)	<0.001	0.27 (0.462)	<1
4.	Number of fingers with neoangiogenesis	4.09 ± 2.52	0.48 ± 1.06	0.44 ± 0.75	2.02 (0.459)	<0.001	2.29 (0.444)	<0.001	0.27 (0.462)	1
5.	Number of fingers with micro hemorrhages	1.51 ± 2.13	0.13 ± 0.43	0.12 ± 0.33	1.39 (0.32)	<0.001	1.4 (0.313)	<0.001	0.01 (0.323)	1
6.	FMD values	13.98 ± 12.92	16 ± 6.86	16.49 ± 7.72	-2.02 (2.412)	1	2.51 (2.318)	0.843	-0.49 (2.396)	1

Sayan Sinha Roy[1], Raghuraman Sondrarajan[1], Manphool Singhal[1], Ashok Kumar Yadav[1], Shefali Sharma[1], Arihant Jain[1], Deepesh Lad[1], Alka Khadwal[1], Pankaj Malhotra[1], Gaurav Prakash[1]

[1]Postgraduate Institute of Medical Education and Research, Chandigarh, India

Background: Microvasculopathy and endothelial dysfunction play an important role in the development of post-transplant complications, including sinusoidal obstruction syndrome, transplant-associated thrombotic microangiopathy, and steroid-resistant GVHD. The aim of this study is to investigate non-invasive, real-time assessment of post-hematopoietic stem cell transplant microvasculopathy and endothelial dysfunction by using nail fold video capillaroscopy (NFVC), and flow-mediated dilation (FMD).

Methods: Thirty-five post-alloHCT recipients from post-transplant day 100 and onwards, 31 post-autoHCT recipients from post-transplant day 100 and onwards, and 35 healthy individuals (controls) were included. NFVC was performed using an Optilia video capillaroscope under 200X magnification. Images for each participant were analyzed according to the European Alliance of Associations for Rheumatology criteria. For statistical analysis, the following parameters were considered for each participant - median capillary density derived from the capillary density of 8 fingers, median capillary diameter derived from maximum capillary apical diameters of 8 fingers, number of fingers with dilated capillary, neoangiogenesis, and microhemorrhages. Flow-mediated dilatation of the right brachial artery was observed using high-resolution ultrasound using the principle of post-occlusive reactive hyperemia and analyzed using edge-detecting software.

Results: The mean age in the allo-HSCT cohort was 28.03(SD ± 15.6) years, auto-HSCT cohort was 41.35 (SD ± 16.67) years and the control group was 32.54 (SD ± 14.44) years. The mean duration since transplant to the assessment of vasculopathy was 23.11 (SD ± 23.18) months and 37.77 (SD ± 39.42) months in the allo-HCT and auto-HSCT cohorts respectively. Allo-HSCT recipients had significantly higher median capillary apical diameter (Mean=20.56 microns, SD ± 5.17) compared to auto-HSCT recipients (Mean=16.19 microns, SD ± 3.31)($p < 0.001$) and controls (Mean=14.66 microns,SD ± 2.61)($p < 0.001$). The number of fingers showing dilated capillary was significantly higher in the allo-HSCT recipients (Mean=3.06, SD ± 2.35) compared to auto-HSCT recipients (Mean=1.03, SD ± 1.75)($p < 0.001$) and controls (Mean=0.76, SD ± 1.23)($p < 0.001$). The number of fingers showing neoangiogenesis was significantly higher in the allo-HSCT group (Mean=4.09, SD ± 2.52) compared auto-HSCT group (Mean=0.48, SD ± 1.06)($p < 0.001$) and controls (Mean=0.44, SD ± 0.75) ($p < 0.001$). Allo-HSCT recipients had a significantly higher number of fingers with microhemorrhages (Mean=1.51, SD ± 2.13) compared to auto-HSCT recipients (Mean=0.13, SD ± 0.43)($p < 0.001$) and controls (Mean=0.12, SD ± 0.33) ($p < 0.001$), respectively. The median capillary density was significantly lower in the allo-HSCT recipients (Mean=6.63/mm, SD ± 1.03) compared to auto-HSCT recipients (Mean=8.34/mm, SD ± 1.63) ($p < 0.001$) and controls (Mean=8.2/mm, SD ± 0.96)($p < 0.001$). In the allo-HSCT group, 18 patients had low median capillary density (< 7 capillaries/mm), whereas, in the auto-HSCT group, 5 patients had low median capillary density (< 7 capillaries/mm). None of the healthy participants had low median capillary density. The allo-HSCT cohort had lower values of FMD (Mean=13.98, SD ± 12.92) than the auto-HSCT cohort (Mean=16, SD ± 6.86) and healthy controls (Mean=16.49, SD ± 7.72) but these differences were not statistically significant ($p = 1$ and $p = 1$, respectively).

Conclusions: The result from our study indicates the presence of structural microvasculopathy in the post-allo-HSCT setting and suggests alloreactivity as a cause of microvascular damage. NFVC holds promise as a research and clinical tool in the real-time assessment of post-transplant microvasculopathy.

Disclosure: "Nothing to declare".

15 - Non-infectious Late Effects, Quality of Life and Fertility

P584

MARKERS OF BONE REMODELING IN SURVIVORS OF PEDIATRIC ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: IMPACT OF HEAVY RESISTANCE TRAINING

Lise Marie Krogh[1], Anne Nissen[1], Sarah Weischendorff[1], Bolette Hartmann[2], Jesper Løvind Andersen[3], Martin Fridh[1], Abigail Mackey[3], Klaus Müller[1]

[1]University Hospital Rigshospitalet, Copenhagen, Denmark, [2]University of Copenhagen, Copenhagen, Denmark, [3]University Hospital Bispebjerg and Frederiksberg, Copenhagen, Denmark

Background: Pediatric allogeneic hematopoietic stem cell transplantation (allo-HSCT) is associated with early-onset osteoporosis, carrying a risk of significant morbidity later in life. However, it remains unknown if physical training can improve bone formation in these patients, as the transplantation procedure may cause a risk of sustained dysregulation of the bone forming osteoblast progenitor cells. The aim of this study was to explore the effect of

heavy resistance training on markers of bone remodeling in long-term survivors of pediatric allo-HSCT.

Methods: Seven HSCT-survivors with a median age of 27 years (range: 22-44 years) and a median follow-up of 13 years (range: 10-29 years) after pediatric HSCT as well as 15 age- and sex-matched healthy controls completed an exercise intervention of 12 weeks of supervised resistance training three times per week. Resistance training is generally known to be osteogenic. The training consisted of three lower body exercises. Fasting serum levels of the bone formation marker 'N-terminal propeptide of type I procollagen' (P1NP), and 'C-terminal telopeptide of type I collagen' (CTX), a bone resorption marker, were measured before and after the intervention. In addition, bone mineral density (BMD) in the lumbar spine (L1-L4), total hip and femoral neck was measured by dual-energy x-ray absorptiometry scans.

Results: Resistance training led to significantly and equally increased levels of P1NP in HSCT-survivors and the controls. P1NP increased by 207 % of baseline (range 97-387 %) in the patient group and by 155% (range: 107-299 %) in the group of healthy controls. The percentage increase in P1NP did not differ between patients and controls. In addition, CTX levels increased in the healthy controls after resistance training from 0.62 ng/ml to 0.80 ng/ml, $p = 0.04$, however not significantly for the patients (0.72 ng/ml to 0.78 ng/ml, $p = 0.69$). No changes in BMD were found in either of the groups within this limited observation period.

Conclusions: Despite previous high-dose cytotoxic therapy, long term survivors of pediatric allo-HSCT respond to resistance training with improvement of bone formation, comparable to that of healthy controls. This suggests that resistance training might be a promising non-pharmacological approach to prevent the early decline in bone mass and should be considered as part of a follow-up program to counteract long-term sequela after pediatric allo-HSCT.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P585

LONG-TERM THYROID DISORDERS AFTER PAEDIATRIC HCT FOR MALIGNANT UNDERLYING DISEASES

Natalia Zubarovskaya[1], Paulina Kurzmann[2], Dorothea Bauer[1,2], Stefan Riedl[1], Christina Peters[1,2], Anita Lawitschka[1,2]

[1]St. Anna Children's Hospital Vienna, Medical University Vienna, Vienna, Austria, [2]Children's Cancer Research Institute Vienna, Vienna, Austria

Background: Thyroid disorders (TD) after TBI-conditioned paediatric patients are well studied, and we previously described the incidence of functional and structural TD with a significant correlation between immune dysregulation (ID) post-HCT and thyroid dysfunction in patients with structural changes. No impact of cGVHD and prolonged immunosuppression was found. Yet we aimed to investigate the occurrence of TD in patients after chemo-and TBI-based conditioning, and the impact of pre-transplant chemotherapy (CT), transplant characteristics, and ID.

Methods: In this retrospective study we included patients after first HCT from MUD/MSD after MAC and RIC for malignant diseases over a 15-year observation. The incidence and risk factor (RF) analysis were assessed for TD in general, for functional or structural TD, and for functional *plus* structural TD.

Results: 126 patients with a median age of 11.4 years and a median observation time of 8.1 years were included. MAC was applied in 78% (98/126): TBI- conditioning in 67% (66/98) and Treosulfan-based (Treo) conditioning in 22%. RIC (28/126) comprised of Fludarabine, Thiotepa, Melphalan. 63% (79/126) were grafted from MUD, and 37% (47/126) from MSD. BM was the stem cell source in 83% (104/126). CT was given in 73% (92/126) of patients. Acute GVHD II-IV was observed in 63% (80/126) and chronic GVHD moderate/severe in 24% (31/126). Delayed T-cell reconstitution (CD4+Tcell <100/mcl) at day+360 was evident in 61% (77/126) and humoral ID in 72% (91/126).

The 5/10-year cumulative incidence (CI) of all TD was 43% and 72%. Regarding conditioning 10-year CI was 83% for TBI, 69% for Treo and 52% for RIC. We found of 27% functional, 22% structural, and 51% functional *plus*structural TD. In univariate analysis risk RF were CT ($p = 0.0001$), age <10 years at HCT ($p = 0.02$), MAC ($p = 0.02$), MUD ($p = 0.03$), and aGvHD ($p = 0.04$). Multivariate analysis confirmed these RF except aGvHD. Binary analysis did not show a correlation between TD and delayed T- cell reconstitution and humoral ID.

The 5/10-year CI of functional *plus* structural TD was 23% and 38%. Regarding conditioning 10-year CI was 47% for TBI, 36% for Treo and 20% for RIC. Manifestations comprised of subclinical and manifest hypothyroidism in 46% and 54%, respectively. Positive thyroid antibodies were observed in 25%. Morphologic changes were volume alterations, volume changes combined with nodules, and nodules in 35%, 40%, and 25%, respectively. Two patients developed papillary carcinoma later on. RF in univariate analysis were CT ($p = 0.002$), age <10 years at HCT ($p = 0.02$), and MAC ($p = 0,03$). Multivariate analysis confirmed age<10 years only.

Conclusions: Our study assessed the incidence of the various forms of TD, and confirmed known RF, but found no impact of cGVHD and ID. Importantly, we identified pre-transplant CT as a significant RF for the development of TD, which should be considered for future studies. In contrast to other studies the CI of Treo-associated TD seems remarkable. The correlation between the nature of structural changes and the different kinds of TD over time needs further evaluation in a larger cohort.

Clinical Trial Registry: retrospective study

Disclosure: no conflict of interest.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P586

PREDICTING MORTALITY AND RELAPSE IN REDUCED INTENSITY TRANSPLANTATION FOR MYELOID DISEASE: THE EASIX SCORE IN PRACTICE

Chris Armstrong[1], Eibhlin Conneally[1], Catherine Flynn[1], Nicola Gardiner[1], Hayley Foy-Stones[1], Mairead Ní Chonghaile[1], Nina Orfali[1]

[1]St. James' Hospital, Dublin, Ireland

Background: Reduced intensity allogeneic haematopoietic stem cell transplantation (alloSCT) is an effective treatment for high-risk myeloid malignancies. However, outcomes post-transplant are variable and the available predictive scores for treatment-related mortality (TRM) and relapse are limited. The Endothelial Activation and Stress Index (EASIX) has been shown to predict outcomes at four time-points: pre-transplant, day zero, at GVHD onset and 1-year post-transplant. The score can be calculated using readily available standard laboratory parameters (LDH (U/L) x creatinine (mg/dL) / platelets ($x10^9$ /L). We here interrogate its validity in a large cohort of homogenously treated patients.

Methods: We performed a retrospective analysis of 174 patients undergoing reduced intensity alloSCT for myeloid disease (Table 1). All received fludarabine, busulfan and rabbit anti-thymocyte globulin (Flu/Bu/ATG) conditioning between 2015-2022. We

calculated the EASIX score for each of the four time-points and assessed its ability to predict overall survival, TRM and relapse. Statistical analysis was conducted using STATA.

Table 1: Demographics

Sex	
Male	106
Female	68
Age	Median: 60 Range 27-74
Disease	
AML	91
MDS	43
MPN	40
Donor	
Sibling	77
Unrelated	97
GVHD	
Acute	103/173
Chronic	25/164
Mortality	49
Non-relapse	19
Relapse	30
EASIX	
Pre-conditioning	Mean: 31 Range: 03.-17.54
Day 0	Mean 15.5 Range 1.07-180.9
At GVHD onset	Mean 3.5 Range 0.4-51.43
1 Year	Mean 1.69 Range 0.47-11.23

Results: Pre-conditioning, an EASIX score greater than a mean of 3.1 predicted an increased risk of TRM ($p = 0.05$) and reduced OS ($p = 0.006$, HR 2.16). Relapse could not be predicted at this time-point.

At D0 the mean EASIX score was 15.5. OS/TRM and relapse could not reliably be predicted at this time-point.

At the onset of GVHD ($n = 103$), the mean score was 3.5. A score >3.5 was associated with an increased risk of relapse ($p = 0.01$) (*fig.1*), reduced overall survival ($p = 0.01$) and an increased risk of TRM ($p = 0.05$).

At 1-year post-transplant ($n = 113$) the mean score was 1.18. Scores above this were significantly associated with reduced OS ($p = 0.008$) and relapse ($p = 0.01$).

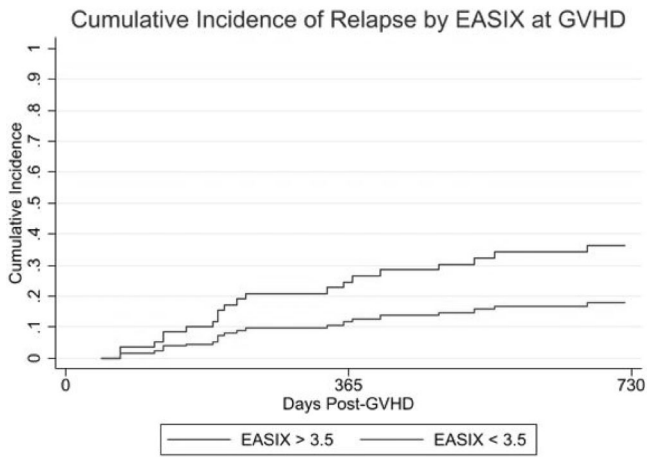


Fig.1: Cumulative incidence of relapse by EASIX at GVHD onset, cut-off 3.5.

Conclusions: The EASIX score utilises universally available biomarkers and is easily applied in a clinical setting. In our homogenously treated cohort, the score demonstrated utility in predicting OS, TRM or relapse at a number of important time-points.

At the pre-conditioning time-point the score reliably predicts both OS and TRM. This can be combined with established predictive tools, including the age-adjusted HCT-CI, during pre-transplant counselling to better objectively risk-stratify patients individually. This is particularly pertinent in this older cohort, where transplant eligibility continues to grow, primarily due to a fitter aging populace and less toxic pre-transplant therapies. Additionally, as a surrogate of endothelial dysfunction, the score may highlight pre-transplant co-morbid organ dysfunction and provide and estimation of resilience.

As ATG is employed in the immediately prior to D0 with this conditioning protocol, a large majority of patients are severely thrombocytopenic at stem-cell infusion. Therefore, the discriminatory value of the score appears limited for predicting outcomes in this treatment cohort.

At GVHD onset and at 1-year post-transplant the score is particularly adept at predicting survival and relapse. We postulate this reflects those patients with persistent thrombocytopenia and raised LDH, which in myeloid disease are frequently hallmarks of disease activity.

We validate the clinical utility of this score and these data now underpin our ongoing prospective study of RIC patients with myeloid disease, investigating cytokine biomarkers and their potential correlation with the EASIX score and clinical outcomes.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P587

IRON OVERLOAD FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION: PREVALENCE, SEVERITY AND MANAGEMENT IN CHILDREN AND ADOLESCENTS WITH MALIGNANT AND NON-MALIGNANT DISEASES

Alessandro Cattoni[1], Giulia Capitoli[1], Sara Casagranda[1], Paola Corti[1], Marta Adavastro[1], Alessandro Molinaro[1], Filiberto Di Gennaro[1], Sonia Bonanomi[1], Andrea Biondi[1], Stefania Galimberti[1], Adriana Balduzzi[1]

[1]Università degli Studi di Milano-Bicocca, Monza, Italy

Background: Iron overload (IOL) is a frequently reported complication following hematopoietic stem cell transplantation (HSCT) which has been extensively assessed in the field of hemoglobinopathies, but has not been thoroughly characterized after HSCT in pediatric malignancies.

Our aim was to assess prevalence, severity, risk factors and management of IOL, as defined by means of biochemical (serum ferritin) and radiological tools (T2*-MRI), in a cohort of pediatric patients transplanted for either malignant or benign diseases.

Methods: Monocentric, retrospective, observational study. All the 163 patients alive and in continuous remission 24 months after HSCT, out of the 219 consecutive children and adolescents transplanted at our Institution between 2012 and 2018, were included in the study. IOL was classified into four categories, i.e. absent, mild, moderate and severe.

Results: Of the 163 patients, 73% had some degree of IOL, which was mild, moderate and severe in 37%, 29% and 7%, respectively. Moderate/severe IOL was more frequent among

patients diagnosed with a malignant *versus* benign disease (43% vs 19%; *p* 0.0065).

Ferritin trend lines showed a "bell-shaped" distribution, with the highest levels being recorded during the first 6 months after HSCT, followed by a spontaneous reduction. Both pre-HSCT (1659 *versus* 617 ng/mL, $p < 0.001$) and maximum post-HSCT (2473 ng/mL *versus*1591 ng/mL, $p < 0.001$) median ferritin levels were statistically higher among patients with malignancies.

Radiological assessment of IOL confirmed a more severe degree in malignant compared to benign disorders (median T2*-MRI 4.20 msec, IQ: 3.0-6.40 *versus* 7.40, IQ: 4.90-11.00, respectively - *p* 0.008). T2* levels were associated with the number of transfusions performed (*p* 0.0006), with a steeper drop in T2* values for the first 20 transfusions and a milder slope subsequently.

T2* and ferritin values showed a statistically significant negative exponential relationship ($p < 0.0001$), though ferritin levels ≥1000 ng/mL showed a poor specificity (48%) and positive predictive value (53%) in discriminating moderate-to-severe from absent-mild IOL as assessed by T2*-MRI, but high sensitivity (92%) and negative predictive value (91%).

In a multivariable model, >20 transfusions (OR 4.07, 95% CI 1.61-10.68, *p* 0.003) and higher pre-HSCT ferritin levels ($p < 0.001$) were associated with the risk of developing moderate-to-severe IOL. A sibling donor (OR 0.29, 95% CI 0.10-0.77, *p* 0.015) and a non-malignancy (OR 0.27, 95% CI 0.08-0.82, *p* 0.026) were protective factors.

Phlebotomies (66%), low-dose oral chelators (9%) or a combined approach (25%) were started at a median of 12 months after HSCT in 78% of the patients with IOL. Six% of the patients treated exclusively with phlebotomies (median 14, significantly higher in patients >40 kg) discontinued them due to poor venous accesses, lack of compliance or hypotension, whereas 39% of patients treated with chelators developed mild renal or hepatic side effects which resolved upon tapering or discontinuation.

Conclusions: Patients with malignancies showed statistically higher pre- and post-HSCT ferritin levels and lower T2*. High ferritin recorded upon T2*-MRI showed unsatisfactory diagnostic accuracy in predicting IOL, thus, T2*-MRI should be regarded as a key element to confirm IOL after HSCT in patients with elevated ferritin levels. IOL treatment is feasible after HSCT.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P588

THROMBOPOIETIN RECEPTOR AGONISTS FOR PERSISTENT SEVERE THROMBOCYTOPENIA AFTER ALLOGENEIC STEM CELL TRANSPLANTATION – 5 YEARS SINGLE CENTRE RETROSPECTIVE ANALYSIS

Kristina Pahek[1], Nadira Durakovic[2,3], Lana Desnica[2], Ranka Serventi Seiwerth[2], Zinaida Perić[2,3], Radovan Vrhovac[2,3], Drazen Pulanic[2,3]

[1]General Hospital Cakovec, Cakovec, Croatia, [2]University Hospital Centre Zagreb, Zagreb, Croatia, [3]Medical School University of Zagreb, Zagreb, Croatia

Background: Persistent severe thrombocytopenia may occur as a complication after allogeneic hematopoietic stem cell transplantation (alloHSCT) associated with significant morbidity and mortality, and a few small studies showed that thrombopoietin receptor agonists (TPO-RAs) may be useful in that setting.

Methods: A retrospective study was conducted on patients who received TPO-RAs eltrombopag or romiplostim because of severe persistent thrombocytopenia after alloHSCT at the University Hospital Centre Zagreb, Croatia, from 1/2018 until 11/2022.

Results: 17 patients (median age 46 (range 23-65) years, 64.7% female) received TPO-RAs after alloHSCT. Fifteen (88.2%) underwent alloHSCT for haematological malignancies, for 8 (47.1%) this was second alloHSCT, 11 (64.7%) received peripheral blood stem cells, 3 (17.7%) had myeloablative conditioning, and 11 (64.7%) were transplanted from haploidentical donor. Nine (52.9%) patients received post-transplant cyclophosphamide. Ten (58.8%) had acute GvHD and 1 patient (5.9%) experienced chronic GvHD. Seven (41.2%) patients received eltrombopag and 8 (47.1%) received romiplostim, while 2 (11.8%) patients received both TPO-RAs post alloHSCT. Median time from alloHSCT to start TPO-RAs was 119 (range 49-335) days. The median platelet count before initiation of TPO-RAs was 12,000 (range 0-30,000)/mcL. Initial dose of eltrombopag was 50 mg/day. Median maximal dose of eltrombopag was 75 (range 50-150) mg/day. Median initial dose of romiplostim was 3 (range 1-4) mcg/kg once weekly and median maximal dose was 4 (range 2-7) mcg/kg once weekly. In total 13 (76.5%) patients receiving TPO-RAs responded; among them 3 (17.7%) achieved platelet response (platelets > 20/mcL without transfusion support and no bleeding), 3 (17.7%) achieved partial response (platelets > 50/mcL without bleeding), 7 (41.2%) achieved complete response (platelets > 100/mcL without bleeding), while 4 patients (23.5%) did not respond to TPO-RAs treatment. The median time to platelet response was 35 (range 1-198) days. The median duration of TPO-RAs treatment was 124 (range 19-536) days. One patient developed hepatotoxicity while receiving eltrombopag which was resolved after switching to romiplostim. Another patient switched from eltrombopag to romiplostim because of lack of efficacy. One patient transformed from MDS/MPN JAK2 to acute myeloid leukaemia (AML) during treatment with romiplostim, and another patient with AML who underwent second alloHSCT relapsed again with AML while receiving romiplostim. At the last follow-up 10 (58.8 %) patients were alive.

Conclusions: Results of this single-centre retrospective analysis confirmed successful usage of TPO-RAs with 76.5% patients who achieved platelet response with well-known safety profile in the setting of demanding persistent severe thrombocytopenia after alloHSCT, that needs to be further evaluated in larger prospective studies.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P589

SUCCESSFUL TREATMENT OF A CASPR2/LGI1-ANTIBODY POSITIVE AUTOIMMUNE ENCEPHALITIS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION FOR MYELOFIBROSIS

Patrick Hess[1], Martina Crysandt[1], Simone C Tauber[2], Jörg B Schulz[2], Steffen Koschmieder[1], Fabian Beier[1], Tim H Brümmendorf[1], Edgar Jost[1]

Oncology, Hemostaseology and Stem Cell Transplantation, RWTH Aachen University, Aachen, Germany, RWTH Aachen University, Aachen, Germany

Background: Complications involving the central nervous system occur in about 10 % of patients after allogeneic stem cell

transplantation (SCT). Encephalitis is a rare complication after SCT and is mostly related to toxic agents, viral infections (e.g., by HHV6, HSV1 or JC virus) or autoimmune disease. Here, we describe a patient developing CASPR2/LGI1-antibody positive autoimmune encephalitis 18 months after SCT for myelofibrosis.

Methods: We describe a 57-year-old male patient after SCT for post polycythemia vera myelofibrosis transplanted with bone marrow stem cells from his haploidentical son. Starting at month 2 after SCT, he developed acute and chronic graft versus host disease (GVHD) of skin, gut and liver requiring immunosuppressive treatment with steroids and ciclosporine. 18 months after transplantation, he developed marked confusion and disorientation, including delusional symptoms. In addition, the patient complained of retrograde amnesia and disturbance of temporal perception. MRI and EEG did not reveal any pathological abnormalities. Analysis of cerebrospinal fluid revealed mild inflammation with pleocytosis of 10 cells/ul without blood-brain-barrier dysfunction. A brain biopsy was performed, showing mild lympho-monocytic meningeal infiltration. In blood serum, 1:320 anti-CASPR2-Ab were detected as well as 1:32 anti-LGI1-Ab. Re-analyses after 4 month showed 1:10 anti-CASPR2- Ab and negative anti-LGI1-Ab. The patient received a combination therapy of 500 mg intravenous prednisolone for 3 days and 2 cycles of plasmapheresis. He was subsequently treated with 2 g/kg body weight intravenous immunoglobulines (IVIG) for 5 days and received 4 weekly intravenous doses of 1000 mg rituximab. Further administration of rituximab was omitted because he suffered CMV reactivation.

Results: After starting this combination therapy, there was a rapid initial partial improvement in confusion and delusional perception, followed by a longer period of slow improvement in neuropsychological symptoms such as memory and executive functions, as assessed by repetitive neuropsychological testing 1, 3 and 14 months after onset of autoimmune encephalitis. In the further course, the patient experienced no more subjective cognitive impairment. CSF analysis was normal 20 and 26 months after onset of neurological symptoms. Now, 3 years after diagnosis of autoimmune encephalitis, there is no evidence of relapse, and CASPR2 and LGI1-Ab are no longer detectable in the serum. However, the patient still has signs of chronic skin and liver GVHD requiring continued immunosuppression with corticosteroids and ruxolitinib.

Conclusions: Autoimmune encephalitis is a rare adverse event after SCT. CASPR2/LGI1-antibody associated disease has been described in patients after SCT. A relationship between GVHD and the occurrence of CASPR2/LGI1 antibodies is assumed. Given the recent and substantial diagnostic improvements of autoimmune encephalitis, we speculate that this disease was significantly underdiagnosed in the past. Treatment with corticosteroids, IVIG, plasmapheresis, and rituximab was feasible, well tolerated and successful in our patient, confirming previous reported cases in the literature. The patient now shows long-term remission of his autoimmune encephalitis, with almost complete neurological reconstitution and no recurrence after a 3-year follow-up. Given the rarity but clinically very relevant consequences of this disease, patients with autoimmune encephalitis should be included in registries to obtain more information and treatment results in the future.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P590

SERIAL QUALITY OF LIFE EVALUATIONS OF MYELOMA PATIENTS TREATED WITH UPFRONT ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOLLOWED BY BORTEZOMIB MAINTENANCE

Kristopher Lamore[1], Richard LeBlanc[2], Jean Roy[2], Imran Ahmad[2], David Ogez[3]

[1]Université de Lille, Lille, France, [2]Institut Universitaire d'Hémato-Oncologie et de Thérapie Cellulaire, Montréal, Canada, [3]Hôpital Maisonneuve-Rosemont, Montréal, Canada

Background: Allogeneic (allo) hematopoietic cell transplantation (HCT) may be curative for multiple myeloma (MM) patients but remains hampered by high rates of toxicity (nonrelapse mortality: 12%), moderate/severe chronic graft-versus-host disease (cGVHD; 57%) and relapse (48%) (LeBlanc R., BMT 2022). This study aimed to evaluate (1) the quality of life (QoL) in recipients of tandem autologous/allo HCT and (2) the impact of cGVHD on QoL.

Methods: Between 11/2014 and 09/2018, 39 newly diagnosed young (age 50 years or less) or high-risk (ISS 3, t(4;14) with ISS II-III, t(14;16), 17p-, chromosome 1 abnormalities or plasma cell leukemia) MM patients were enrolled in a prospective phase II study of upfront tandem autologous/allo HCT followed by bortezomib (Btz) maintenance every 2 weeks for 1 year (NCT02308280) in an attempt to decrease both relapse and cGVHD incidence and severity (Claveau JS., TCT 2022). We prospectively collected questionnaires assessing QoL (EORTC-QLQ-C30, EORTC-QLQ-MY20, FACT-BMT) and GVHD before transplant (T1), then every 3 months during Btz maintenance (T2 to T5) and at the end of treatment (T6 to T8). Paired Wilcoxon tests were performed to explore QoL scores evolution over time (between T1 vs T2-T8) and Spearman's rank-order correlations were conducted to study the associations between QoL scores and cGVHD scores at each measurement time.

Results: Among the 39 patients participating in this trial, 13 patients were excluded due to early myeloma recurrence (n = 5), death (n = 4), not having completed T1 measures (n = 2), or having stopped Btz before the end of treatment (n = 2). The final sample includes 26 patients (14 males), with a median age of 55 (range: 35-65) years, among whom 7 had myeloma recurrence after 15 months (T6) and 1 died. More than 80% of the patients presented cGVHD symptoms between T3 and T7. In total, 701 of 755 questionnaires were completed (7.17% of missing data) across the 8-time measurements and were included in this analysis. Participants had high levels of QoL at all times. However, cognitive functioning and global health status decreased significantly during treatment (T1 vs. T2-T5; $p < .05$), while fatigue and dyspnea symptoms were reported more frequently (T1 vs. T2-T5; $p < .05$). Surprisingly, participants reported a better emotional well-being after transplant (T1 vs. T2, T4-T8; $p < .05$). Cognitive functioning after treatment cessation (T6-T8) was still significantly and negatively impacted ($p < .01$). Furthermore, QoL scores were significantly correlated to lung, energy and psychological GVHD domains.

Conclusions: Chronic GVHD is recognized as a significant threat to QoL. However, our results highlight that allo HCT does not impact general QoL negatively. Furthermore, as QoL was associated to specific GVHD domains, therapeutic actions can be implemented. Supportive care including psychological and neuropsychological interventions, as well as adapted physical activity, is particularly needed for MM patients receiving autologous/allo HCT. Behavioral interventions should be developed and offered to all patients to help them cope with adverse effects induced by these curative treatments.

Clinical Trial Registry: NCT02308280, https://clinicaltrials.gov/

Disclosure: Nothing to declare. This study was supported by the Myeloma Canada Research Chair and the Maryse and William Brock Research Chair in Applied Research into Stem Cell Transplantation, both at Université de Montréal.

15 - Non-infectious Late Effects, Quality of Life and Fertility

P591

IMPACT OF PRE - TRANSPLANT PULMONARY FUNCTION TESTS (PFTS) IN PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANT FOR (AUTO SCT) MULTIPLE MYELOMA (MM) PATIENTS

Indumathy Varadarajan[1], Omar Elghawy[1], Wen You[1]

[1]University of Virginia, Charlottseville, United States

Background: Impact of poor pre transplant PFTs on Auto SCT in MM has not been published extensively. This is a single center retrospective analysis which aims to analyze the impact of poor PFTs on ICU transfer within 30 days of Auto SCT and 1 yr overall survival(OS) in patients(pts) undergoing auto SCT for MM. State of Virginia hosts counties with the highest and the lowest per capita income in United states. Hence, we have used our centers data to further analyze the Impact of race and socio-economic status on Pre transplant PFT.

Methods: Single center retrospective data was collected on pts >/18 yrs undergoing Auto SCT for Myeloma from 2012 to 2022. Pts receiving chemo intensive regimens prior to transplant were excluded. Poor baseline PFT was defined as FEV1 \< 65% or DLCO < 65%. Logistic regression analysis was used to control socioeconomic variables. The 30-day ICU transfer is considered as a binary outcome. Log-rank test results and Cox hazard ratio of 1-year overall survival is reported in the analysis. To analyze the impact of Socio- economic and racial /ethnic factors on Pre transplant PFT, we used the Social Vulnerability Index developed by the CDC, which is developed based on 15 social factors including level of education that determine overall vulnerability. We have also classified zip codes as urban-rural using 2013-ruralurban continuum codes provided by the US Department of Agriculture to also investigate the impact of possible vulnerability by the rurality status of the patient's area of residence.

Results: A total of 337 patients were identified. Median age 61 yr (SD = 8.5). 39.2% Female, 21.4% Black, 3.9 % Hispanic, 72.1 % White. 42.7 % were smokers and 26.3 % of full set were > 10 pack year. 33% of the pts were from the rural area. 3%(N = 10) of patient population were transferred to ICU within 30 days of Auto SCT. 17.8% (N = 60) had either FEV1 or DLCO < 65%. 4.2% (N = 14) died within one year after the transplant date. There was no difference in the 30 day ICU transfers (HR 1.29, p = 0.46) or 1 yr mortality (HR -0.95, p = 0.95) between the Poor baseline PFT and good baseline PFT in Univariate and Multivariate analysis. Although mean values of socioeconomic variables, may indicate that patients with poor PFT live in areas with higher SVI index, as compared to patients without poor baseline PFT, these changes did not have a statistical significance. The stepwise regression reveals that patients who smoke are more likely to have poor baseline pulmonary function compared to non-smokers.

Conclusions: Poor PFT did not have a statistically significant adverse effect on 30 day ICU transfer, or 1 yr Overall Survival in patients undergoing Auto SCT for MM. High SVI did not have any direct impact on baseline PFT. However large multi-center studies are needed to confirm these findings.

Disclosure: No conflicts of interest to disclose.

18 - Paediatric Issues

P592

UBTF-TD – IMPACT OF THE NEW KID ON THE BLOCK ON HSCT IN PEDIATRIC MDS

Brigitte Strahm[1], Miriam Erlacher[1], Sebastian Stasik[2], Ayami Yoshimi[1], Julia-Annabell Georgi[2], Gudrun Göhring[3], Shlomit Barzilai[4], Ivana Bodova[5], Jochen Buechner[6], Albert Catala[7], Valérie De Haas[8], Barbara De Moerloose[9], Michael Dworzak[10], Henrik Hasle[11], Kirsi Jahnukainen[12], Krisztián Kállay[13], Marko Kavcic[14], Paul Kjollerstrom[15], Franco Locatelli[16], Riccardo Masetti[17], Sophia Polychronopoulou[18], Natalia Rotari[19], Markus Schmugge[20], Owen Smith[21], Jan Starý[22], Dominik Turkiewicz[23], Marek Ussowicz[24], Marcin Wlodarski[25,19], Peter Noellke[19], Christian Tiede[2], Charlotte Niemeyer[19]

[1]Pediatric Hematology and Oncology, University Medical Centre, Freiburg, Germany, Hospital Carl Gustav Carus, Dresden, Germany, Hannover Medical School, Hannover, Germany, [4]Pediatric Hematology Oncology, Schneider Children's Medical Center of Israel,Tel Aviv University, Israel, Petah Tikva, Israel, National Institute of Children's Diseases, Bratislava, Slovakia, University Hospital, Oslo, Norway, Hospital Sant Joan de Deu, Barcelona, Spain, [8]Dutch Childhood Oncology Group, Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, Ghent University Hospital Gent, Gent, Belgium, [10]St. Anna Children's Hospital, Medical University of Vienna and St. Anna Children's Cancer Research Institute (CCRI), Vienna, Austria, Aarhus University Hospital, Aarhus, Denmark, [12]Division of Hematology-Oncology and SCT Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, Central Hospital of Southern Pest - National Institute of Hematology and Infectious Diseases, Budapest, Hungary, University Children's Hospital, Ljubljana University Medical Centre, Ljubljana, Slovenia, [15]Pediatric Hematology Unit, Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal, [16]Catholic University of the Sacred Heart, Rome, Rome, Italy, Rome, Italy, [17]Paediatric Oncology and Haematology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, Aghia Sophia Children's Hospital, Athens, Greece, [19]Pediatric Hematology and Oncology, University of Freiburg, Freiburg, Germany, University Children's Hospital, Zurich, Switzerland, [21]Pediatric Haematology, Our Lady's Children's Hospital, Dublin, Ireland, Charles University and University Hospital Motol, Prague, Czech Republic, Section of Pediatric Oncology, Hematology, Immunology and Nephrology, Skåne University Hospital, Lund, Sweden, Wroclaw Medical University, Wroclaw, Poland, St. Jude Children's Research Hospital, Memphis, United States

Background: The upstream binding transcription factor (UBTF) is a regulator of protein synthesis and cell growth. Recently, UBTF tandem duplications (*UBTF*-TD) have been identified in 9% of patients with relapsed pediatric AML and in 4% of de novo AML. Of note, *UBTF*-TD occurs mutually exclusive with other AML subtype-defining alterations. We analyzed the impact of mutated *UBTF*-TD (*UBTF*^{mut}) on outcome of HSCT for primary pediatric MDS with excess blast (MDS-EB).

Methods: We first studied patients < 18 years of age with primary MDS-EB registered with the European Working Group of MDS in Childhood (EWOG-MDS) and consecutively diagnosed in Germany between 7/1998 and 6/2021. We then extended the study to 235 patients with MDS-EB diagnosed in 19 European countries.

Results: We identified 104 patients with MDS-EB diagnosed in Germany. Of those, 25 pts (24%) carried a *UBTF*-TD, 79 were *UBTF*^{wt}. Median age at diagnosis was 11.0 years in *UBTF*^{mut} patients and 9.8 years in *UBTF*^{wt}. Metaphase cytogenetics was normal in 72% vs 33%, showed trisomy 8 in 24% vs 13%, monosomy 7 in 0% vs 40%, structural complex changes in 0% vs 7% or random aberrations in 0 vs 7% of *UBTF*^{mut} and *UBTF*^{wt}, respectively. Consistent with the absence of monosomy 7 in the *UBTF*^{mut} cohort, none of the patients with *UBTF*^{mut} was known to carry a genetic predisposition to myeloid neoplasia, while germline mutations were present in 30 *UBTF*^{wt} patients (*GATA2* 15, *RUNX1* 7, *SAMD9/SAMD9L* 6, *NF1* 2). Since presence of a

germline condition often implies special considerations for HSCT, we excluded patients with predisposition syndromes from the analysis. Therapy prior to HSCT in the 25 *UBTF*^{mut} and 47 *UBTF*^{wt} pts was comparable and consisted of AML-type therapy in 32% vs 21%, less intensive chemotherapy 8% vs 15% and no therapy in 60% vs 64% pts, respectively. Preparative regimens included busulfan/cyclophosphamide/melphalan in 76% of *UBTF*^{mut} and 72% of *UBTF*^{wt} patients. Donor was a MSD, MUD, MMUD or MMFD in 16% vs 28%, 64% vs 57%, 12% vs 6% and 8% vs 9% of the *UBFT*^{mut} vs *UBTF*^{wt} patients, respectively. All but 4 patients engrafted. Cumulative incidence of °II-IV acute GvHD and chronic GvHD were comparable (0.38 [0.22-0.66] vs 0.36 [0.24-0.53] and 0.17 [0.06-0.49] vs 0.24 [0.14-0.41] in *UBFT*^{mut} vs *UBTF*^{wt}, respectivly). Disease-free survival (DFS), cumulative relapse incidence (CIR) and non-relapse mortality at 5 years were 0.43 (0.22-0.64) vs 0.60 (0.45-0.75), 0.29 (0.14-0.56) vs 0.20 (0.11-0.36), 0.24 [0.12-0.49] vs 0.15 (0.08-0.30), in *UBTF*^{mut} and *UB*TF^{wt} cohort, respectively. Patients with normal karyotype and *UBTF*^{mut} had a significantly inferior DFS of 0.34 (0.09-0.51) than those with UBTF^{wt} of 0.77 (0.59-0.69) ($p = 0.03$) due to higher CIR. These results and in particular data on the somatic landscape of *UBTF*^{mut} indicating a dismal outcome for patients with *WT1* mutations will be substantiated on the extended European cohort.

Conclusions: *UBTF*-TD mutations characterize a myeloid neoplasia often presenting as primary pediatric MDS-EB. The presence of *UBTF*-TD has a significant impact on outcome of HSCT and outlines an urgent need for therapeutic strategies for the affected patients.

Clinical Trial Registry: n.a.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P593

TREOSULFAN BASED CONDITIONING FOR HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) IN CHILDREN: ON BEHALF OF THE UK PAEDIATRIC BMT GROUP

Tom Altmann[1,2], Beki James[3], Robert Chiesa[4], Persis Amrolia[4], Sophie Hambleton[1,2], Andrew R. Gennery[1,2], Rachael Hough[5], Ben Carpenter[5], Reem Elfeky[4], Oana Mirci-Danicar[6], Sanjay Tewari[7], Katharine Patrick[8], Gibson Brenda[9], Anna-Maria Ewins[10], Salah Ali[3], Robert Wynn[11], Kanchan Rao[4], Mary Slatter[2,1], Su Han Lum[1,2]

[1]Newcastle University, Newcastle upon Tyne, United Kingdom, [2]Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, [3]The Leeds Teaching hospitals NHS Trust, Leeds, United Kingdom, [4]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [5]University College London Hospital's NHS Foundation Trust, London, United Kingdom, [6]Bristol Royal Hospital for Children, Bristol, United Kingdom, [7]The Royal Marsden Hospital, London, United Kingdom, [8]Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom, [9]Royal Hospital for Children, Glasgow, Glasgow, United Kingdom, [10]Royal Hospital for Children, Glasgow, United Kingdom, [11]Royal Manchester Children's Hospital, Manchester, United Kingdom

Background: Treosulfan, in combination with fludarabine, is increasingly used as part of pre-HSCT conditioning for malignant and non-malignant disorders in children. This multicentre study compared transplant outcomes in 537 paediatric patients after treosulfan based conditioning for first haematopoietic stem cell transplantation (HSCT) between 2015 and 2021 at 9 transplant centres in the UK.

Methods: The primary endpoints were overall survival (OS), event-free survival (EFS; survival without graft failure, relapse/recurrence, and second procedures) and transplant-related mortality (TRM). Secondary endpoints were grade II-IV aGvHD, cGvHD, veno-occlusive disease (VOD) and thrombotic microangiopathy (TMA). Subgroup differences in OS, EFS were evaluated by log-rank test. Cox-regression model was used for multivariate analysis. Competing risks methods were used for the cumulative incidence of aGvHD, cGvHD, VOD and TMA, with death as the competing event, subgroup differences were evaluated by the Fine-and-Gray model.

537 paediatric patients received fludarabine-treosulfan based conditioning. Median age at transplantation: 3.9 years (range: 0.1-19 years). 132 (25%) patients had malignant disorders and 405 (75%) had non-malignant disorders: 268 non-SCID inborn errors of immunity, 42 SCID, 79 non-malignant haematological disorders, 11 inborn errors of metabolism and 5 osteopetrosis. Donors were: 169 matched family, 269 matched unrelated, 29 mismatched family/unrelated and 70 haploidentical (> 2 antigen mismatches). Stem cell source was: marrow 215, unmanipulated peripheral blood stem cell (PBSC) 205, T cell receptor (TCR) ab/CD19 deleted PBSC 83, and cord blood 34. 352 (66%) patients received fludarabine, treosulfan and thiotepa, 185 (34%) receiving only fludarabine and treosulfan. 52 (10%) patients received no serotherapy. 42 (8%) received no post HSCT GvHD prophylaxis. Median duration of follow up was 3.1 years (range 0.2-7.8). 3-year overall survival (OS) was 85% for the whole cohort, 72% for malignant, and 89% for non-malignant disorders ($p < 0.001$). There was no significant difference in OS between those who received fludarabine-treosulfan only compared to additional thiotepa. Event-free survival (EFS) was inferior in malignant (58%) compared to non-malignant disorders (83%, $p = 0.001$). EFS was significantly better (82%) in patients receiving fludarabine-treosulfan compared to 75% with additional thiotepa ($p = 0.03$). There was no difference in TRM (9%) between malignant and non-malignant groups and no difference between fludarabine-treosulfan (7%) and additional thiotepa (9%, $p = 0.61$). Malignant patients had significantly more Grade II-IV and III-IV aGVHD. The incidence of chronic GVHD at 1 year for the whole cohort was low at 6%. The incidence of VOD was 2% and TMA 4% and no differences were found according to indication or additional thiotepa.

Conclusions: This large, multicentre, multi-disease cohort shows that treosulfan based conditioning offers good overall and event-free survival in children that require HSCT for a variety of conditions. The addition of thiotepa does not affect overall survival or TRM.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P594

EXCELLENT GLOBAL QOL IN ADULT SURVIVORS AFTER PEDIATRIC HCT - BUT THE CATCH IS HIDDEN IN THE DETAILS

Anita Lawitschka[1,2], Dorothea Bauer[1,2], Jacqueline Frichs[1], Natalia Zubarovskaya[1], Susanne Matthes[1], Christina Peters[1,2], Bernhard Holzner[3,4], Gerhard Rumpold[3,4], Thomas Pletschko[5], Lena Fichtinger[5], David Riedl[3,4]

[1]St. Anna Children's Center, Medical University of Vienna, Vienna, Austria, [2]Children's Cancer Research Institute, Vienna, Austria, [3]Tirol Kliniken, Innsbruck, Austria, [4]Medical University of Innsbruck, Innsbruck, Austria, [5]Medical University of Vienna, Vienna, Austria

Background: Research on long-term quality of life (QoL) of adult survivors of pediatric HCT is scarce. We measured QoL in

correlation with socio-demographic, disease (malignant versus non-malignant underlying diseases, UD), medical (chronic GVHD, comorbidities) and HCT details. Outcomes were compared with age- and gender-matched healthy controls, survivors of adult HCT and after conventional chemotherapy.

Methods: Adult survivors (n = 180) of unicentric pediatric HCT (1982-2008) were recruited. Data of 84 pts were retrieved from medical records or self-reported. Chronic GVHD was evaluated according the NIH 2005 criteria, and comorbidities were classified according CTCAE v3.0. The German version of the EORTC QLQ-C30 and the EORTC QLQ-HDC29 were used to measure QoL. One- and two-way analyses of variance (ANOVAs) were performed to analyze the effect of UD and transplant-associated complications. Stepwise linear regression models were calculated to evaluate the impact of clinical and sociodemographic variables.

Results: 52 male and 32 female pts (mean age of 24.4 years) participated (response rate 74%). Time from HCT to study entry was mean 13.4 years and the majority of pts had a malignant UD (74%), and myeloablative conditioning (67%). Of 24 cGVHD pts (29%), 17/24 patients had experienced severe cGVHD; 78% of pts developed at least one kind of comorbidity (18% CTCAE grade 1, 51% CTAE grade 2, 31% CTCAE grade 3-4). We found no impact of UD, cGVHD and comorbidities on QoL, but a significant (p = .042) interaction effect between UD and cGVHD.

Most impaired pts (cGVHD 2-3 and CTCAE 3-4) reported lower global QoL (67.4 vs 83.0, p = .037) than less impaired pts (cGVHD 0-1 and CTCAE 0-1). In multivariate analysis higher global QoL scores significantly correlated with lower age at HCT (p = .015), malignant UD (p = .009), and a higher monthly income at study entry (p = .002). In comparison to the healthy age- and gender-matched control (German population) global QoL was similar, but most subscales were reported significantly worse by pts (table).

QLQ-C30	*HSCT survivors (n = 84) mean (SD)*	*Healthy control (n = 2448) mean (SD)*	*p*			
Global QoL	78.3 (22.8)	75.0 (19.6)	.14			
QLQ-C30	*Male HSCT survivors (n = 43) mean (SD)*	*Male healthy control (n = 191) mean (SD)*	*p*	*Female HSCT survivors (n = 28) mean (SD)*	*Female healthy control (n = 208) mean (SD)*	*p*
Global QoL	81.8 (20.0)	97.8 (7.5)	**<.001**	77.97 (20.81)	84.3 (17.2)	.08
Functioning Scales						
Physical Functioning	93.3 (12.9)	97.8 (7.5)	**.025**	86.67 (18.86)	97.0 (10.1)	**<.001**
Role Functioning	87.2 (21.2)	95.6 (13.8)	**.014**	85.71 (23.88)	97.3 (11.4)	**<.001**
Emotional Functioning	77.1 (21.8)	84.4 (21.6)	**.047**	77.88 (19.07)	86.0 (19.8)	**.042**
Cognitive Functioning	86.4 (17.9)	96.3 (11.6)	**<.001**	89.88 (15.93)	96.9 (10.3)	**.002**
Social Functioning	86.4 (23.9)	96.3 (13.2)	**.002**	82.14 (30.74)	97.1 (11.6)	**<.001**
Symptoms						
Fatigue	23.8 (26.2)	10.8 (20.7)	**<.001**	21.83 (21.91)	10.1 (17.4)	**.001**
Nausea/ Vomiting	4.3 (11.0)	2.1 (10.0)	.20	4.76 (14.24)	2.0 (8.3)	.13
Pain	13.2 (20.8)	7.8 (18.7)	.095	16.07 (23.34)	7.2 (17.6)	**.016**
Dyspnea	9.30 (18.29)	2.3 (10.8)	**.001**	7.14 (18.94)	2.1 (9.3)	**.022**
Insomnia	13.95 (24.38)	6.6 (20.6)	**.044**	13.10 (20.63)	5.6 (16.2)	**.027**
Appetite Loss	6.7 (17.2)	2.1 (11.1)	**.021**	7.14 (16.62)	3.4 (14.4)	.21
Constipation	1.6 (7.1)	0.7 (4.8)	.31	3.57 (13.88)	1.4 (7.6)	.21
Diarrhea	10.1 (20.0)	1.0 (8.3)	**<.001**	9.52 (19.99)	3.5 (13.4)	**.038**
Financial Difficulties	8.53 (20.69)	2.6 (13.6)	**.022**	11.90 (26.00)	2.6 (11.6)	**.001**

Comparing HCT survivors without cGVHD, our patients showed significantly better functioning and symptom scores than those after adult HCT (Pallua et al, 2010). When comparing cGVHD pts differences became less significant. Our malignant subgroup rated their QoL significantly better (78.3 vs 66.4, p = .002) compared to adult AML HCT pts (Messerer et al, 2008); in comparison to adult AML pts after conventional chemotherapy global QoL was similar, but most subscale scores were significantly better in pediatric survivors.

Conclusions: Global QoL of our study group was comparable with the healthy control but most subscales were reported significantly worse by our patients. Risk factor analysis confirmed previous research emphasizing employment and monthly income. In comparison to adult HCT survivors our patients showed significantly better results, which was true even in comparison to AML patients after conventional chemotherapy. Interestingly, we found no general impact of cGVHD, comorbidities, and high-dose conditioning as non-malignant pts after RIC did not rate their QoL better. The better global QoL in non-malignant UD with cGVHD may be partly explained by the longer transplant-specific follow-up care but remains to be proven in larger studies.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P595

IMPACT OF ATLG GRAFALON® EXPOSURE ON ACUTE GVHD AND REMISSION-STATE SPECIFIC RELAPSE RATE AFTER HSCT IN THE PAEDIATRIC FORUM ALL COHORT

Lisa V.E. Oostenbrink[1], Erik G.J. von Asmuth[1], Cornelia M. Jol-van der Zijde[1], Anja M. Jansen-Hoogendijk[1], Carly Vervat[1], Robbert G.M. Bredius[1], Maarten J.D. van Tol[1], Marco W. Schilham[1], Petr Sedlacek[2], Marianne Ifversen[3], Adriana Balduzzi[4], Peter Bader[5], Christina Peters[6], Dirk Jan A.R. Moes[7], Arjan C. Lankester[1], on behalf of the FORUM Study Group

[1]Willem-Alexander Children's Hospital, Leiden, Netherlands, [2]Motol University Hospital, Prague, Czech Republic, [3]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, [4]Clinica Pediatrica Università degli Studi di Milano Bicocca, Monza, Italy, [5]University Hospital Frankfurt, Frankfurt am Main, Germany, [6]St. Anna Children's Hospital, Children's Cancer Research Institutev, Vienna, Austria, [7]Leiden University Medical Centre, Leiden, Netherlands

Background: ATG serotherapy in the HSCT setting is used for in vivo T-cell depletion to reduce the risk of graft failure and aGvHD/cGvHD. In contrast to ATG Thymoglobulin, few studies are published investigating the pharmacokinetics (PK) and -dynamics (PD) of anti T-lymphocyte globulin (ATLG) Grafalon® and no population PK models are published. This prospective study describes the population PK of ATLG and the relationship between ATLG exposure and clinical outcome in a homogeneous cohort of paediatric ALL patients.

Methods: ATLG treated patients transplanted with a matched-unrelated donor between 2014 and 2020, who participated in the international FORUM study (*Peters, JCO, 2020*) were included. Median cumulative dose of ATLG was 45 mg/kg (range 15-45), administered before transplantation at days -3, -2 and -1. Serum samples were

collected and analysed by quantitative flowcytometry to determine the active ATLG concentration (*Oostenbrink, Front in Immun, 2019*). Population PK analysis was analysed using NONMEM®. The relation between ATLG exposure and outcome was determined with competing risk and landmark analyses using Gray's test.

Results: In total 813 samples from 121 paediatric ALL patients were available for the population PK analysis. Clinical outcome parameters were obtained for a representative cohort of 101 patients. A two-compartmental model with parallel linear and non-linear clearance best described the ATLG concentration-time data. Bodyweight, allometrically scaled, was added as covariate since it significantly explained ATLG pharmacokinetic variability. ATLG exposure, expressed as the day active ATLG concentration fell <1 AU/mL (median day 17 post-HSCT, range 1-42), was significantly associated with aGvHD grade II-IV. The incidence of aGvHD grade II-IV was significantly higher in patients who reached the active ATLG threshold level within 17 days after transplantation ($p < 0.001$; <=day 17 50% *vs.* > 17 days 8.2%). The incidence of severe aGvHD grade III-IV was low (4/101 patients) and exclusively seen in patients that cleared their ATLG within 19 days after HSCT. By stratifying for remission state, we showed that patients in CR2-3 had a significantly higher relapse risk when ATLG exposure was high, while this effect was not seen in those in CR1 (cumulative incidence of relapse at 2 years post-HSCT, $p = 0.010$, <=17 days CR1 16%, >17 days CR1 16%, <=17 days CR2-3 14%, >17 days CR2-3 51%). This trend held when accounting for conditioning, with a 2.3 times higher 1-year relapse rate in the CR2-3/TBI and high ATLG exposure group compared to those with low exposure, and a 2.5 times higher rate in the chemo-conditioning group with high ATLG exposure, even though patients in CR2-3 with chemo-conditioning had high exposure more often than those with TBI (chemo-group, <=17 days: $n = 5$, >17days: $n = 15$; TBI-group: <=17 days: $n = 20$, >17days: $n = 9$, $p = 0.0037$).

Conclusions: This study describes the first ATLG population PK model in a large homogenous paediatric ALL cohort. A clear relationship between active ATLG exposure and aGvHD incidence, and an increased risk of relapse for patients in CR2-3 with long ATLG exposure was observed. These data underline the importance of optimizing individualized dose recommendations for ATLG Grafalon® in order to improve the outcome in paediatric HSCT.

Clinical Trial Registry: ClinicalTrials.gov: NCT01949129

Disclosure: The work described in this study is in part funded by a research grant from Neovii Pharmaceuticals AG.

18 - Paediatric Issues

P596

A RETROSPECTIVE STUDY ANALYZING THE OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN AND ADOLESCENTS WITH THERAPY-RELATED MYELODYSPLASTIC SYNDROME

Eva-Maria Kornemann[1], Senthilkumar Ramamoorthy[1], Miriam Erlacher[1], Gudrun Göhring[2], Marcin Wlodarski[1], Valérie De Haas[3], Barbara De Moerloose[4], Michael Dworzak[5], Henrik Hasle[6], Kirsi Jahnukainen[7], Krisztián Kállay[8], Riccardo Masetti[9], Markus Schmugge[10], Jan Starý[11], Dominik Turkiewicz[12], Marek Ussowicz[13], Michael H. Albert[14], Peter Bader[15], Birgit Burkhardt[16], Johann Greil[17], Peter Lang[18], Franco Locatelli[19], Tania Masmas[20], Roland Meisel[21], Ingo Müller[22], Johannes H. Schulte[23], Ansgar Schulz[24], Petr Sedlacek[11], Marco Zecca[25], Peter Nöllke[1], Ayami Yoshimi[1], Charlotte M. Niemeyer[1], Brigitte Strahm[1]

[1]Medical Center-University of Freiburg, Freiburg, Germany, [2]Hannover Medical School, Hannover, Germany, [3]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, [4]Ghent University Hospital, Gent, Belgium, [5]St. Anna Kinderspital, Vienna, Austria, [6]Aarhus University Hospital, Aarhus, Denmark, [7]University of Helsinki and Helsinki University Hospital, Hus, Finland, [8]Central Hospital of Southern Pest- National Institute of Hematology and Infectious Diseases, Budapest, Hungary, [9]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [10]University Children's Hospital Zurich, Zurich, Switzerland, [11]Charles University and University Hospital Motol, Prague, Czech Republic, [12]Skåne University Hospital, Lund, Sweden, [13]Wroclaw Medical University, Wroclaw, Poland, [14]University Hospital, LMU, Munich, Germany, [15]University Hospital Frankfurt, Frankfurt am Main, Germany, [16]University Hospital Münster, Münster, Germany, [17]University of Heidelberg, Heidelberg, Germany, [18]University of Tübingen, Tübingen, Germany, [19]Catholic University of the Sacred Heart, Rome, Italy, [20]Copenhagen University Hospital, Copenhagen, Denmark, [21]Heinrich Heine University, Düsseldorf, Germany, [22]University Medical Center of Hamburg-Eppendorf, Hamburg, Germany, [23]Charité Berlin, Berlin, Germany, [24]University Medical Center Ulm, Ulm, Germany, [25]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Background: Therapy-related myelodysplastic syndrome (t-MDS) following chemo- and/or radiotherapy of primary malignancies in childhood or adolescence is clinically, cytogenetically and molecularly heterogeneous and generally associated with poor outcome. Allogeneic hematopoietic stem cell transplantation (HSCT) can cure some patients, but risk factors predicting outcome of HSCT are not well defined.

Methods: We identified 145 patients (70 female and 75 male) included in the registry of the European Working Group of MDS in Childhood (EWOG-MDS) who were transplanted for t-MDS following treatment of hematological neoplasia (leukemia/lymphoma, 74), brain tumor (19), solid tumor (48) or multiple malignancies (4). Median age at HSCT was 10.7 years (range 3.4-27.6) and median interval from primary malignancy to t-MDS 3.6 years (range 0.4-18.5). The highest blast count prior to HSCT was <5% in 21 patients, 5-9% in 29, 10-19% in 37, 20-29% in 26 and ≥ 30% in 32. Cytogenetic aberrations were present in 80% of patients and consisted of monosomy 7/del(7q-), structural complex changes, 11q23/KMT2A rearrangements or other aberrations in 31%, 22%, 8%, and 19%, respectively. Next generation sequencing including 28 genes performed in bone marrow samples of 85 patients revealed at least one mutation in 49% (42/85) of patients; most frequently affected were *TP53* (12) *RUNX1* (9), *ASXL1* (9) and the RAS pathway genes *PTPN11* (7), *KRAS* (5) and *NRAS* (2). Following a preparative regimen with busulfan, cyclophosphamide and melphalan (63), or other busulfan-based (19), treosulfan-based (36) or alternative conditioning regimens (28) patients were transplanted from a MSD (46), an unrelated donor (95) or an HLA-haploidentical donor (4).

Results: The 5-year probabilities of overall survival (OS) and disease-free survival (DFS) were 0.48 (0.39-0.57) and 0.41 (0.32-0.50), respectively. Cumulative incidence rates of t-MDS relapse (CIR) and non-relapse mortality (NRM) were 0.34 (0.27-0.43) and 0.22 (0.16-0.30), respectively. DFS was comparable for patients with t-MDS following hematological neoplasia 0.49 (0.37-0.61), brain tumor 0.40 (0.17-0.63) or solid tumor 0.33 (0.18-0.48). However, patients with t-MDS after brain tumor had a significantly higher NRM of 0.49 (0.31-0.79) compared to 0.14 (0.08-0.25) for hematological neoplasia and 0.21 (0.12-0.37) for solid tumor, $p < 0.01$. Patients with a structural complex karyotype showed an inferior DFS (0.20 [0.04-0.36]) compared to normal karyotype (0.48 [0.28-0.68]), monosomy7/del(7q) (0.50 [0.34-0.66]), 11q23/KMT2A rearrangements (0.40 [0.01-0.79]) or other aberrations (0.49 [0.29-0.69]), $p < 0.02$. *TP53* mutations were associated with a dismal

outcome (DFS 0.08 [0.00-0.24]). Although grouping patients according to highest blast count prior to HSCT had no significant impact on DFS, patients with <5% bone marrow blasts at any evaluation prior to HSCT showed a significantly lower relapse rate compared to patients with higher blast percentages (0.05 [0.01-0.32]) versus 0.39 (0.30-0.49, $p < 0.01$). Donor type, conditioning regimen and stem cell source did not significantly affect outcome.

Conclusions: HSCT resulted in a 5-year DFS of 48% in this high-risk group of 145 patients with t-MDS. Cytogenetics and gene mutation profiles had the strongest impact on outcome. Characterization of the genetic profile, including the identification of germline variants, will be required for informed treatment decisions and will help elucidate the pathogenesis of t-MDS.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P597

MIXED DONOR CHIMERISM IN PAEDIATRIC B-ALL PATIENTS BRIDGED TO TRANSPLANT WITH BLINATUMOMAB – A REPORT FROM THE UK AND IRELAND PAEDIATRIC BSBMTCT GROUP

Oana Mirci-Danicar[1], Madeleine Powys[2], Giorgio Ottaviano[3], Khushnuma Mullanfiroze[3], Rebecca Palmer[1], Claire Horgan[2], Wing Roberts[4], Valerie Broderick[5], Angus Hodder[3], Andrea Blotkamp[1], Pamela Evans[5], Katharine Patrick[6], Mary Slatter[4], Persis Amrolia[3], Beki James[7], Robert Wynn[2], Kanchan Rao[3]

[1]Bristol Royal Hospital for Children, Bristol, United Kingdom, [2]Royal Manchester Children's Hospital, Manchester, United Kingdom, [3]Great Ormond Street Hospital for Children, London, United Kingdom, [4]Great North Children's Hospital, Newcastle, United Kingdom, [5]Children's Health Ireland at Crumlin, Dublin, Ireland, [6]Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom, [7]Leeds Children's Hospital, Leeds, United Kingdom

Background: Blinatumomab is an effective tool to bridge paediatric patients with ALL to HSCT. Blinatumomab containing regimens pre-HSCT are associated with lower levels of minimal residual disease (MRD) and less toxicity compared with conventional chemotherapy relapse protocols. This allows more children to proceed to HSCT in MRD negative remission. Historically, post-HSCT mixed donor chimerism (MDC = < 95% donor) identifies patients with high relapse risk. The impact of pre-HSCT Blinatumomab on post-HSCT engraftment dynamics, including chimerism and the impact on relapse, is not well understood.

Methods: Data was collected from consecutive paediatric patients aged 1–16 years who received Blinatumomab prior to HSCT in seven UK and Republic of Ireland transplant centres between 2014-2022. Control data was collected from patients who received non-Blinatumomab bridging therapy to HSCT at two of the seven centres between 2010-2021. Infants, Primary Refractory, MPAL and patients with less than 100 days follow-up post-HSCT were excluded. Peripheral blood chimerism at 1, 3, 6, 9, 12 months and last follow-up post-HSCT were analysed. Primary and secondary graft failure (GF) were defined as failure to achieve donor engraftment at 1 month post HSCT or initial engraftment followed by whole blood donor chimerism <50% at any time point, respectively. Relapse was defined as disease ≥0.01% by any method.

Results: The Blinatumomab (n = 45) and control (n = 40) groups were comparable in terms of conditioning regimen (93% TBI-based), donor type and stem cell source (Table 1). Median follow-up was 1 year for Blinatumomab and 2.5 years for the control group. MDC occurred in 53% (24/45) of the Blinatumomab group, compared to 20% (8/40) in the control group (p 0.002). Increasing number of Blinatumomab cycles was associated with higher incidence of MDC (1 cycle 32% vs ≥2 cycles 74%, p 0.02). In both Blinatumomab and control groups, MDC developed early post HSCT with 91% (29/32) MDC occurring within 6 months. There were 2 primary and 4 secondary GF in the Blinatumomab and none in the control group. Overall relapse rate was 22%: 13.3% (6/45) in the Blinatumomab and 32.5% (13/40) in the control group. Immunosuppression cessation or DLI in response to MDC had no significant impact on relapse free survival.

Conclusions: This is the first report that pre-transplant Blinatumomab is associated with significant increased MDC post-HSCT in paediatric ALL patients. It is likely this MDC reflects reduced pre-transplant treatment intensity as the current UK Relapse Guidelines combines Blinatumomab with less intensive reinduction chemotherapy than IntReALL or COG protocols. Increased MDC in the Blinatumomab group is not yet associated with higher relapse rates, although the follow-up in the Blinatumomab arm is short. The 13.3% GF rate among the Blinatumomab group who received TBI-conditioning is similarly concerning. This may reflect recovering autologous immunity post Blinatumomab leading to allogeneic rejection. Longer follow-up is needed to confirm these preliminary findings.

	Blinatumomab group N = 45	Control group N = 40	P value
Age, median years (CI95%)	9.4 (7.8-10.5)	4.5 (4-6.3)	<0.0001
Follow-up, median days (CI95%)	384 (281-594)	899 (717-1815)	<0.0001
Previous HSCT/CAR19 T cell			ns
HSCT	-	1	
CAR19	6	2	
None	39	37	
Stem cell source			ns
BM	32	30	
PB	4	5	
UCB	8	5	
PBSC + BM	1	-	
Donor			ns
Matched related	14	9	
Matched unrelated	18	22	
Miss-matched	13	9	
Conditioning			ns
TBI-based	43	36	
Chemo-Based	2	4	

Disclosure: Nothing to declare.

18 - Paediatric Issues

P598

EXCELLENT OUTCOMES OF REDUCED-TOXICITY EX-VIVO T-DEPLETED HAPLOIDENTICAL HAEMATOPOIETIC CELL TRANSPLANTATION WITH CD45RA-DEPLETED MEMORY T CELL ADD-BACK IN PAEDIATRIC MALIGNANT AND NON-MALIGNANT DISEASES: 8-YEAR RESULTS

Michaela Seng[1,2], Ah Moy Tan[1,2], Rajat Bhattacharyya[1,2], Vijayakumari K[1], Thi Ngoc Anh Pham[1], Bianca Chan[1,2], Prasad Iyer[1,2], Shui Yen Soh[1,1,2,2], Mya Soe Nwe[1,2], Joyce Lam[1,2], Mei Yoke Chan[1,2,2], Enrica Tan[1,2], Wing Hang Leung[1,3]

[1]KK Women's and Children's Hospital, Singapore, Singapore, [2]Duke-NUS Medical School, Singapore, Singapore, [3]University of Hong Kong, Hong Kong, Hong Kong, SAR of China

Background: Barriers to urgent paediatric stem cell transplants in cosmopolitan Singapore include the lack of local donors, significant cost and time for procurement and concerns using cryopreserved donor products during the COVID-19 pandemic. We report our experience with reduced-toxicity haploidentical transplants in a single paediatric centre over the last 8 years, which has allowed life-saving transplants to proceed.

Methods: Review of retrospective data was approved by institutional ethics (CIRB 2020/2294). Eligible haploidentical donors were selected according to donor age, KIR-mismatch, CMV/EBV serostatus, recipient donor-specific antibodies (DSA) and ABO compatibility. GCSF-mobilised peripheral blood stem cells were divided in a 9:1 or 8:2 ratio for TCRαβ -depletion and CD45RA-depletion respectively using the CliniMACS™ platform (Miltenyi Biotec, Bergish-Gladbach, Germany). Target CD34+ doses were a minimum CD34+ cell dose of 5 x 10^6/kg and a maximum TCRαβ + CD3+ cell dose of 2.5 x 10^4/kg. Day 0 CD45RA-CD3+ doses ranged between 1 – 5 x 10^6/kg. Data was censored at patient's last visit.

Results: Forty patients underwent TCRab-depleted haploidentical transplant between 2014-2022. Reduced-toxicity conditioning was based on a haploidentical consortium backbone of Total Lymphoid Irradiation (TLI) 6 Gy/ Fludarabine 160 mg/m^2, Melphalan 140 mg/m^2 and Thiotepa 10mg/kg for acute myeloid leukemia (AML); or Total Body Irradiation 12 Gy, Fludarabine 160 mg/m^2 and Melphalan 100mg/m^2 for acute lymphoblastic leukemia (ALL). Non-malignant conditioning regimens varied depending on the risk of rejection. Serotherapy alone or serotherapy and TLI were used for lymphoablation depending on physician choice and patient factors. Desensitisation was performed for patients with clinically relevant DSA by solid-phase assay. Short-course Tacrolimus was used as anti-GvHD prophylaxis from day -2 to day +30.

18/40 cases were malignant (AML/MDS = 7, ALL = 5, Neuroblastoma = 3, JMML = 3) and 22/40 non-malignant (Bone Marrow Failure Syndromes = 2, Fanconi Anaemia = 2, Severe Aplastic Anaemia = 4, Transfusion-dependent Thalassaemia = 8, Chronic Granulomatous Disease = 2, Wiskott-Aldrich Syndrome = 1, CD40 ligand deficiency = 1, Severe Combined Immunodeficiency = 2).

2-year disease-free survival (DFS) for all malignant cases was 72% (13/18). Within the leukemia cohort, 2-year DFS was 80% (12/15). Treatment-related mortality (TRM) was 5% (1/18).

2-year overall survival (OS) for non-malignant cases was 91% (20/22). TRM was 9% (2/22). Within the bone marrow failure syndrome cohort, 2-year OS was 75% (6/8). Within the Thalassaemia and PID cohorts, 2-year OS and DFS were 100% respectively in both groups.

Graft rejection occurred in 4 patients (SAA = 2, ALL = 1, JMML = 1), all were successfully rescued with a haploidentical transplant using a different donor. There were 8 deaths due to relapse of primary disease (n = 5) or refractory viral infections (n = 3). We observed an incidence of acute GvHD grade II-IV in 22.5% (9/40) of patients, and moderate to severe chronic GvHD in 5% (2/40) patients.

Conclusions: We have established a successful and robust T-depleted haploidentical programme for children in Singapore with excellent long-term outcomes of TCRab depleted haploidentical transplants in a wide spectrum of malignant and non-malignant diseases. Disease-specific outcomes will be presented in future reports.

Clinical Trial Registry: Not Applicable

Disclosure: Wing Leung is an employee of Miltenyi Biotec.

All other authors have nothing to declare.

18 - Paediatric Issues

P599

GUT MICROBIOTA DIVERSITY BEFORE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION AS PREDICTOR OF MORTALITY AND HIGH-GRADE AGVHD IN CHILDREN

Davide Leardini[1], Edoardo Muratore[1], Daniele Zama[1], Francesco Baccelli[1], Tamara Belotti[1], Francesca Gottardi[1], Marco Fabbrini[2], Federica D'Amico[2], Silvia Turroni[2], Patrizia Brigidi[2], Marek Ussowicz[3], Jowita Fraczkiewicz[3], Marco Zecca[4], Simone Cesaro[5], Pietro Merli[6], Franco Locatelli[6], Arcangelo Prete[1], Riccardo Masetti[1]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [2]University of Bologna, Bologna, Italy, [3]Wroclaw Medical University, Wrocław, Poland, [4]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [5]Azienda Ospedaliera Universitaria Integrata, Verona, Italy, [6]Bambino Gesù Children's Hospital IRCCS, Catholic University of the Sacred Heart, Rome, Italy

Background: Relationship between gut microbiota (GM) diversity and overall survival (OS) after allogeneic stem cell transplantation (HSCT) has been demonstrated in adult recipients. Pediatric patients harbor a GM with peculiar features highly different from the adult counterpart and specific data on this population are missing.

Methods: We examined the impact of GM diversity and composition on clinical outcomes in a multicenter cohort of 97 pediatric HSCT recipients. Stool samples were collected before transplantation and at the time of neutrophil engraftment. GM was profiled by 16S rRNA amplicon sequencing and diversity was estimated using the Shannon index. A global-to-local networking approach was also used to characterize the ecology and functional structure of the GM.

Results: Median value for diversity calculated with the Shannon index was 2.79 and 2.08 in the samples before HSCT and at the engraftment, respectively. Patients were stratified into higher- and lower-diversity groups using the median diversity value for each time point. Patients with higher diversity before HSCT compared to the lower-diversity group exhibited a higher probability of OS (86.7 ± 5.1 (SE) vs 65.1 ± 8.0 (SE))(p = 0.042) with no difference in relapse-free survival (RFS)(77.8 ± 6.2 (SE) vs 58.6 ± 10.2 (SE))(p = 0.157). Patients with higher diversity also experienced lower grade II-IV aGvHD (20.0 ± 6.0 (SE) vs 44.4 ± 7.4 (SE))(p = 0.015), lower grade III-IV aGvHD (4.4 ± 3.1 (SE) vs 17.8 ± 5.7 (SE))(p = 0.039) and a trend towards lower gut aGvHD (11.1 ± 4.7 (SE) vs 24.4 ± 6.4 (SE))(p = 0.091). No differences were found between the diversity groups in terms of blood-stream infections (BSI) (21.4 ± 6.3 (SE) vs 23.3 ± 6.4 (SE))(p = 0.897). The higher-diversity group was characterized by higher relative abundances of the families *Veillonellaceae*, *Prevotellaceae*, *Bacteroidaceae*, *Christensenellaceae*, *Ruminococcaceae* and *Porphyromonadaceae*, whereas the lower-diversity group showed an overabundance of *Enterococcaceae* and *Enterobacteriaceae*. Network analysis of patients belonging to the higher-diversity group showed *Blautia*, *Faecalibacterium*, *Oscillospira*, *Bacteroides* and *Parabacteroides* as hub nodes, known as short-chain fatty acids producers. The lower-diversity group showed *Enterococcus* as the only hub node. When considering the groups based on diversity at engraftment, no differences were found in terms of OS (75.2 ± 7.0 (SE) vs 76.5 ± 7.2 (SE))(p = 0.903), RFS (67.5 ± 7.1 (SE) vs 71.0 ± 8.5 (SE))(p = 0.372), cumulative incidence of grade II-IV aGvHD (37.8 ± 7.2 (SE) vs 28.9 ± 6.8 (SE))(p = 0.573), grade III-IV aGvHD (11.1 ± 4.7 (SE) vs 11.1 ± 4.7 (SE))(p = 0.999), gut aGvHD (17.8 ± 5.7 (SE) vs 17.8 ± 5.7 (SE))(p = 1.000) and BSI (25.0 ± 6.9 (SE) vs 20.0 ± 6.0 (SE))(p = 0.857).

Conclusions: In pediatric HSCT recipients, GM diversity and composition before transplant correlate with survival and the likelihood of developing high-grade aGvHD.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P600

LONG-TERM COMPLICATIONS IN CHILDREN UNDERGOING ALLOGENEIC HSCT FOR MALIGNANCIES WITH A TREOSULFAN OR A BUSULFAN BASED CONDITIONING: RESULTS OF AN AIEOP RETROSPECTIVE STUDY

Francesco Saglio[1], Marco Zecca[2], Daria Pagliara[3], Adriana Balduzzi[4], Arcangelo Prete[5], Francesco Paolo Tambaro[6], Maura Faraci[7], Elisabetta Calore[8], Franco Locatelli[3,9], Franca Fagioli[1,10]

[1]Regina Margherita Children's Hospital AOU Città della Salute e della Scienza di Torino, Turin, Italy, [2]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [3]IRCCS Bambino Gesù Children's Hospital, Rome, Italy, [4]Università degli Studi di Milano-Bicocca, Fondazione MBBM, Ospedale San Gerardo, Monza, Italy, [5]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [6]Azienda Ospedaliera di Rilievo Nazionale Santobono-Pausilipon, Napoli, Italy, [7]IRCCS Istituto Giannina Gaslini, Genova, Italy, [8]University of Padova, Padova, Italy, [9]Catholic University of the Sacred Heart, Rome, Italy, [10]Università degli Studi di Torino, Turin, Italy

Background: Children undergoing hematopoietic stem cell transplantation (HSCT) and becoming long-term survivors have an increased risk of developing long-term toxicities, in part attributable to the conditioning regimen. In this retrospective multicenter study, we evaluated the impact of the use of either Treosulfan or Busulfan on the occurrence of late effects.

Methods: The study included all patients undergoing HSCT between 2006 and 2017 in AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) Centers for acute lymphoblastic leukemia (ALL), acute myelogenous leukemia or myelodysplastic syndrome (AML/MDS) after a conditioning regimen including either Treosulfan (Treo) or Busulfan (Bu). As long-term side effects, the occurrence of impairment of growth, gonadal, thyroid and pulmonary function, cataract, secondary malignancies were investigated. The occurrence of each late effect was calculated as cumulative incidence (CI) to adjust the analysis for competing risks (i.e., leukemia relapse and death). The differences in terms of CI were compared using Gray's test. Multivariable analysis was performed using logistic regression. All statistical analyses were performed using NCSS software (Hintze, 2001; NCSS PASS, Number Crunched Statistical System, Kaysville, UT, USA).

Results: The study included 693 patients (315 females and 378 males) with a median age of 8 years (range 0-23) at the time of HSCT: 584 received a Bu-based and 109 a Treo-based conditioning regimen. At baseline, patients in the Bu group were younger ($p < 0.001$), mostly affected by AML/MDS ($p < 0.001$) and in first complete remission ($p < 0.001$). The Treo group received an HSCT from a partially matched unrelated donor (MMUD) in a larger proportion of the cases ($p = 0.04$) and cord blood as stem source in fewer cases ($p = 0.02$). The median follow-up was of 4.5 years. For gonadal toxicity we considered only patients older than 10 years ($n = 270$) and in univariable analysis Bu was correlated with a statistically significant increased risk of developing gonadal toxicity compared to Treo: 41% (95%CI 34-49) versus 12% (95%CI 5-25) ($p = 0.002$). For growth impairment we considered only patients younger than 10 years ($n = 423$): Bu was correlated with an increased risk of developing growth impairment compared to Treo: 10% (95%CI 7-15) versus 2% (95%CI 0-16) but this difference was not statistically significant ($p = 0,1$). The two groups didn't show any statistically significant difference in terms alteration of thyroid function, cataract, occurrence of secondary malignancies and alteration of pulmonary function. In multivariable analysis patients in the Treo group showed a reduced risk of developing gonadal toxicity (RR 0,27 95%CI 0,12-0,59 $p = .0011$), especially as male patients (RR 0,15 95%CI 0,09-0,23 $p < 0.001$) and younger children (> 5 years RR 3,66 95%CI 2-6,6 $p < 0.001$; > 10 years RR 5,895%CI 3.3-10 $p < 0.001$; > 15 years RR 10.9 95%CI 6-19.7 $p < 0.001$).

Conclusions: This study shows that the use of Treosulfan in the conditioning regimen is associated with a reduced risk of developing gonadal toxicity, while in our study we did not observe a statistically significant association between growth impairment, alteration of thyroid function, cataract, occurrence of secondary malignancies and alteration of pulmonary function and the exposure of one of these two drugs.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P601

LESS SEVERE GRAFT-VERSUS-HOST-DISEASE IN PEDIATRIC PATIENTS RECOVERING WITH HIGH VΔ2 + T-CELLS AFTER ALLOGENEIC HSCT WITH UNMANIPULATED BONE MARROW GRAFTS: A SINGLE CENTER PEDIATRIC COHORT STUDY

Thilo Müller[1], Lina Alasfar[1], Lisa Zimmermann[1], Friederike Preuß[1], Lena Oevermann[1]

[1]Charité - Universitätsmedizin Berlin, Berlin, Germany

Background: A delayed immune reconstitution (IR) is a main risk factor for mobidity and mortality in patients undergoing allogeneic HSCT. There are no studies systematically describing the reconstitution of δγ T-cells and their subtypes in pediatric patients receiving unmanipulated bone marrow (BM) grafts (which remains a frequently used stem cell source in this group of patients). In this study, we examine the IR of δγ T-cells and their subpopulations in a paediatric cohort of 49 patients with unmanipulated BM grafts. We investigate the impact of transplant modalities on IR and the effect of high versus low γδ T-cells on HSCT outcomes.

Methods: Peripheral blood samples of 49 pediatric patients (29 with malignancy, 20 with haematological disorders) receiving unmanipulated BM grafts at the department of Paediatric Haematology and Oncology, Charité - Universitätsmedizin Berlin, were analysed using flow-cytometry for T-cell receptor (TCR) immunophenotyping. Samples were collected once prior to the start of the conditioning regimen and after HSCT on days +15, +30, +60, +100, +180, +240.

Along with the immunophenotyping, an extensive set of clinical data has been investigated to study the impact of transplant modalities on IR and identify potential confounders. As a third step, we have corelated the IR of γδ T-cell subpopulations with HSCT outcomes.

Results: Patients with matched family donor (MFD) showed a faster reconstitution of γδ T-cells early after HSCT compared to patients with matched unrelated donor (MUD) with a predominance of Vδ2 T-cells during the first two month after HSCT and a switch towards Vδ1 thereafter. After MUD-HSCT, patients generally had low Vδ2 counts until TP d + 240. Patients with high relative abundance of total γδ T-cells and in particular Vδ2 cells had significantly better outcomes in terms of high-grade GvHD incidence, and EBV- and CMV-reactivation rates. These results remain robust even when considering the Vδ2 counts as time-dependent covariate.

Conclusions: Our study provides a quantitative description of IR of γδ T-cell subpopulations in paediatric patients with unmanipulated BM grafts during the first 240 days after HSCT. Recovery of γδ T cells was highly dependent on the donor type. Patients with MUD showed poor Vδ2 reconstitution. Interestingly Vδ1/Vδ2 ratio turned towards Vd1 around d + 100 after HSCT in patients with MFD, which is different compared to IR patterns seen in adults.

Our cohort has well-controlled confounders, we have found no confounder affecting the Vδ2 relative abundance. We suggest that poor IR of Vδ2 cells could be a potential risk factor for acute high-grade GvHD, EBV- and CMV-reactivation.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P602

SUCCESS OF PERSONALIZED RUXOLITINIB TREATMENT BASED ON THERAPEUTIC DRUG MONITORING IN PEDIATRIC PATIENTS WITH PRIMARY AND SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ALLOWING BRIDGING TO HSCT

Michele Massa[1,2], Sara Cairoli[1], Emilia Boccieri[1], Roberto Carta[1], Marco Becilli[1], Giulia Boz[1], Ilaria Pili[1], Francesco Quagliarella[1], Chiara Rosignoli[1], Maria Luigia Catanoso[1], Federica Galaverna[1], Valentina Bertaina[1], Mattia Algeri[1], Maria Giuseppina Cefalo[1], Daria Pagliara[1], Bianca Maria Goffredo[1], Pietro Merli[1]

[1]IRCCS Bambino Gesù Children's Hospital, Rome, Italy, [2]Sapienza Università di Roma, Rome, Italy

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder characterized by hyperinflammation with a mortality as high as 40%. The goal of the treatment is to control inflammation in order to perform hematopoietic stem cell transplantation (HSCT), the only curative treatment for most patients. New evidence is accumulating on the role of Ruxolitinib for the treatment of HLH, but the best therapeutic dosing regimen in children is still unknown.

Methods: We performed a single-center retrospective analysis on children treated with ruxolitinib for HLH (either primary or resistant/relapsed (R/R) secondary) at the Bambino Gesù Children's Hospital in Rome with available results of therapeutic drug monitoring (TDM). Ruxolitinib was started at a 2.5 or 5 mg twice daily dosage depending on body weight on top of standard treatment and later adjusted based on TDM.

Results: A total of 8 children were included, 3 with primary and 5 with R/R secondary HLH. Patient characteristics are shown in table 1. All patients had active disease at ruxolitinib start. Previous treatment consisted of dexamethasone (2), dexamethasone and etoposide (2) and methylprednisolone, anakinra and cyclosporin (1).

The overall response at the end of treatment was 100%: 37.5% had a complete response, 50% had a partial response and 12.5% had improvement in measures of HLH (as defined by Locatelli et al. NEJM 2020). Median time to best response was 21 days (range, 7-28). At one-week follow-up all patients became afebrile, there was a statistically significant reduction in ferritin levels and there was a clear trend toward platelets and neutrophils recovery.

Five patients (62.5%) proceeded to HSCT. Of these, two received a TCRαβ/CD19 depleted haploidentical HSCT, two an HLA 10/10 matched unrelated donor allograft and one an HLA identical sibling HSCT. Three patients with secondary HLH obtained sustained remission and did not undergo transplantation because of physician's decision. Overall survival was 87.5%. One patient affected by SCID died after obtaining HLH improvement because of disseminated *Mycobocterium tuberculosis* infection with multi-organ failure which was already active at treatment start.

Median ruxolitinib level at week 1 was 27.72 ng/ml (range, 0.87-279.66). In two patients the dose was modified based on TDM.

Ruxolitinib was well tolerated by all children. Treatment discontinuation occurred in one patient with Griscelli syndrome due to BCG vaccination reactivation. Three more patients had adverse events possibly related to ruxolitinib: 1 EBV and 1 HHV6 reactivation not requiring treatment and 1 pneumonia (CTACE V.5 G3) successfully treated with antimicrobial therapy. No clear correlation between Ruxolitinib levels and adverse events was present.

Age at ruxo	
Mean (Sd)	1.7 (1.89)
Median (range)	1.17 (0.25-5.95)
Sex no. (%)	
F	6 (75)
M	2 (25)
Diagnosis no. (%)	
primary HLH	3 (37.5)
FHL2	1 (12.5)
Griscelli's s.	1 (12.5)
Chediak-Higashi s.	1 (12.5)
Secondary HLH	5 (62.5)
Benign	
SCID	1 (12.5)
NOD2	1 (12.5)
Unknown	1 (12.5)
Malignant	
ALCL	1 (12.5)
LCH	1 (12.5)

Conclusions: This preliminary study suggests ruxolitinib as a safe and effective therapy for pediatric patients with both primary and secondary HLH. Indeed, the control hyperinflammation obtained allowed to proceed to HSCT, with a very good response rate. TDM is feasible in these patients and potentially increases the effectiveness of this treatment. Further larger studies are warranted in order to corroborate this hypothesis.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P603

THE GRANS STUDY: GRANULOCYTE TRANSFUSION DURING CBT FOR REFRACTORY AML IS ASSOCIATED WITH MASSIVE CD8 T CELL EXPANSION, SIGNIFICANT CRS, AND INDUCTION OF DISEASE REMISSION

Roisin Borrill[1,2], Joanne Konkel[2], Ramya Nataraj[1], Madeleine Powys[1], Srividhya Senthil[1], Helen Campbell[1], Omima Mustafa[1], Denise Bonney[1], Kanchan Rao[3], Beki James[4], Kay Poulton[5,2], Simon Stanworth[6], Robert Wynn[1]

[1]Royal Manchester Children's Hospital, Manchester, United Kingdom, [2]University of Manchester, Manchester, United Kingdom, [3]Great Ormond Street Hospital, London, United Kingdom, [4]Leeds Children's Hospital, Leeds, United Kingdom, [5]Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [6]NHS Blood and Transplant, Oxford, United Kingdom

Background: Although relapse is reduced after cord blood transplant (CBT), the prognosis of post-transplant relapsed/refractory AML is extremely poor, and many patients face palliative care as the only option. We have previously reported T cell expansion and induction of remission in CBT recipients receiving granulocyte transfusions. We now report an innovative, investigator-led clinical trial to assess the safety of granulocyte

transfusions during CBT, the reproducibility of this in-vivo T cell expansion, and disease response in a very high-risk cohort of patients (ClinicalTrials.Gov NCT05425043).

Methods: This single-centre, phase I clinical trial included children referred via the national MDT with post-transplant, relapsed, refractory AML. Patients received a T-replete, HLA-mismatched (5/8-7/8) CBT and 7 doses of granulocytes (10 ml/kg). Granulocytes were a pooled blood component (NHS Blood and Transplant). Flow cytometry and serum cytokine analysis were performed. The comparator group was a historical cohort of 28 paediatric CBT recipients without granulocytes.

Results: Ten patients received CBT with granulocytes. Nine patients were MRD positive or with frank disease and had adverse cytogenetic features, Table 1.

1. Clinical outcomes

Nine patients entered haematological remission, and eight became MRD negative. One patient died of graft failure with detectable disease, and one patient died with drug resistant HSV in leukaemia remission. One patient never achieved MRD negativity and progressed to early haematologic relapse. Seven patients had sustained MRD negative remission, with five patients alive and in complete remission with a median follow up of 8.7 months and two late relapses at 4.9 and 7.8 months. Four patients developed grade II- IV acute GVHD. No chronic GVHD was seen. Immune suppression was stopped at a median of 70 days.

2. T cell expansion and phenotype

T cell expansion occurred in nine patients. The median peak lymphocyte count was significantly higher in granulocyte recipients compared with controls during days 7 to 13 (median 1.73 $x10^9$/L vs 0.1 $x10^9$/L; $p < 0.0001$) and days 14 to 20 (median 0.89 $x10^9$/L vs 0.22 $x10^9$/L; $p = 0.0002$) following CBT, Figure 1. Peak lymphocyte count occurred at a median of 9 days, with a median of 5 days to subsequent nadir. T cells were predominantly $CD8^+$ (median 67.3%) with naïve to effector memory (median 59.6%) and TEMRA (median 33.1%) phenotype switch. These cells were activated with HLA-DR and CD38 co-expression, and cytotoxic with granzyme B and perforin expression, and interferon-gamma production.

3. Cytokine release syndrome

Grade 1- 3 CRS was seen in all patients. There was significantly earlier onset of fever, more days of fever, higher fever and higher CRP than in control patients. Elevated IL 6, interferon-gamma and TNF-alpha were detected in serum.

Table 1: Patient and transplant characteristics

		Number (percentage)
Patient characteristics	Male sex	5 (50)
	Median age, years (range)	6.5 (2- 14)
Diagnosis	AML	10 (100)
Cytogenetic risk	High risk	9 (90) (12p deletion n = 1; complex n = 1; FLT3/NUP98 n = 1; FUS-ERG n = 1; GLIS2 n = 1; KMT2A-MLL10 n = 2; monosomy 7 n = 1; p53 mutation n = 1)
	Standard risk	1 (10) (NPM1 n = 1)
Previous transplant	Yes	10 (100)
	No	0 (0)
Flow MRD status	Flow MRD positive	9 (90) *4 patients with haematologic relapse
	Flow MRD negative	1 (10)
Conditioning	Busulfan-based	3 (30)
	Treosulfan- based	7 (70)
HLA- match	7/8	4 (40)
	6/8	4 (40)
	5/8	2 (20)
Cell dose	TNC (x107/kg), median (range)	10.7 (4.0- 15.0)
	CD34+ (x105/kg), median (range)	2.8 (2.06- 14.01)
Granulocytes	7 doses	10 (100)
	Start date, median (range)	Day +1 (day -4- day +16)

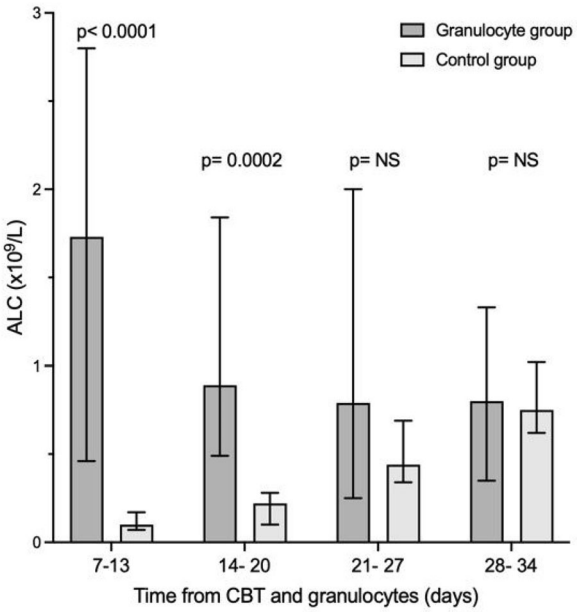


Figure 1: The highest ALC measured in 7 day intervals in the first month following CBT in patients receiving granulocytes and control group. Median values ± 95% confidence interval plotted.

Conclusions: We report reproducible, significant, transient T cell expansion using granulocytes and CBT. The phenotype switch is consistent with that of T cells capable of mediating GVL in xenograft models of leukaemia. There is CRS and disease response in a cohort of patients with AML for whom other treatment options had been exhausted. We hypothesise the T cell response is secondary to mismatched HLA and antigen presentation, and likely augments the GVL seen in CBT.

Clinical Trial Registry: ClinicalTrials.Gov NCT05425043

Disclosure: Nothing to declare.

18 - Paediatric Issues

P604

USE OF ECULIZUMAB IN PEDIATRIC PATIENTS WITH HIGH-RISK TRANSPLANT ASSOCIATED THROMBOTIC MICROANGIOPATHY – RESULTS FROM THE SPANISH GROUP OF BONE MARROW TRANSPLANTATION IN CHILDREN (GETMON)

Maria Isabel Benitez Carabante[1], David Bueno Sánchez[2], Laura Alonso García[1], Julia Marsal Ricoma[3], Ivan Lopez Torija[4], Jose Maria Fernandez Navarro[5], Maria Luz Uria Oficialdegui[1], Blanca Molina Angulo[6], Cristina Beléndez Bieler[7], Pilar Palomo Moraleda[8], Antonio Pérez Martínez[2], Cristina Diaz de Heredia Rubio[1]

[1]Hospital Universitario Vall d'Hebron, Barcelona, Spain, [2]Hospital Infantil Universitario La Paz, Madrid, Spain, [3]Hospital San Joan de Deu, Barcelona, Spain, [4]Hospital Santa Creu i Sant Pau, Barcelona,

Spain, [5]Hospital Universitari i Politècnic la Fe, Valencia, Spain, [6]Hospital Infantil Universitario Niño Jesús, Madrid, Spain, [7]Hospital General Universitario Gregorio Marañon, Madrid, Spain, [8]Hospital Universitario Central de Asturias, Oviedo, Spain

Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is a fatal complication of hematopoietic stem cell transplantation (HSCT) associated with high morbidity and mortality. Eculizumab, a complement C5 inhibitor, has significantly increased the survival of high-risk TA-TMA (hrTA-TMA) patients, however there is still a need for improvement.

Methods: National multicenter retrospective study. Children (from birth to 18 years of age) diagnosed of hrTA-TMA and treated with Eculizumab until December 31, 2021, were included.

Primary endpoint was response to eculizumab. Secondary endpoints included resolution of TA-TMA, overall survival and risk factors associated with survival. Start time for all the endpoints was the date of initiation of eculizumab.

Results: Twenty-nine patients were diagnosed of hrTA-TMA after a first (n = 28) or a second allogeneic HSCT (n = 1) for malignant (n = 17) or non-malignant diseases (n = 12). Median age at transplantation was 12.5 years (1-18). All patients presented ≥3 risk factors: HLA mismatched (n = 19,65%), peripheral blood as stem cell source (n = 15, 52%), use of calcineurin inhibitor (n = 25,86%), total body irradiation (n = 11,38%), viral reactivation (n = 21,72%), grade II-IV GvHD (n = 17,58%). All patients but 1 (96%) were diagnosed following the diagnostic criteria proposed by *Jodele et al*. in 2016. Median time from HSCT to TA-TMA was 154 days (17-387). Eleven (38%) patients were diagnosed of low-intermediate risk TA-TMA and subsequently progressed to hrTA-TMA, with a median period of 46 days (19-284). Twenty-four (83%) patients fulfil the characteristic triad (hypertension, proteinuria and elevated LDH). sC5b-9 was increased in 90% of 20 patients where measured. Seventeen (58%) patients presented extrarenal involvement. Renal (n = 12), pulmonary (n = 1) and gut (n = 1) biopsy confirmed the diagnosis in 12/14(85%) patients. Fourteen (48%) patients required intensive care unit admission.

Median time from hrTA-TMA diagnosis to the initiation of eculizumab treatment was 7 days (1-134). CH50 was monitored to ensure complement blockade. Most patients received eculizumab weekly (n = 25;86%) with a standard body weight adjustment and 4(14%) required intensified treatment. The median duration of eculizumab in patients with resolution of hrTA-TMA was 287 days (70-455).

Overall, 19(65%) patients responded to eculizumab of whom 15(79%) are alive and off treatment and 1 continues treatment.

With a median follow up of 37 months, 16(55%) patients were alive at 12 months after initiation of eculizumab. Extrarenal involvement, mechanical ventilation and renal replacement therapy were more frequent among patients with unresolved TA-TMA and fatal outcome.

Conclusions: This retrospective study provides real world results from a national multicentric cohort and although results have improved with the use of eculizumab over the last years, there is a need for improvement in high-risk patients.

Special attention should be taken to patients with extrarenal involvement and with those who require intensive care support. Strategies of early detection with close monitoring of proteinuria and sC5b9, aggressive treatment of concomitant complications (viral reactivations and GvHD), intensifying the initial induction dose and eculizumab pharmacokinetic monitoring could be the future goals to achieve better results in this severe and still frequently fatal complication.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P605

INFLUENCE OF SEPTIC SHOCK ON THE LONG-TERM CARDIOLOGICAL OUTCOME IN PEDIATRIC PATIENTS AFTER CHEMOTHERAPY AND STEM CELL TRANSPLANTATION

Giulia Casari[1], Claudia Alessia Codazzi[1], Antonia Apicella[1], Francesca Loiacono[1], Francesca Compagno[2], Annalisa Agostini[2], Arianna Panigari[2], Elena Bergami[2], Giovanna Giorgiani[2], Marco Zecca[2]

[1]Pediatric Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [2]Pediatric Hematology/Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Background: Septic shock (SS) remains a life-threatening event and onco-hematological patients are at higher risk due to impairment of immune system. In the recent years a new entity known as Sepsis-Induced Cardiomyopathy (SICM) was defined as global but reversible systolic and/or diastolic dysfunction of one or both ventricles. Unfortunately, it is not known whether SICM is reversible even in patients receiving chemotherapy or the possible influence of a previous episode of SS on long-term cardiological outcome.

Methods: We retrospectively collected data on 432 pediatric patients who were treated for onco-hematological disease at Pediatric Hematology/Oncology of Fondazione IRCCS Policlinico San Matteo, Pavia, between January 2010 and March 2022, of which 275 received hematopoietic stem cell transplantation (HSCT). Patients who experienced an episode of SS according to IPSCC criteria were described and among them we studied who experienced SICM. We considered cardiovascular event (CE) a reduction in ejection fraction LVEF > 10% or LVEF < 53% using the biplane Simpson method and M-mode technique. Patients who experienced CE before SS were excluded from analysis.

Results: In our cohort, 54.9% subjects were male with median age of 5.2 years at start of treatment. 18.5% were affected by hemoglobinopathy, 43.3% by acute leukemia, 5.3% by myelodysplastic syndrome, 11.1% had solid tumors, 5.1% bone marrow aplasia, 3.5% immunodeficiencies and 13.2% lymphoma. 63.7% received HSCT of which 10% underwent an autologous HSCT, 20% from HLA-matched family donor, 46% from HLA-matched unrelated donor and 24% from haploidentical donor.

The cumulative incidence of SS was 7.4% within the entire follow-up and 46.2% of these patients had received a previous HSCT. SICM was identified in 46.1% of SS, reversible in 83% of them. We observed a 21% cumulative incidence of CE, which was dramatically higher in those patients who experience SS compared to those not ($p < 0.01$), with no correlation with SICM. Univariate analysis identified age at diagnosis, malignant disease, HSCT, SS and anthracycline exposure as possible risk factors for the development of CE. Multivariate analysis confirmed SS, HSCT and older age at diagnosis as risk factors. Patients with SS showed an overall survival of 56% vs 83% of controls ($p < 0.01$). To better define the cardiological outcome, we introduced the variable cardiovascular event-free survival and data were confirmed (12% vs 45%; $p < 0.01$).

Conclusions: The prevention and treatment of long-term complications are fundamental for pediatric onco-hematological patients, especially for HSCT. We are improving our knowledge about the mechanisms of chemotherapy-induced CE and in prevention and treatment strategies, but we know that

cardiological outcome is the result of the multiple stress theory, according to which several factors are involved.

From our retrospective study, SS appears to be not only a life-threatening event, but also a cardiovascular risk factor for survivors. Even after the complete remission of the acute event, SS remains a negative prognostic factor, showing reduced survival in these patients.

Currently, no indications regarding pharmacological cardioprotection is indicated. Our hypothesis is that these patients may benefit from cardioprotective therapy after SS. This hypothesis deserves further Investigation to better study the impact of SS on the cardiological outcome.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P606

NAÏVE (CD45RA +) T-CELL-DEPLETED ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM HLA MATCHED DONORS IN PAEDIATRIC PATIENTS

Sara Vinagre[1], Marta Gonzalez Vicent[1], Blanca Molina[1], Elena Sebastián[1], Josune Zubicaray[1], June Iriondo[1], Julian Sevilla[1], Ana Castillo[1], Ana Gomez[1], Lorea Abad[1], Manuel Ramirez[1], Miguel Angel Diaz[1]

[1]Hospital Niño Jesus, Madrid, Spain

Background: In allogeneic hematopoietic stem cell transplantation (HSCT), T lymphocytes play a decisive role in promoting hematopoiesis, transferring immunity to pathogens, and acting as mediators of the graft-versus-leukemia effect (GVL). However, they are also responsible for graft-versus-host disease (GVHD), the main cause of post-transplant morbidity and mortality, especially naive T-cells (CD45RA +) that cause more severe GVHD than memory T-cells. Our hypothesis is that using the new graft-engineering technology in which naïve T-cells are selectively depleted from the donor graft we would reduce or minimize severe acute and chronic GvHD following HSCT.

Methods: We design a prospective observational study in which the patients with high-risk hematologic malignant/non-malignant diseases received an allogeneic naïve T-cell depleted transplant from HLA-matched donors. After conditioning, patients received a CD34+ enriched peripheral blood graft containing a median dose of 7,14x10^6/kg (range: 1,51-18) followed by a CD45RA+ depleted product. On day +1, +15 and + 30, CD45RA+ depleted DLIs scheduled were infused with a median cell number of 1x10^6/kg (range: 1-13,8). Primary and secondary objectives included engraftment, acute and chronic GVHD, and immune reconstitution. Fifty-eight children with a median age of 9 years (range; 1-21) and diagnosed of acute leukemia ALL (n = 20), AML (n = 22), MDS (n = 8), NHL (n = 4) and non-malignant diseases (n = 4) were included in the study between 2016 and 2021. Twenty-one patients were in 1st CR, 19 patients in 2nd CR, 18 in >2nd CR or active/non-treated disease. Median donors age was 18 years (range; 1-51). There were 32 matched related donors (MRD) and 26 matched unrelated donors (MUD).

Results: Fifty-six patients achieved neutrophil engraftment with a median time of 13 (range: 8–27) days. The median time to platelet engraftment was 11 (range: 6-34) days. With a median follow-up of 24 months (range; 3-60), the cumulative incidence of relapse was 33 ± 6% and the cumulative incidence of non-relapse mortality was 9 ± 3%. Only 6 patients developed acute GVHD (CI; 15 ± 4%) (gº 1; 3 cases and gº 2; 3 cases) and 3 patients chronic GVHD (CI; 5 ± 2% %) (mild 2 cases and moderate 1 case).

DFS and OS were 58 ± 7% and 70 ± 6%, respectively. On univariate analysis, MDS (88 ± 11%, p = 0,03), CR at transplant (70 ± 7% vs 32 ± 12%, p = 0,015) and CD34+ cell infused (> 7x10^6/kg, 41 ± 10% vs ≤7x10^6/kg, 73 ± 9%, p = 0,018) were associated with DFS. On multivariate analysis, complete remission at transplant (yes vs no, HR:5; 95%CI, 1,7-14-, p = 0,003) and the number of CD34+ cells infused/kg (≤ 7 vs >7, HR 5; 95% CI,1.7-12,5; p = 0.003) influenced on DFS.

Conclusions: Our results strongly suggest that allogeneic transplant using "naïve" T-cell-depleted grafts from matched related and unrelated donors in children results on no severe GvHD and very low mortality providing a good platform for cell therapy in order to enhance immune reconstitution.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P607

SURVIVAL OUTCOMES OF YOUNG CHILDREN WITH MALIGNANT BRAIN TUMORS AFTER INTENSIVE INDUCTION, MYELOABLATIVE CHEMOTHERAPY AND AUTOLOGOUS HEMATOPOIETIC PROGENITOR CELL RESCUE WITH OR WITHOUT IRRADIATION POST-AUHCR

Sheetal Phadnis[1], Eesha Chakravartty[2], Nathan Robison[3], Ashley Margol[3], Jemily Malvar[3], Hung Tran[3], Kenneth Wong[3], Girish Dhall[1]

[1]Children's of Alabama, Birmingham, United States, [2]New York University Langone Health, New York, United States, [3]Children's Hospital Los Angeles, Los Angeles, United States

Background: Radiation therapy (XRT) is usually delayed in infants and young children due to profound toxicity and deleterious effect on neuropsychological development. However, avoiding irradiation in infants/young children with malignant brain tumors has been associated with inferior survival.

Methods: We reviewed medical records of infants/young children with malignant brain tumors diagnosed at Children's Hospital Los Angeles between 1991-2015, that completed intensive induction followed by myeloablativechemotherapy with autologous hematopoietic progenitor cell rescue (AuHCR), and either did or did not receive XRT post-AuHCR.

Results: Ninety-nine patients were identified (fifty-five medulloblastoma, twenty-one PNET, fifteen AT/RT, and eight choroid plexus carcinoma). Twenty-seven of the ninety-nine patients received irradiation post-AuHCR and seventy-two did not. In the XRT group, 41% of patients had residual tumor post-induction and 44% had disseminated disease versus 18% and 26%, respectively, in no-XRT group. 5-year event-free survival (EFS) and overall survival (OS) for all patients was 63 + 5% and 73 + 5%. 5-year EFS and OS rates for patients receiving XRT post-AUHCR were 69 + 9% and 78 + 8% versus 60 + 6% and 71 + 6%for no-XRT group (p = 0.26 and 0.64). For patients with residual tumor post-induction, 5-year EFS was 65 + 14% for XRT group versus 34 + 14% for no-XRT group (p = 0.12). For patients with localized disease at diagnosis, 5-year EFS was 86 + 9% in XRT group versus 65 + 7% in no-XRT group (p = 0.12). 5-year EFS for patients with disseminated disease in XRT and no-XRT groups was 47%. For medulloblastoma patients, 5-year EFS and OS rates were 65 + 7% and 89 + 10% in XRT group and 67 + 16% and 82 + 6% in no-XRT

group. 5-year EFS was 80 + 13% for AT/RT patients in XRT group versus zero in no-XRT group.

Conclusions: For infants/young children with malignant brain tumors completing AuHCR, administration of XRT did not provide significant survival advantage, with the exception of AT/RT.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P608

CYCLOPHOSPHAMIDE AND THIOTEPA COMBINATION INCREASES RISK OF TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY

Christine S Higham[1], Kristin A Shimano[1], Sandhya Kharbanda[1], Alexis Melton[1], Julia Chu[1], Gabriel Salinas Cisneros[1], Lena E Winestone[1], Jasmeen Dara[1], James N Huang[1], Michelle L Hermiston[1], Janel R Long-Boyle[1], Christopher C Dvorak[1]

[1]University of California, San Francisco, San Francisco, United States

Background: Transplant associated thrombotic microangiopathy (TA-TMA) is a complication of hematopoietic stem cell transplant (HSCT) associated with endothelial injury that leads to end organ damage and high morbidity/mortality. Myeloablative conditioning regimens are a known risk factor, though specific chemotherapies that mediate the damage have not been identified.

Methods: We conducted a retrospective chart review of patients who had received conditioned autologous and allogeneic HSCT between 2012 and August 2022 at UCSF Benioff Children's Hospital, San Francisco. We excluded patients undergoing gene therapy or triple tandem transplants for brain tumors. Neuroblastoma tandem transplants were classified a single transplant occurrence. N-acetylcysteine (NAC) prophylaxis was given per institutional standard of care December 2016- May 2019 and May 2022-present for patients at high risk for developing TA-TMA as described in Higham et al Blood Advances 2021;5(8). Prophylactic defibrotide was given to patients at high-risk for VOD or on clinical trial NCT#03384693 for TA-TMA prophylaxis.

Results: A total of 523 transplants were performed with 40 patients developing TA-TMA (Table 1). Overall incidence of TA-TMA was higher in patients who receive conditioning with both cyclophosphamide (Cy) and Thiotepa (TT) (24.4%, 95% CI, 12.2-36.2%) compared to conditioning with either Cy or TT (10.9%, 95% CI, 6.6-15.2%) or without either Cy or TT (0.9%, 95% CI, 0-2%; $p < 0.001$). This holds true when looking at allogeneic and autologous transplants separately. In allogeneic transplants, those who received cyclophosphamide and thiotepa as part of conditioning had a TA-TMA incidence of 35.7% (95% CI, 15.7-55.7%) compared to 11.7 % (95% CI, 7-16.4%) with conditioning with cyclophosphamide or thiotepa and an incidence of 1.3% (95% CI, 0-3%) if neither were in the conditioning regimen ($p < 0.001$). There was an incidence of TA-TMA of 19.1% (95% CI, 10-30.2%) in autologous transplants with cyclophosphamide & thiotepa conditioning while TA-TMA did not occur in transplants conditioning either cyclophosphamide or thiotepa or neither ($p < 0.001$). All but one of the patients undergoing autologous transplant who received Cy & TT conditioning had neuroblastoma and underwent planned tandem transplants.

In allogeneic transplants, endothelial damage may be mitigated by high-dose NAC. In patients who received Cy & TT as part of their conditioning for allogeneic transplant, there was a 0% (95% CI, 0-50%) incidence of TA-TMA in those who received high dose NAC prophylaxis compared to 43.8% without high-dose NAC (95% CI, 20.9-66.7%; $p = 0.127$). In autologous patients getting Cy & TT, prophylactic defibrotide may be preventive against development of TA-TMA: prophylaxis 5.6% (95% CI, 0-16.2%) vs no prophylaxis 27.6% (95% CI, 11.3-43.9%; $p = 0.062$).

Table 1.

	All	Allogeneic	Autologous
Total transplants	523	389 (74%)	134 (26%)
Age at transplant (years) (range)	6.7 (0.2-27.4)	8.24 (0.2-27.4)	4.2 (0.8-23.6)
Sex			
• Male	313 (60%)	236 (61%)	77 (57%)
• Female	210 (40%)	153 (39%)	57 (43%)
HSCT indication:			
• Leukemia/Lymphoma/MDS	245 (47%)	233 (60%)	12 (9%)
• Neuroblastoma*	92 (17%)	-	92 (69%)
• Other solid tumors	30 (6%)	-	30 (22%)
• BMF	19 (4%)	19 (5%)	-
• SAA	28 (5%)	28 (7%)	-
• Inborn errors of immunity	77 (15%)	77 (20%)	-
• Hemoglobinopathies	9 (2%)	9 (2%)	-
• Inborn errors of metabolism	23 (4%)	23 (6%)	-
Conditioning:			
• No Cy or TT	239 (46%)	166 (43%)	73 (55%)
• Cy or TT	210 (40%)	196 (50%)	14 (10%)
• Cy & TT	74 (14%)	27 (7%)	47 (35%)
Prophylactic defibrotide	95 (18%)	71 (18%)	24 (18%)
Prophylactic high dose N-acetylcysteine^	43 (8%)	30 (8%)	13 (10%)
TA-TMA	40 (8%)	31 (8%)	9 (7%)

*neuroblastoma tandem transplants counted as one transplant occurrence
^ NAC dosing TID starting day +2: 70mg/kg; max 6000mg
HSCT hematopoietic stem cell transplant, *MDS* myelodysplastic syndrome

Conclusions: This data shows that individually Cy or TT is damaging to the endothelium and the combination is even worse, significantly increasing risks of developing TA-TMA. Alternative conditioning regimens should be considered whenever possible. Prophylaxis with defibrotide or NAC, depending on transplant type, may mitigate this damage, and these agents warrant prospective trials.

Disclosure: Christine Higham receives research funding from Jazz Pharmaceuticals and has consulted for Omeros Corporation. Kristin Shimano receives research funding from Novartis, Pfizer, and Daiichi-Sankyo and has served on an advisory board for Dova Pharmaceuticals. Michelle Hermiston has served on advisory boards for Novartis and Sobi Pharmaceuticals. Christopher Dvorak has consulted for and served on advisory boards for Alexion Inc. and Omeros Corporation.

18 - Paediatric Issues

P609

CD28-COSTIMULATED CD19 CAR T CELLS FOR PEDIATRIC RELAPSED AND REFRACTORY MATURE B-CELL LYMPHOMA

Elad Jacoby[1,2], Etai Adam[1,2], Alon Abramovich[1], Adi Shapira[3], Daphna Hutt[1], Orit Itzhaki[1], Bella Bielorai[1,2], Amos Toren[1,2]

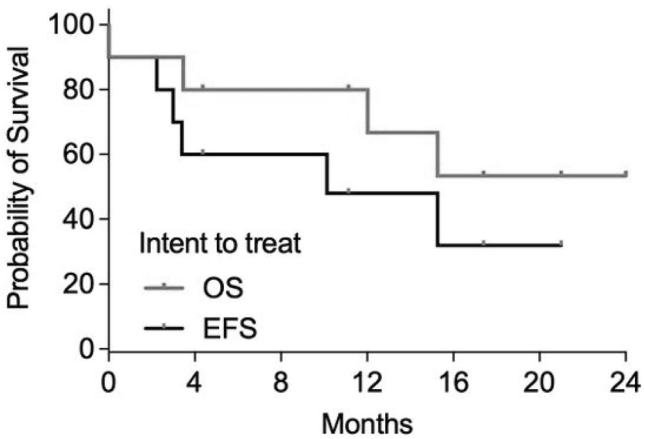
564

[1]Sheba Medical Center, Tel Hashomer, Israel, [2]Tel Aviv University, Tel Aviv, Israel, [3]Rambam Medical Center, Haifa, Israel

Background: The outcome of children with relapsed and refractory mature B-cell lymphomas (R/R B-NHL) is dismal. CAR-T cells targeting CD19 have been approved for adults with R/R B-NHL, but pediatric data is limited.

Methods: We conducted a clinical trial evaluating the safety and efficacy of CD19 CAR-T cells harboring a CD28 costimulation domain in patients with B-cell malignancies failing 2 or more lines of therapy. Patients received 10^6 CAR-T cells per kilogram after lymphodepletion with fludarabine and cyclophosphamide. Results of the pediatric mature B-cell lymphomas are presented.

Results: Between 2018 and 2022, ten children with relapsed/refractory mature B-cell lymphomas were enrolled. Patients had Burkitt lymphoma/leukemia (n = 6), diffuse large B-cell lymphoma (DLBCL, n = 1) and primary mediastinal B-cell lymphoma (PMBCL, n = 3). The median age at enrollment was 11 years (range, 3.5-17.5). Patients received a median of 2.5 lines of therapy before enrollment. Five had responded to the last therapy line and relapsed, while 5 patients were refractory to the previous therapy. Seven patients were apheresed with active disease, one with minimal-residual disease in the bone marrow, and two in remission. The median time between apheresis and CAR-T infusion was 11 days (range, 10-94). One patient rapidly progressed during the production period (within 1 week of apheresis) and died of his disease prior to lymphodepletion and CAR-T therapy. Nine patients were infused, six patients developed cytokine-release syndrome (mostly grade 1) and four patients developed neurotoxicity (2 grade 1, 2 grade 4). Overall, 7 patients had a complete response and 2 a partial response within 1 month, of them one with a further CR and one had progressive disease by 3 months. Of the 6 patients with Burkitt lymphoma, one patient had died prior to lymphodepletion, two relapsed (67 and 304 days post CAR-T), one had residual debilitation from severe neurotoxicity (leading to death in remission) and 2 remained in CR. Out of the 3 patients with PMBCL, 2 had ongoing remissions and one had a partial response, subsequently requiring additional therapy. The patient with DLBCL achieved a CR but relapsed within 3 month. All relapses occurred within 1 year. The 12-months event-free survival and overall survival were 53% and 74%, respectively, in the per-protocol cohort, and 48% and 66% in the intent-to-treat cohort (figure 1).



Conclusions: In this rare cohort of patients, CD28-based CD19 CAR-T cells induced clinical remissions in pediatric R/R B-NHL. Remissions were durable in patients with PMBCL and in some patients with Burkitt lymphoma.

Clinical Trial Registry: clinicaltrials.gov NCT02772198

Disclosure: EJ reports honoraria from Novartis.

All other authors have nothing to declare.

18 - Paediatric Issues

P610

THE COMBINATION OF EVEROLIMUS AND MYCOPHENOLATE MOFETIL FOR GVHD PROPHYLAXIS AFTER ALLOGENEIC HSCT IN CHILDREN WITH ACUTE RENAL FAILURE – A SINGLE CENTER RETROSPECTIVE ANALYSIS

Felix Zirngibl[1], Pimrapat Gebert[2,3], Bianca Materne[2,3], Michael Launspach[1,3], Annette Künkele[1,3,4,5], Patrick Hundsdoerfer[1,6], Sandra Cyrull[1], Hedwig E. Deubzer[1,3,4,5], Jörn-Sven Kuehl[7], Arend von Stackelberg[1], Angelika Eggert[1,3,4,5], Peter Lang[8], Lena Oevermann[1], Johannes H. Schulte[1,4,5]

[1]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt – Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, [2]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt – Universität zu Berlin, and Berlin Institute of Health, Institute of Biometry and Clinical Epidemiology, Berlin, Germany, [3]Berlin Institute of Health, Berlin, Germany, [4]German Cancer Consortium (DKTK), Heidelberg, Germany, [5]German Cancer Research Center (DKFZ), Heidelberg, Germany, HELIOS Klinikum Berlin Buch, Berlin, Germany, Hematology and Hemostaseology, University of Leipzig, Leipzig, Germany, [8]Pediatric Hematology and Oncology, University Hospital Tübingen, Tübingen, Germany

Background: Acute kidney injury (AKI) occurs in 21-84% of pediatric hematopoetic stem cell transplantation (HSCT) cases in the literature and continues to be a severe problem. Acute and chronic graft versus host disease (GVHD) are decisive determinants for the success of allogeneic HSCT. However, ciclosporin A (CsA), the most important immunosuppressive agent for the prevention of GVHD in pediatrics is known to be nephrotoxic. In this retrospective single center analysis, we evaluated the practice at our institution to substitute CsA with the combination everolimus/mycophenolate mofetil (MMF) as GVHD-prophylaxis after first allogeneic HSCT in patients with severe AKI.

Methods: This retrospective cohort study analyses the clinical course of 57 pediatric patients who were treated with the combination everolimus/MMF for prophylaxis of GVHD after first allogeneic HSCT at Charité University Medicine Berlin. As a control cohort served 74 Patients undergoing first allogeneic HSCT in the same period of time who did not receive everolimus at any date post-transplantation. Patients undergoing mismatched family donor transplantation without subsequent calcineurin inhibitor treatment for GVHD prophylaxis were excluded. Endpoints of the study were development of retention parameters after switch to everolimus, overall survival, incidence of relapse of the underlying disease and acute and chronic GVHD in both treatment groups.

Results: After everolimus was startetd plasma creatinine decreased from a mean of 299.6% (± 174.6) of baseline measured at the day of HSCT to 159.7% (± 74.2) 14 days later ($p < 0.001$), plasma cystatin C decreased from 207.8% (± 66.9) of baseline to 126.0% (± 37.4) ($p < 0.001$), respectively. We observed an incidence of grade II-IV acute GVHD at day 100 of 10.0% in the everolimus group vs 13.0% in the control cohort with a hazard ratio of 0.88 (95% CI: 0.29 – 2.6; $p = 0.822$). The incidence of severe chronic GVHD was 11.5% in the everolimus group and 6.2% in the control cohort (HR 2.15, 95% CI: 0.61 – 7.65; $p = 0.24$). Overall survival (OS) after two years was 79.8% (everolimus) vs 85.6% (control cohort) and did not differ significantly between the two groups (hazard ratio of 1.42; 95% CI: 0.65 – 3.10; $p = 0.38$).

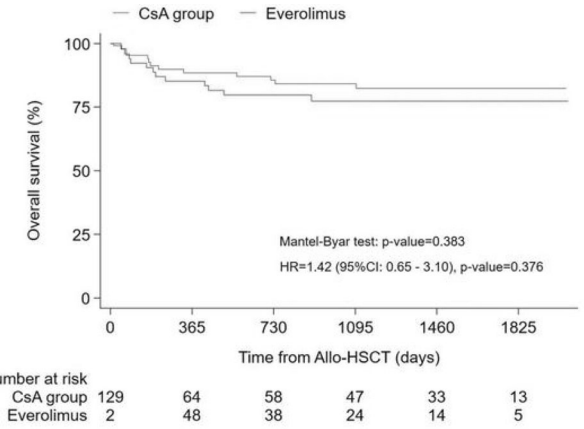


Figure 1: Overall survival of patients. CsA= Ciclosporin A. HR= Hazard ratio, Allo-HSCT= allogeneic hematopoetic stem cell transplantation.

Conclusions: In conclusion, switch to everolimus/MMF restored renal function and the outcomes of patients in the everolimus group were not worse than those in the control group. Consequently, switching the GHVD prophylaxis medication from CsA to everolimus/MMF for patients incuring AKI is a feasible strategy for children undergoing first allogeneic HSCT.

Clinical Trial Registry: Not applicable.

Disclosure: The authors have nothing to declare.

18 - Paediatric Issues

P611

OUTCOME OF TREOSULFAN-BASED CONDITIONING IN 93 INFANTS WITH SCID – A MULTICENTRE RETROSPECTIVE COHORT ANALYSIS

Sinéad Greener[1], Su Han Lum[1], Zohreh Nademi[1], Stephen Owens[1], Eleri Williams[1], Robert Chiesa[2], Persis Amrolia[2], Austen Worth[2], Claire Booth[2], Winnie Ip[2], Kanchan Rao[2], Giovanna Luccini[2], Juliana Silva[2], Sophie Hambleton[1], Terry Flood[1], Mary Slatter[1], Andrew R. Gennery[1]

[1]Children's Haematopoietic Stem Cell Transplant Unit, Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, [2]Great Ormond Street Hospital, London, United Kingdom

Background: Conditioning is associated with long-term outcomes in infants with severe combined immunodeficiency (SCID). This multicentre study compared transplant outcomes in 93 infants with SCID who received fludarabine-treosulfan for first haematopoietic stem cell transplantation (HSCT) between 2006-2021 at two supraregional immunology transplant centres in the UK.

Methods: Primary endpoints were overall survival (OS), event-free survival (EFS; survival without graft failure and second procedures) and transplant-related mortality (TRM). Secondary endpoints were grade II-IV aGvHD, cGvHD and graft failure. Subgroup differences in OS and EFS were evaluated by log-rank test. Competing risks methods were used for the cumulative incidence of aGvHD, cGvHD, VOD with death as the competing event, subgroup differences were evaluated by Gray's test

Results: Median age at transplant was 6 months (range 1.2-17 months). Donors were matched family donor (MFD, n = 27, 29%), matched unrelated donor (MUD, n = 34, 37%), mismatched unrelated donor (MMUD, n = 16, 17%) and haploidentical donor (HID, n = 16, 17%). Stem cell sources were marrow (n = 28, 30%), unmanipulated peripheral blood stem cells (PBSC) (n = 19, 20%), T cell depleted PBSC (n = 16, 17%; 13 TCRab/CD19 depletion; 2 CD3/CD19 depletion; 1 CD34 selection) and cord blood (CB) (n = 30, 32%). Ninety (97%) received treosulfan–fludarabine based conditioning and three (3%) received fludarabine-treosulfan-thiotepa based conditioning. Alemtuzumab was the most common serotherapy (n = 59, 63%), then ATG (n = 19, 20%) and 15 (16%) received no serotherapy. GvHD prophylaxis were CSA + MMF (n = 71, 76%), CSA (n = 11, 12%), CSA + MTX (n = 1, 1%) and none (n = 10, 11%).

Median time to neutrophil and platelet engraftment was 18 (range 9-73) and 19 (7-61) days respectively. The 5-year OS and EFS for the entire cohort was 82% (95% CI, 72-88) and 80% (95% CI, 70-88) respectively. Five year OS in MFD was 75% (95% CI, 53-88), MUD 84% (95% CI, 65-93%), MMFD/MMUD 81% (95% CI, 52-94), HID 93% (95% CI, 60-99) (p = 0.66). Cumulative incidence of VOD was 1.1% (0-8%). Cumulative incidence of grade II-IV aGvHD was 19% (11-32%) and grade III-IV aGvHD was 5% (2-13%). 1-year cumulative incidence of chronic GvHD was 6% (2-13%). Median follow-up was 5.3 years (0.24-14.9). Donor (p = 0.66), stem cell source (p = 0.6) and serotherapy (p = 0.34) had no impact of survival. 5 patients had second procedures: 2 second transplants (GvHD; poor T cell immune reconstitution), 1 CD34 stem cell boost and 2 donor lymphocyte infusion for poor immune reconstitution. The cause of death in 15 patients was: infection (n = 6), pneumonitis (n = 3), GvHD (n = 2), TMA (n = 1), leukaemia (n = 1) encephalopathy (n = 1), and unknown (n = 1). In long-term survivors, median myeloid chimerism was 99.5% (range 0-100) and median T-lymphocyte chimerism was 100% (range 18-100%). Long-term disease outcome and immune reconstitution are being evaluated.

Conclusions: Treosulfan-based conditioning is well tolerated in infants with SCID with very low risk of VOD.

Keywords: SCID; treosulfan, infants

Disclosure: No disclosure.

18 - Paediatric Issues

P612

MULTIVARIATE ANALYSIS OF THE NK CELLS FACTORS EFFECT ON ACUTE LEUKEMIA RELAPSE AND TRM AMONG CHILDREN AFTER HAPLO HSCT WITH AB T CELL DEPLETION

Svetlana Glushkova[1], Kirill Voronin[1], Dmitriy Pershin[1], Viktoria Vedmedskaya[1], Yakov Muzalevskii[1], Alexei Kazachenok[1], Elena Kurnikova[1], Svetlana Radygina[1], Maria Ilushina[1], Rimma Khismatullina[1], Larisa Shelikhova[1], Dmitriy Balashov[1], Alexei Maschan[1], Michael Maschan[1]

[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: NK alloreactivity was described as one of the major mechanisms of leukemia control among the recipients of ex-vivo T cell depleted grafts from haploidentical donors. This retrospective study continues to explore the effect of NK-related factors on the incidence of leukemia relapse and non-relapse mortality. Multivariate analysis (MVA) allowed us to measure the effect of graft NK cells dose and KIR mismatch independent of the other important factors such as aGvHD and pre-HSCT MRD on the outcomes: relapse and transplant-related mortality (TRM).

Methods: Two pediatric acute leukemia cohorts: 170 ALL (acute lymphoblastic leukemia) patients and 94 AML (acute myeloblastic

leukemia) patients first transplanted in complete remission. Median follow-up for survivors was 3 years, median age at HSCT was 9 years old. All grafts were haplo-identical and processed with αβ T cell depletion method at one center from January 2012 to April 2021. KIR mismatch was predicted with the help of ligand-ligand model, based on HLA genotyping, for 33% of patients. Median of graft NK cells dose was 31 million cells per kilogram. Pre-HSCT MRD analysis was provided for all ALL cohort and for 35 patients inside AML cohort (AML MRD analysis was performed since 2017). MVA was done using Cox Proportional Hazards regression for cause-specific hazards of relapse and non-relapse mortality. Factors included in the models are factors of interest and known important factors. Proportional hazards assumption has been assessed visually using log-log plots and Schoenfeld residuals. Software used: R 4.0.2, mstate 0.2.12.

Results: Among 170 patients with ALL 44 relapsed and 11 died due to the non-relapse reasons (for 114 patients inside B-ALL cohort 28 relapsed and 8 died from non-relapse mortality (NRM), for 56 T-ALL patients' cohort 16 and 3 respectively). There were 94 patients with AML among them 21 relapsed and there were 2 cases of NRM.

MVA results for AML cohort indicated that, transfusion of graft NK cells dose of greater than the median value can reduce the risk of relapse by 12 times ($p = 0.08$) for the group of patients with predicted KIR mismatch, for NK KIR match cohort, on the contrary, greater than the median value NK cells dose increases the relapse risk by 24 times ($p = 0.008$). Acute GVHD is significantly associated with a reduced relapse risk, as expected, while positive MRD at HSCT had a trend to be associated with a higher relapse risk. We present the analysis for the AML group with the MRD data, since the significance of the contribution of NK cells factors remains the same in the analysis of the whole AML cohort.

MVA results for ALL cohort confirmed the effects of known relapse risk factors, such as aGvHD grade 2-4, MRD and TBI, while found no significant correlation of relapse risk with NK-related factors.

Conclusions: NK related factors have different effects among children with ALL and AML, transplanted with αβ T cell-depleted haploidentical grafts. In the AML cohort an interaction of NK cell dose and KIR mismatch was detected.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P613

HLA-HAPLOIDENTICAL STEM CELL TRANSPLANTATION WITH POST-TRANSPLANTATION CYCLOPHOSPHAMIDE (HAPLO-PTCY) IN CHILDREN WITH NON-MALIGNANT DISEASES: A RETROSPECTIVE ANALYSIS OF 192 PATIENTS TRANSPLANTED IN CURITIBA, BRAZIL

Carmem Bonfim[1,2,3], Rafaella Muratori[2,3], Alberto Cardoso Martins Lima[2], Samantha Nichele[2,3], Adriana Koliski[2], Rebeca Amália Toassa Gomes Mousquer[2], Cilmara Cristina Kuwahara Dumke[1], Fernanda Moreira de Lara Benini[1], Polliany Roberta Dorini Pelegrina[1], Adriana Mello Rodrigues[2,1], Carolina Martins de Almeida Peixoto[1], Juliana Luiza de Mello Bach[1], Joanna Paula Trennepohl[2,3], Lara Maria Miranda Gouvea[3], Samir Kanaan Nabhan[2,3], Gisele Loth[2,1], Ricardo Pasquini[2,3]

[1]Hospital Pequeno Principe, Curitiba, Brazil, [2]Hospital de Clinicas da UFPR, Curitiba, Brazil, [3]Hospital Nossa Senhora das Gracas, Curitiba, Brazil

Background: HLA-haploidentical cell transplantation with post-transplantation cyclophosphamide (HAPLO-PTCy) is an important treatment strategy for patients with nonmalignant diseases(NMD) lacking a matched related or unrelated donor. HAPLO-PTCy allows the effective use of HLA-haploidentical family donors, especially in resource-limited countries.

Methods: This retrospective study reports the outcomes of 192 children with NMD diseases who received an upfront HAPLO-PTCY between April-2008 and June-2022 in 3 pediatric HSCT centers. The median age was 7 years (0.2months–17.5years) and 73% were male. Preparatory regimens varied according to the disease type. Fanconi Anemia(FA) patients) received a modified approach (Bonfim et al;Lancet Hematology 2022). Table 1 summarizes diagnoses and HSCT details.

Results: Primary graft failure (GF) occurred in 14 patients (7.7%), while 10 (5.5%) developed secondary GF. The 28-day incidence of neutrophil recovery was 97% (95%CI:94-99). One-year incidence of GF was 12.5% (95%CI:8-18) and 23 patients were rescued with a 2nd transplant (HAPLO-PTCy;$n = 21$) and 13 are alive. In the multivariate analysis (MVA), a higher CD34 cell dose (> 4.9x10*6/kg;$p = 0.03$), absence of donor specific antibodies ($p = 0.01$), and diagnosis of FA ($p = 0.006$) were associated with a lower incidence of GF. The 100-day incidence of grade II-IV acute-GvHD was 28.6% (95%CI: 22-35) and 2-year incidence for chronic-GvHD was 17% (95%CI:12-23). In the MVA, FA was associated with a higher incidence of developing both acute ($p = 0.002$) and chronic GvHD ($p < 0.0001$). The risk of chronic GvHD was also higher for patients receiving transplants using mother as the donor ($p = 0.0003$) or receiving a higher TNC dose (> 6.6 x10*8/kg,$p = 0.02$). Forty-seven patients died and the main causes of death were infections (30%), GvHD (30%) and GF (26%). The 1-year and 3-year event-free survival (EFS - rejection and death) were 75% (95%CI:69-81) and 69% (95%CI:62-75), respectively. In the MVA the presence of DSAs ($p = 0.01$) and the lack of serotherapy in the preparatory regimens were associated with a lower EFS ($p = 0.005$). The 100-day CMV reactivation was 60% (95% CI:53-67) and the 100-day incidence of hemorrhagic cystitis was 20% (95%CI:14-26). After a median follow-up of 30 months, the 1- and 3-year overall survival (OS) was 83% (95%CI:77-88) and 76% (95%CI:68-81). There was no difference in OS according to the disease groups: acquired aplastic anemia: 89%(95%CI:73-96); Inherited bone marrow failures: 83%(95%CI:72-90); immunodeficiencies: 80%(95%CI:68-87) or other NMD: 87%(95%CI:56-96). In MVA, age ($p = 0.004$), DSA ($p = 0.003$), and serotherapy ($p = 0.005$) were independent predictors of poor survival.

table 1. Patients and HSCT

Disease Type, n (%)	Acquired aplastic anemia **36 (18.8%)**	Aplastic Anemia (36)
	Inherited BMFS **67 (34.9%)**	Fanconi Anemia (50) Congenital Dyskeratosis (7) Congenital amegakaryocytic thrombocytopenia (3) Blackfan Diamond Anemia (1) MECOM (1) Other congenital BMF (5)
	Immunodeficiencies **74 (38.5%)**	SCID (39) Wiskott Aldrich (22) Congenital Neutropenia (1) CD40L deficiency (1) Chediak Higashi (3) XIAP (3) HLH (2) CGD (2) IPEX (1)
	Others **15 (7.8%)**	Adrenoleukodystrophy (9) Sickle Cell Anemia (4) Osteopetrosis (2)
ABO Matching, n (%)	ABO incompatibility	75 (39)
CMV patient, n (%)	Positive	175 (91.1)

Donor Type, n (%)	Father	118 (61.5)
	Mother	47 (24.5)
	Sibiling	19 (9.9)
	Other	8 (4.2)
DSA status, n (%)	Negative DSA	183 (95.3)
	Positive DSA	9 (4.7)
Preparatory regimens	TBI based (100 - 400 cGy)	118 (61.5)
	Busulfan based	73 (38)
Serotherapy	+ ATG or Campath	130 (67.7)
GVHD prophylaxis	PTCY 100mg + CSA + MMF	137 (71.4)
	PTCY 50-60mg + CSA + MMF	51 (26.6)
	PTCY 100mg +sirolimus	4 (2)
CD34 (x10^6/kg), median (range)		4.90 [1.2, 20.0]
TNC (x10^8/kg), median (range)		6.60 [2.2, 25.0]
Year of HCT, median (range)		2018 [2008, 2022]
HSC Source, n (%)	Bone Marrow	185 (96)
	Peripheral Blood	7 (4)

Conclusions: This is one of the largest experiences using HAPLO-PTCy for children with NMD in the world. These data demonstrate that this strategy is feasible, effective, and associated with excellent outcomes across all disease groups. Although results have improved, additional strategies are needed to decrease the incidence of GF, prevent GvHD and mitigate the risk of infections.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P614

COMPARISON OF SUBCUTANEOUS VERSUS INTRAVENOUS ALEMTUZUMAB WITH FLUDARABINE/MELPHALAN BASED CONDITIONING IN ALLOGENEIC STEM CELL TRANSPLANTATION FOR PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

Alexandra Plavsa[1], Tara Suresh[2], Stuti Dalal[2], Shalini Shenoy[2], Alexander Ngwube[3]

[1]Creighton University Health Sciences Campus - Phoenix, Phoenix, United States, [2]St Louis Children's Hospital, St Louis, United States, [3]Phoenix Children's Hospital, Phoenix, United States

Background: For non-malignant conditions like sickle cell disease (SCD), intravenous distal alemtuzumab-containing conditioning regimens have been used for host immunoablation prior to allogenic stem cell transplantation (HSCT) to facilitate donor engraftment in a reduced intensity approach. Alemtuzumab may be administered subcutaneously in this setting, but limited literature exists regarding outcome evaluations comparing the two routes of drug administration in SCD HSCT. The objective of this study was to compare efficacy and toxicity after subcutaneous(subQ) or intravenous (IV) alemtuzumab in pediatric HSCT recipients with SCD.

Methods: In this multicenter retrospective analysis, pediatric HSCT recipients of HLA-matched related or unrelated marrow received fludarabine/melphalan with subQ (N = 13) or IV (N = 36) alemtuzumab at either St Louis Children's Hospital, Missouri, USA or Phoenix Children's Hospital, Arizona, USA between January 1, 2011, and December 31, 2021. The cumulative dose of alemtuzumab was 33 mg (< 10 years of age) or 48 mg (≥10 years), between days −21 and −19, fludarabine (150 mg/m2; days −8 to −4), and melphalan (140 mg/m2; day −3). GVHD prophylaxis included tacrolimus and a short course methotrexate ± abatacept. Outcome analysis included toxicities during alemtuzumab administration, incidence of acute graft-versus-host disease (aGVHD), CMV reactivation risk, and chimerism analysis until 6 months post HSCT.

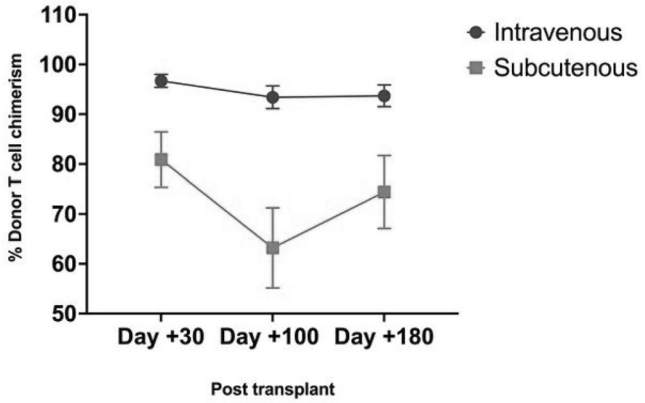
Results: Alemtuzumab doses were administered after premedication with benadryl, tylenol and hydrocortisone. In the 49 patients evaluated, grade 2 or higher infusion-related reactions within 24 hours of the subQ or IV alemtuzumab doses was 3 (23.1%) versus 22 (61.1%) respectively (p = 0.038). Incidence of hypertension was higher in the IV group (75%) compared to the subQ group (23.1%) (p = 0.002). There were no significant difference between the subQ and IV groups in the rate of CMV reactivation (p = 0.6), aGVHD (p = 0.8), or disease free survival at 6 months (p = 1). The median donor T cell chimerism at 6 months in the IV group was 100% (IQR = 7) compared to 76.5% (IQR = 34) in the subQ group. No difference was noted in myeloid chimerism levels between the groups.

Conclusions: There were fewer and less severe reactions when alemtuzumab was administered subcutaneously compared to intravenously. T cell chimerism was lower at 6 months in the subQ alemtuzumab group compared to the IV group. There was no difference in disease-free-survival between the two groups suggesting that subQ alemtuzumab had an advantage over IV administration to offset acute toxicities. Further analysis of outcomes at later time-points are underway.

Table 1

	Intravenous group (N = 36)	Subcutaneous group (N = 13)	Total (N = 49)	p value
Sex				
Male	17 (47.2%)	8(61.5%)	25(51%)	0.5202
Reason for transplant				
Less severe	6(16.7%)	2(15.4%)	8(16.3%)	
Less severe with complications	16(44.4%)	3(23.1%)	19(38.8%)	
Severe	14(38.9%)	8(61.5%)	22(44.9%)	0.3167
Donor type				
Unrelated	21(58.3%)	7(53.8%)	28(57.1%)	
Related	15(41.7%)	6(46.2%)	21(42.9%)	1.0000
Infusion reaction				
Grade				
0	6(16.7%)	7(53.8%)	13(26.5%)	
1	8(22.2%)	3(23.1%)	11(22.4%)	
2	14(38.9%)	3(23.1%)	17(34.7%)	
3	8(22.2%)	0(0%)	8(16.3%)	0.0380
Alemtuzumab dose at infusion reaction				
No reaction	4(11.1%)	7(53.8%)	11(22.4%)	
Test dose	13(36.1%)	5(38.5%)	18(36.7%)	
First dose	9(25%)	0(0%)	9(18.4%)	
Second dose	10(27.8%)	1(7.7%)	11(22.4)	0.0051
Hypertension post alemtuzumab				
Yes	27(75%)	3(23.1%)	30(61.2%)	0.00201

Figure 1



Disclosure: No conflict of interest.

18 - Paediatric Issues

P615

CMV SEROLOGY MATCH IS NOT CORRELATED WITH BETTER OUTCOMES IN PEDIATRIC MALIGNANCIES USING HLA-MATCHED SIBLING DONORS BELOW THE AGE OF 12: A PDWP/EBMT STUDY

ELİF İNCE[1], Jacques-Emmanuel Galimard[2], Marianne Ifversen[3], Arnaud Dalissier[4], Zofia Szmit[5], Franco Locatelli[6], Oana Mirci-Danicar[7], Petr Sedlacek[8], Jean-Hugues Dalle[9], Mouhab Ayas[10], Rose-Marie Hamladji[11], Adriana Balduzzi[12], Jan Styczynski[13], Yves Bertrand[14], Elena Skorobogatova[15], Abdelghani Tbakhi[16], Katrine Kielsen[3], Vassiliki Kitra-Roussou[17], Franca Fagioli[18], Pichler Herbert[19], Andreas H. Groll[20], Mahmoud Aljurf[21], Mervi Taskinen[22], Marc Bierings[23], Mohamed Bayoumy[24], Mohsen Al Zahrani[25], Ivana Bodova[26], Roland Meisel[27], Simone Cesaro[28], Krzysztof Kalwak[5], Selim Corbacioglu[29]

[1]Ankara University, Ankara, Turkey, [2]EBMT Statistical Unit, SorbonneUniversity, Saint-Antoine Hospital, AP-HP, INSERM UMRs 938, Paris, France, [3]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, [4]EBMT Paris Study Unit, Sorbonne University, Saint-Antoine Hospital, AP-HP,INSERM UMRs 938, Paris, France, Wroclaw, Poland, Italy, [7]Bristol Royal Hospital for Children, Bristol, United Kingdom, [8]University Hospital Motol, Prague, Czech Republic, Robert Debre Hospital, GHU APHP Nord-Université de Paris Cité, Paris, France, King Faisal Specialist Hospital & Research Center, Riyadh, Middle, Saudi Arabia, [11]CentrePierre et Marie Curie, Alger, Algeria, [12]Pediatric Bone Marrow Transplant Unit, Fondazione MBBM -Milano Bicocca University, Monza, Italy, [13]University Hospital, Collegium Medicum UMK, Bydgoszcz, Poland, [14]Hématologie Pédiatrique Hospices Civils de Lyon and University Claude Bernard Lyon 1, Lyon, France, [15]The Russian Children's Research Hospital, Moscow, Russian Federation, [16]King Hussein Cancer Centre, Amman, Jordan, [17]St Sophia Children`s Hospital Oncology Centre 'Marianna V. Vardinogiannis – ELPIDA', BMT Unit, Athens, Greece, [18]Pediatric Onco-Hematology, Stem Cell Transplantation and Cell Therapy Division, Regina Margherita Children's Hospital, University of Turin, Turin, Italy, St. Anna Children's Hospital, Medical University of Vienna, Vienna, Austria, [20]University Children's Hospital, Muenster, Germany, [21]King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, [22]Hospital for Children and Adolescents, Helsinki University Hospital and Helsinki University, Helsinki, Finland, [23]Princess Maxima Center/University Hospital for Children (WKZ), Stem Cell Transplantation, Utrecht, Netherlands, [24]King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia, [25]King Abdul - Aziz Medical City, Riyadh, Saudi Arabia, [26]Pediatric University Teaching Hospital, BMT Unit, II Children`s Clinic, Bratislava, Slovakia, [27]Division of Pediatric Stem Cell Therapy, Hematology and Clinical Immunology, Heinrich-Heine-University, Düsseldorf, Germany, [28]Pediatric Hematology Oncology Unit, Azienda Ospedaliera Universitaria Integrata, Verona, Italy, Oncology and Stem Cell Transplantation, University of Regensburg, Regensburg, Germany

Background: Cytomegalovirus (CMV) is a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation. CMV seropositive (CMV+) patients have inferior outcomes compared to seronegative (CMV-) patients. Superior outcomes were reported for CMV+ patients in case of CMV+ donors in studies where both adult and pediatric patients are included. Therefore, the impact of donor (D) serology for a CMV+ recipient (R) on transplant outcomes in children with malignant hematological diseases was analyzed in a large registry-based study.

Methods: We included CMV+ patients below 18 years (y) reported to EBMT who received an unmanipulated transplant with bone marrow (BM) or peripheral blood (PB) from a matched sibling (MSD) without serotherapy or a matched unrelated donor (MUD;10/10) with serotherapy for malignant hematological diseases between 2007 and 2020, excluding patients receiving posttransplant cyclophosphamide. The impact of donor serology on CMV+ patients on overall survival (OS), progression free survival (PFS), relapse incidence (RI) and non-relapse mortality (NRM) was evaluated in 2 categories (R + /D +, R + /D-), for MSD and MUD transplants respectively. For Cox multivariable analyses, variables for adjustment were stem cell source, age at transplant, donor age, female to male transplant, year of transplant, disease risk index, and total body irradiation. Due to a qualitative interaction between the donor CMV and the donor age on the outcome of the patient receiving a MSD transplant, the analysis for this group was split according to the median of MSD age at transplant (i.e 12y).

Results: There were 2338 CMV+ patients (MSD = 1267, MUD = 1071) with a median follow-up of 2.7y (95%CI: 2.5 - 2.9). The outcomes of the MSD and MUD groups are given in the table. Compared to R + /D-, R + /D+ had a significantly better OS (HR, 0.62; p = 0.01), PFS (HR, 0.69; p = 0.03) and NRM (HR, 0.42; p = 0.006) for MSD transplants with donor age ≥12y. MSD transplants with donor age <12y however had a significantly worse OS (HR, 1.58; p = 0.03) but no significant difference for PFS (HR, 1.27; p = 0.12), RI (HR, 1.24; p = 0.2) or NRM (HR, 1.44; p = 0.4). In MUD, R + /D +, compared to R + /D-, had a significantly better OS (HR, 0.68; p = 0.002), better PFS (HR, 0.75; p = 0.009) and better NRM (HR, 0.47; p < 0.001).

	OS (IC95%)	PFS (IC95%)	RI (IC95%)	NRM (IC95%)
MSD				
R + /D + ≥ 12 yrs (n = 504)	72.8 (68–77)	64.6 (59.7–69.1)	27.6 (23.3–32)	7.8 (5.4–10.7)
R + /D- ≥12 yrs (n = 111)	63.9 (53.5–72.6)	56.3 (45.8–65.4)	27.5 (19.1–36.5)	16.2 (9.7–24.3)
R + /D + < 12 yrs (n = 422)	74.6 (69.3–79.2)	61 (55.4–66.1)	33.6 (28.4–38.8)	5.4 (3.3–8.2)
R + /D- <12 yrs (n = 228)	83.1 (76.9–87.8)	65.9 (58.6–72.2)	30.4 (23.9–37.1)	3.8 (1.8–7)
MUD				
R + /D +	76.8 (72.7–80.4)	67.7 (63.3–71.7)	25.3 (21.4–29.3)	7 (5–9.4)
R + /D-	68.1 (63.3–72.5)	60.2 (55.2–64.9)	25.7 (21.5–30.2)	14.1 (11–17.6)

Conclusions: Our data shows that donor CMV serology combined with donor age ≥12y have a substantial impact on survival in CMV+ patients in MSD as well as in MUD for hematological malignant diseases. For MUD donors, who are all adults, and for MSD with donor age ≥12y, R + /D+ transplants have better OS compared to R + /D-. But for MSD with donor age <12y, OS is worse in R + /D+ transplants compared to R + /D- with pOS 75% vs 83.1%. This finding has not been reported previously and although not statistically significant the observed higher RI and NRM could be the reason of significantly worse OS.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P616

GRAFT CRYOPRESERVATION EFFECTS ON THE OUTCOMES OF ALLOGENEIC HAEMATOPOIETIC CELL TRANSPLANTS IN PAEDIATRIC POPULATION: A MULTICENTRE UK STUDY

Ruta Barkauskiene[1], Angharad Pryce[1], Rachel Pearce[2], John A. Snowden[3], Ram Malladi[4], Victoria Potter[5], Julia Lee[2], Marie Wilson[2], Antonio Paglucia[1], Chloe Anthias[1], Rachel Pawson[6], Robert Danby[1]

[1]Anthony Nolan, London, United Kingdom, [2]BSBMTCT Data Registry, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [3]BSBMTCT, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, [4]BSBMTCT, Cambridge University Hospitals, Cambridge, United Kingdom, [5]BSBMTCT, King's College Hospital NHS Foundation Trust, London, United Kingdom, [6]NHS Blood and Transplant, Oxford, United Kingdom

Background: Due to COVID-19 pandemic, allogeneic haematopoietic cell transplantation (HCT) graft cryopreservation was recommended by national and international bodies to guarantee graft availability before the start of patient conditioning [1-4]. Whether graft cryopreservation has any effect on paediatric patient outcome in allogeneic haematopoietic cell transplantation (HCT) remains unclear. Further evidence in paediatric field separate from adult populations essential as patient physiology and transplantation practices differ between these groups, with paediatric patients more likely to receive BM harvest grafts.

Methods: Paediatric patients receiving an unrelated or sibling donor allogeneic cryopreserved HCT (excluding cord blood) in the UK from 1st of June to 31st of August 2021 were included in the study. Paediatric patients receiving fresh HSC grafts from 1st June 2018 to 31st of August 2019 were controls.

Data were collected from individual transplant centres by British Society of Blood and Marrow Transplantation[RP1] and Cellular Therapy (BSBMTCT) registry.

Engraftment, aGvHD, relapse rate, PFS and OS were analysed.

Results: 193 paediatric patients received cryopreserved HSC grafts, of which 101 (53%) were BM harvests and 392 controls received fresh HSC grafts, of which 271(69%) were BM harvests. This difference was statistically significant ($p = 0.01$). The median follow-up time for cryopreserved group was 12 months and 33 months in control group ($p = 0.01$). These were the only statistically significant differences in paediatric patient characteristics between the groups.

There was no statistically significant difference in neutrophil and platelet engraftment between cryopreserved and control grafts. The median time to neutrophil and platelet engraftment was the same between the groups: 17 days for neutrophils (range,0-61, $p = 0.60$) and 20 days for platelets (range, 4-90, $p = 0.88$). The frequency of graft failure was 1% in both groups ($p = 0.67$).

Acute GvHD occurred in 45% of paediatric HCTs with cryopreserved and in 39% with fresh grafts but this difference was not statistically significant ($p = 0.20$). Relapse[RP1] rate for malignant conditions only at 18 months was 31% (95% CI: 14-50%) in cryopreserved and 19% (95%CI:14-25%) in the control group. This difference was not statistically significant with HR of 0.72 (95%CI:0.40-1.31, $p = 0.28$).

PFS for malignant conditions only at 18 months post-HCT was 56% (95%CI: 35-73%) and 70% (95%CI: 62 - [RP2] 77%) with cryopreserved and fresh control grafts, respectively ($p = 0.17$).

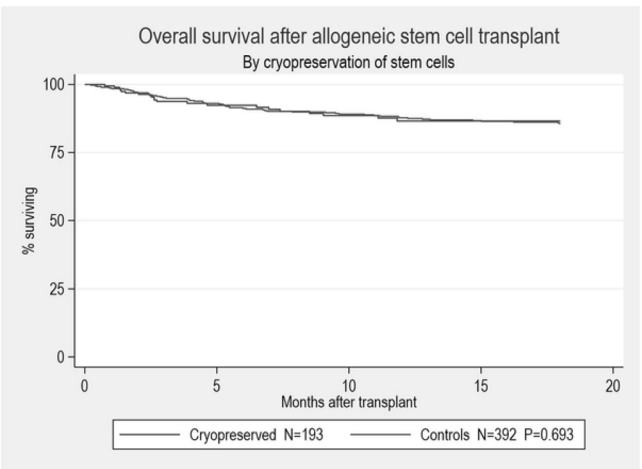
There was no statistically significant difference in OS at 18 months ($p = 0.26$); 66% (95% CI: 52-77%) in paediatric patients who received cryopreserved versus 77% (95% CI: 66-85%) in paediatric patients with fresh control grafts (Figure 1).

Table 1. Comparisons between cryopreserved and fresh graft paediatric groups.

		Data	Cryopreserved N = 193 difference[1]	Fresh controls N = 392	P for
Age at transplant	Years & months	Median (range)	8y 3 m (2m – 17y 10m)	7y 4 m (1m – 17y 11m)	0.60
Follow-up	Months	Median (95% CI)	12 m (11-12 m)	33 m (32-34m)	**0.01**
Engraftment	Neutrophils > 0.5 x 10^9/l (days)	Median (range)	17 d (0-47 d)	17d (0-61d)	0.60
	Platelets > 20 x 10^9/l (days)	Median (range)	20d (4-77d)	20d (7-90d)	0.88
Graft failure		N (%)	1 (1%)	5 (1%)	0.67
Acute GvHD (grade I-IV)	At day 100	%	45%	39%	0.20
Relapse rate (by competing risk)	At 18 months Malignant diagnoses only	% (95% CI)	31% (14-50%)	19% (14-25%)	0.28
Progression free survival	At 18 months Malignant diagnoses only	% (95% CI)	56% (35-73%)	70% (62-77%)	0.17
Overall survival	At 18 months	Kaplan-Meier	estimate (95% CI)	86% (78-90%)	86% (82-89%)
0.69					

[1] By Cox regression except where noted
2 By Fisher's exact test

Figure 1. OS of paediatric patients receiving cryopreserved versus fresh grafts.



Conclusions: Our retrospective, multicentre UK study of allogeneic HCT in paediatric population did not find a statistically significant difference in engraftment times, graft failure, aGVHD and most importantly OS. There was no statistically significant difference between the groups in PFS and RR when only malignant conditions were analysed. HSC graft cryopreservation remains is safe graft processing option in paediatric population.

Clinical Trial Registry: BSBMTCT Clinical Trials Committee has approved the study (Study ref. CTCR 20-01).

Disclosure: Nothing to declare.

18 - Paediatric Issues

P617

TOTAL BODY IRRADIATION FOR CHILDHOOD ALL: LOWER INCIDENCE OF LATE EFFECTS WITH INCREASED FRACTIONATION

Hilde Hylland Uhlving[1], Mogens Bernsdorf[2], Tania Masmas[1], Kaspar Sørensen[1], Lena Specht[2], Marianne Ifversen[1]

Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

Background: The FORUM study has established total body irradiation (TBI) as a pivotal part of pre-HSCT conditioning for childhood ALL, yet evidence regarding different TBI schedules and their toxicities is sparse. We therefore investigated the clinical signs of acute inflammation and late effects comparing TBI in 6 versus 3 fractions, and 3-dimensional (3D) versus 2D radiation planning technology.

Methods: We retrospectively compared 3 national paediatric ALL cohorts transplanted in Denmark. TBI 12 Gy was delivered as:

(1) 3 fractions between 2008-2011 (n = 12),

(2) 6 fractions with 2D planning technology 2012- 2015 (n = 16) and

(3) 6 fractions with 3D planning technology 2016-2020 (n = 14).

Results: Patient age, donor age and disease state at HSCT were comparable between cohorts. Cohort 3 had more patients with T-ALL (42.9%) compared to cohort 1 (25%) and 2 (12.5%). In cohort 3, two patients received haplo-transplantation compared to none in the other cohorts.

There were no significant differences between cohorts in the incidence of acute GvHD (67%, 56% and 71%, respectively) or chronic GvHD (25%, 31% and 7%). Time to first hospital discharge post-HSCT was comparable (median 28, 32 and 31 days, respectively). The level of acute inflammation assessed as maximum value of C-reactive protein (median 101, 125 and 123 mg/l) and ferritin (median 5408, 4900 and 6190 mikrog/l) during the first 3 months were not significantly different.

Pulmonary function parameters did not show significant differences between cohorts, although cohort 1 experienced a larger decrease in FEV_1% predicted during the first year post-HSCT (-13% vs. -0,3 and -1,1%, p = 0.061). The differences were equalized at 2 and 5 years follow-up, when compared to baseline and to cohorts 2 and 3.

At 2 years follow-up, cohort 1 had a higher incidence of cataract (33%) than cohort 2 (7%) and 3 (0%) (p = 0,038). At 5 years follow-up, cataract was seen in 80% of cohort 1 and 36% of cohort 2 (p = 0.08). Cohort 3 had not yet reached 5 years follow-up.

The number of patients in need of hormonal substitution 5 years post-HSCT was consistently higher in cohort 1 compared to cohort 2 (thyroid hormone 66 vs. 30%, growth hormone 25 vs. 8%, sex hormone 42 vs. 23%). The differences did not reach statistical significance.

Conclusions: No difference was found in acute toxicity when altering fractionation in 12 Gy total dose TBI from 3 to 6 fractions. A non-statistically significant difference was seen in late effects as 12 Gy TBI in 6 fractions had fewer incidences of cataract and endocrinopathies than 12 Gy TBI in 3 fractions. Longer follow-up and possibly larger cohorts are warranted to compare late toxicity in 12Gy/6F between 2D and 3D radiation planning.

Future protocols should require TBI delivered in small fractions to reduce the risk of long-term effects. The current evidence does not support further TBI specific requirements, though further studies are needed.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P618

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION ASSOCIATED THROMBOTIC MICROANGIOPATHY IN PEDIATRIC PATIENTS: CLINICAL CHARACTERISTICS AND DEFIBROTIDE THERAPY

Jiayu Wang[1], Yanhui Luo[1], Jun Yang[1], Bin Wang[1], Chenguang Jia[1], Jie Zheng[1], Yuanfang Jing[1], Wei Chen[1], Wei Yang[1], Guanghua Zhu[1], Maoquan Qin[1], Sidan Li[2]

[1]Beijing Children's Hospital, Beijing, China, [2]Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China

Background: To summarize and analyze the clinical characteristics of allogeneic hematopoietic stem cell transplantation (allo-HSCT) associated thrombotic microangiopathy (TA-TMA) in pediatric patients and the efficacy of defibrotide therapy.

Methods: We retrospectively analyzed the single-center experience of children who underwent allogeneic HSCT in Beijing Children's Hospital from January 2018 to December 2021. 274 pediatric patients received 284 allogeneic HSCT, among which 36 children were diagnosed as TA-TMA.

Results: The median time to diagnosis in 36 children with TA-TMA was 41 (-2-402) days after transplantation, and 28 children showed organ involvement, including 13 with neurological symptoms, 15 with renal involvement, and 18 with gastrointestinal involvement. The overall response rate of defibrotide was 73.5% (25/34) in 34 children with TMA who were treated with defibrotide. And the therapy of defibrotide could effectively improve the survival rate of patients (84.0% vs 33.3%, P = 0.005). Univariate analysis suggested that primary malignant diseases (P = 0.05), LDH level at diagnosis (P = 0.038), the highest level of LDH (P = 0.009), TMA with renal involvement (P = 0.004), TMA involvement of ≥2 systems (P = 0.01), diffuse alveolar hemorrhage syndrome (P = 0.005), and EBV infection (P = 0.018) had an impact on the prognosis of the children. Multivariate analysis suggested that TMA with renal involvement significantly affected the survival of the children (P = 0.043). The incidence of TMA significantly reduced the survival rate in transplanted children (69.4% vs 91.5%, P = 0.000).

Table. Parameters affecting prognosis of TA-TMA patients

Univariate	P
LDH level at diagnosis	0.038
The highest level of LDH	0.009

EBV infection (whole blood)	0.018
Renal involvement	0.004
≥2 systems involvement	0.01
Diffuse alveolar hemorrhage	0.005
Malignant diseases	0.05
Multivariate	P
Renal involvement	0.043

Conclusions: Our study preliminarily shows that defibrotide is safe and effective in the treatment of pediatric patients of TA-TMA, which can improve the survival of children and is worthy of further exploration.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P619

SAFETY AND POTENTIAL EFFECTIVENESS OF ANAKINRA AS THERAPY AND STEROID-SPARING AGENT IN THE MANAGEMENT OF INFLAMMATORY COMPLICATIONS IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN

Gianluca Dell'Orso[1], Stefano Giardino[1], Filomena Pierri[1], Giulia Ferrando[1], Roberta Caorsi[1], Elio Castagnola[1], Maura Faraci[1]

[1]IRCCS Istituto G. Gaslini, Genova, Italy

Background: An excessive cytokine storm is associated to acute inflammatory post-transplant complications. High dose steroids are associated with severe side effects. A targeted inhibition of single cytokine based on Anakinra, IL-1 receptor antagonist, might represent a potential strategy.

Methods: Between 2017 to 2022, 10 children received an intravenous or subcutaneous off-label treatment with anakinra at HSCT Unit, in Istituto Gaslini. Treatment choice was approved by internal review board for off-label use of drugs. Informed consent was signed. Efficacy was described as reduction of CRP and/or improvement of temperature trend and/or resolution of symptoms and related objective or imaging findings.

Results: Median duration of anakinra administration was 32 days (10-180 days) at doses ranging from 2.5mg/kg/day to 10 mg/kg/day. In 3 patients, dosage was later increased according to clinical response. Median follow-up was 0.94 years. Anakinra was successful in patients affected by Mevalonate Kinase Deficiency (P2, P3) and Chronic Granulomatous Disease (P1) before HSCT, with no additional toxicity nor long term side effects.9 patients received anakinra after allogeneic HSCT. We can support the hypothesis of a direct effective role of anakinra in P4, P8, P9, P10.

P5 developed severe facial cellulitis before engraftment. Anakinra was introduced to avoid steroids potential negative effect on engraftment and immune reconstitution. Acute inflammation resolved with stabilization of local reaction and later slow improvement of skin fibrosis. 5 patients received anakinra during ongoing long-term steroid treatment, but only in P1 steroid dose was increased.

P1 and P4 received anakinra again due to hyperinflammation associated to later infections; they were already receiving high-dose steroids and low-dose steroids due to severe cGvHD and a previous aGvHD. P7 was receiving steroids due to a previous capillary-leak syndrome.

P3 developed a severe peri-engraftment syndrome and received anakinra in association with steroids and mechanical ventilation to manage severe respiratory failure. After graft failure, anakinra was continued in order to prevent MKD-related inflammatory events, successfully. No further increase in steroid dose was required.

Pt. 6 developed severe multi-systemic inflammation in the early post-transplant period, unresponsive to maximal steroid treatment, anakinra, cyclosporine, etanercept, ruxolitinib and tocilizumab.

P1, P4 and P7 suffered from severe infections during follow-up following anakinra suspension, at least 1 months after anakinra suspension and all of them during concomitant long-term immunosuppressive treatment or chemotherapy for leukemia relapse. No other additional relevant tocixities related to anakinra were reported.

Conclusions: Anakinra can represent a promising and safe steroid-sparing strategy in HSCT patients. No relevant side effects, increase in infections rate nor impact on immune reconstitution were observed. Severe infections reported are not related to IL1-R inhibition because of the short half-life of anakinra and time-span between treatment and infection in P4 and P5, and a significant ongoing immunosuppression in all 3 patients. A direct role and effectiveness of IL-1 blockade in treatment of post-transplant complications can be better clarified though prospective clinical trials to reduce performance bias, particularly related to association with steroid treatment.

Clinical Trial Registry: not applicable

Disclosure: Conflict of interest: nothing to declare.

18 - Paediatric Issues

P620

IMPACT OF VITAMIN D LEVEL ON OUTCOME AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDHOOD

Bernd Gruhn[1], Susan Wittig[1], Helen Schneider[1]

[1]Jena University Hospital, Jena, Germany

Background: Vitamin D deficiency is often associated with severe disease progression and poor outcome in many chronic and malignant diseases. This is attributed primarily to the immunological and antiproliferative effects of vitamin D. Children receiving allogeneic hematopoietic stem cell transplantation (HSCT) are at risk for vitamin D deficiency because of long duration of hospital stay, inadequate exposure to UVB radiation, and damaged mucosa of the gastrointestinal tract. This study aimed to demonstrate the association of vitamin D level with outcome in a pediatric population undergoing allogeneic HSCT.

Methods: We analyzed 186 children with a median age of 11 years who underwent an allogeneic HSCT in a single center. Only patients with available 25-hydroxycholecalciferol (25(OH)D) level data were included. The donor was HLA-matched unrelated in 50% of transplants, HLA-identical related in 25% of transplants, HLA-mismatched unrelated in 15% of transplants, and HLA-haploidentical related in 10% of transplants. Conditioning regimen was myeloablative in all cases and based on total body irradiation in 66% of transplants or chemotherapy alone in 34% of transplants. Vitamin D deficiency was defined as a 25(OH)D level < 30 nmol/L according to the published data of the Robert Koch Institute, Germany. We divided the study population into two patient groups with and without vitamin D deficiency to assess the impact of vitamin D level on outcome after HSCT.

Results: The median vitamin D level before HSCT and on day +100 after HSCT was 31.0 nmol/L and 26.0 nmol/L, respectively.

Overall, 86 patients (46.2 %) had vitamin D deficiency before HSCT. By use of binomial logistic regression patient age > 11 years (OR = 1.95; p = 0.043) and HSCT in the period from January to June (OR = 1.92; p = 0.049) were significant risk factors for vitamin D deficiency before HSCT. The Wilcoxon signed-rank test showed a significant decrease of the median 25(OH)D level from 43.9 nmol/L to 33,0 nmol/L (p = 0.001) within the first 100 days after HSCT in patients who did not have vitamin D deficiency before HSCT. Interestingly, we observed a significantly increased transplant-related mortality (TRM) in children with vitamin D deficiency before HSCT (27.5 % versus 20.5 %; p = 0.049). In addition, we found a significantly reduced overall survival (OS) in children with vitamin D deficiency before HSCT (45.3 % versus 66.7 %; p = 0.004). In patients with malignant diseases, we observed a significantly reduced event-free survival (EFS) in children with vitamin D deficiency before HSCT (35.5 % versus 52.7 %; p = 0.032). Furthermore, vitamin D deficiency on day +100 after HSCT proved to be a significant risk factor for the development of chronic graft-versus-host disease (GVHD) (27.6 % versus 10.5 %; p = 0.027). In multivariate analysis, vitamin D deficiency before HSCT was an independent risk factor for OS (p = 0.005) and for EFS (p = 0.014).

Conclusions: Our study identified vitamin D deficiency before HSCT as a significant risk factor for increased TRM, reduced OS, and reduced EFS. Children who were vitamin D deficient on day +100 after HSCT had a significantly higher risk for the development of chronic GVHD than those without vitamin D deficiency.

Disclosure: The authors declare to have no potential conficts of interest.

18 - Paediatric Issues

P621

SYMPTOMATIC AVASCULAR NECROSIS OF THE BONE IN CHILDREN AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Victoria Bordon[1], Thomas De Rijcke[2], Julie De Cat[2], Helenna Herremans[2], Sophie Van Lancker[1], Jans Lennart[1], Sophie Lauwagie[1]

[1]Ghent University Hospital, Ghent, Belgium, [2]Ghent University, Ghent, Belgium

Background: Avascular necrosis of the bone (AVN) is defined as nontraumatic ischemic bone necrosis.

The pathogenesis of AVN is still a matter of controversy. It can result from multiple triggering factors such as local vascular damage, increased intraosseous pressure and mechanical stress leading to demineralization, death of trabecular bone, and collapse. Multiple drugs used in oncology, such as chemotherapy, immune suppressors, but also radiotherapy, can play a role in the development of AVN

AVN is a debilitating condition affecting survivors' quality of life after allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT).

Methods: This study is a retrospective analysis of all consecutive allogeneic transplants performed in pediatric patients (0-18 years) between January 2012 and December 2022.

All transplants were performed at the Pediatric ward of the Ghent University Hospital (Ghent, Belgium).

The orthopedic files of patients who had a history of bone/joint pain were analyzed, and the diagnosis of symptomatic AVN had to be confirmed by MRI of the affected joint(s) to be able to be included in this study.

Results: 125 consecutive allo-HSCT were performed in 120 children during the study period.

Six patients with symptomatic AVN after the allo-HSCT procedure were found; this gives an incidence of 5 % in the whole group.

The median age at allo-HSCT in the whole group was 6 years. Patients who developed symptomatic AVN after the transplant procedure were significantly older (P = 0.0079) at the time of transplant than patients without AVN. The patients with AVN were transplanted at a mean age of 6.4 (0.5-18), and the mean age at transplant for the AVN group was 12.1 years (6.9-16.9).

The AVN was diagnosed after a mean time of 18 months after the transplant (7-18 months).

The most affected joints were the knee, followed by the hip, ankle and shoulder. All patients had bilateral AVN-affected joints.

At the moment of this analysis, 2 young patients underwent joint surgery, and one underwent joint replacement.

Conclusions: Avascular necrosis is a skeletal complication that severely impacts the quality of life. Pediatric patients who underwent an allo-HSCT have an incidence of symptomatic and severe AVN of 5%. This incidence is an underestimation but includes the severe and most invalidating cases.

The diagnosis is most frequently made in long-term follow-up visits. The joint affection is mostly bilateral, adding morbidity to this complication.

Age is a risk factor for these severe cases. Teenagers at the moment of the allo-HSCT are at higher risk. It seems that bone metabolism is more affected by chemo and radiotherapy as well as immunosuppressors at the time of accelerated growth. The extent of the impact of the chemotherapy and steroids used during up-front treatment and the exact impact of the conditioning regimes have to be elucidated.

The results of this study can improve the long-term structural follow-up of patients post-transplant, making earlier diagnosis and treatment possible. However, more research in pathophysiology and non-invasive treatment of AVN is needed.

Disclosure: No conflict of interest.

18 - Paediatric Issues

P622

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR JUVENILE MYELOMONOCYTIC LEUKEMIA USING INTRAVENOUS BUSULFAN, FLUDARABINE, AND MELPHALAN REGIMEN; A PROSPECTIVE SINGLE-ARM PHASE II STUDY BY JPLSG

Kazuo Sakashita[1], Nao Yoshida[2], Hideki Muramatsu[3], Yoshitoshi Ohtsuka[4], Kennichiro Watanabe[5], Miharu Yabe[6], Harumi Kakuda[7], Yuko Honda[8], Atsushi Manabe[9]

[1]Nagano Children's Hospital, Azumino, Japan, [2]Japanese Red Cross Aichi Medical Center Nagoya First Hospital, Nagoya, Japan, [3]Nagoya University Graduate School of Medicine, Nagoya, Japan, [4]Hyogo College of Medicine, Nishinomiya, Japan, [5]Shizuoka Children's Hospital, Shizuoka, Japan, [6]Tokai University School of Medicine, Isehara, Japan, [7]Chiba Children's Hospital, Chiba, Japan, [8]University of Occupational and Environmental Health, Kitakyushu, Japan, [9]Hokkaido University Graduate School of Medicine, Sapporo, Japan

Background: Juvenile myelomonocytic leukemia (JMML) is a rare hematologic malignancy of infancy and childhood that is classified as a myelodysplastic/myeloproliferative neoplasm. Most patients with JMML require allogeneic hematopoietic cell transplantation (HCT) as curative therapy. Busulfan (BU) is an alkylating agent that

has been widely used as a conditioning regimen in HCT for patients with JMML. Busulfan (BU) + cyclophosphamide (CY) + melphalan (MEL) is the current standard conditioning regimen as reported by the European Working Group of Myelodysplastic Syndromes in children and the European Society for Blood and Marrow Transplantation. In the past, the Japanese retrospective analysis showed the relatively favorable results of BU +fludarabine (FLU) + MEL regimen, with an OS of 72% and an EFS of 53% (Yabe M. Int J Hematol 2015). In this study, the Japan Pediatric Leukemia/Lymphoma Study Group (JPLSG) conducted a nationwide prospective study, JMML-11, to validate the efficacy and safety of BU + FLU + MEL regimen.

Methods: Patients for the JPLSG JMML-11 trial were recruited between July 2011 and June 2017. All patients who met the eligibility criteria (suitable donor identified, without organ dysfunction and uncontrolled infections) could proceed to HCT. The donor selection was made by the physician in charge. Conditioning regimen (BU + FLU + MEL) was intravenous BU (16 doses administered every 6 hour) with dose adjustment based on pharmacokinetics study on days -11 to -8, FLU (30 mg/m^2/day, or 1 mg/kg/day for patients < 10 kg or < 1 year-old) on days -7 to -4, and MEL (90 mg/m^2/day, or 3 mg/kg/day for patients < 10 kg or < 1 year-old) on days -3 to -2.

Results: The number of registered cases was 31. Of those, 28 cases were eligible, with 3 cases excluded due to discontinuation before the start of pretreatment. The 1-year post-transplant EFS was 57% (95% CI:37%–73%). The 3-year OS, the 3-year EFS, the 3-year relapse rate, and the 3-year TRM were 63% (42%–78%), 52% (32%–69%), 18% (6%–34%), and 21% (9%–38%), respectively. Body surface area (BSA) (0.4 m^2 ≤ BSA < 0.5 m^2), RAS pathway mutation, WBC count before conditioning regimen (> 7.0 ×10^9/L), and actual dose of FLU (< 120 mg/m^2) and MEL (< 180 mg/m^2) were significantly associated with inferior EFS and OS. In addition, spleen size before conditioning regimen (< 4 cm) and HLA-matched unrelated bone marrow donors were significantly associated with better OS. Whereas RAS pathway mutation and WBC count before conditioning regimen (> 7.0 ×10^9/L) were risk factors for relapse, and BSA (0.4 m^2 ≤ BSA < 0.5 m^2) and abnormal karyotype were risk factors for TRM. In addition, higher WBC count before conditioning regimen (> 7.0 ×10^9/L) was associated with engraftment failure.

Conclusions: These results indicate that the BU + FLU + MEL regimen may provide similar outcomes to BU + CY + MEL regimen and could become one of the standard conditioning regimens for patients with JMML.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P623

COMORBIDITY SCORING PREDICTS OUTCOMES AFTER HAPLOIDENTICAL TRANSPLANTATION IN PEDIATRIC NON-MALIGNANT DISEASES

Koray Yalcin[1,2], Seda Ozturkmen[3], Suna Celen[1], Hayriye Daloglu[3], Suleimen Zhumatayev[4,5], Betul Bozkurt[4], Deniz Dereli[6], Irem Karaman[6], Vedat Uygun[3], Volkan Hazar[4], Gulsun Karasu[4,3], Akif Yesilipek[4,3]

[1]Bahcesehir University Goztepe Medicalpark Hospital Pediatric Bone Marrow Transplantation Unit, Istanbul, Turkey, [2]Acıbadem University Institute of Health Science Medical Biotechnology, Istanbul, Turkey, [3]Medicalpark Antalya Hospital Pediatric Bone Marrow Transplantation Unit, Antalya, Turkey, [4]Medicalpark Goztepe Hospital Pediatric Bone Marrow Transplantation Unit, Istanbul, Turkey, [5]Nazarbayev University, Astana, Kazakhstan, [6]Bahcesehir University School of Medicine, Istanbul, Turkey

Background: Haploidentical hematopoietic stem cell transplantation (haplo-HSCT) is increasingly preferred in pediatric non-malign diseases. There are many factors affecting the success of haplo-HSCT and there is a need for objective criteria proceeding to haplo-HSCT in pediatric non-malign diseases.

Methods: This study involved 33 pediatric patients who underwent haplo-HSCT with post-cy procedure for non-malign diseases. To decide the pre-HSCT condition, a scoring system involving previous HSCT (1 point), organ dysfunction (1 point), and active infection (1 point) was applied. Organ dysfunction is determined by Common Terminology Criteria for Adverse Events-2017 Guideline. Active infection is identified by CMV reactivation, fungal infection, blood-stream infection, abscess, and pneumonia.

Results: Characteristics of the patients and HSCT features are presented in Table-1.

Any organ dysfunction or active infection in pre-HSCT period is found to be related to a lower survival rate (p < 0,01). Consistent with these data, our scoring system is associated with survival rates (p < 0,01). All the patients with "score 0" are alive (n = 9). Only 3 of 14 patients with "score 1" are dead but all the patients with "score 2" or "score 3" are dead (n = 10). Regarding HSCT-related complications, patients with a higher score (2&3) had more grade 3-4 aGvHD (p < 0,01).

In our study, 3 of 4 graft failures were observed with bone marrow as a stem cell source and more grade 3-4 aGvHD was observed with peripheral blood/bone marrow combination (p < 0,01).

Sibling haplo donor was better than parents regarding aGvHD rates (p = 0,04). And there was no difference between the mother and father as the donor.

Older donor age (> 32 years – median age-) was related to higher grade 3-4 aGvHD risks. And HSCT from female to male is related to more grade 3-4 aGvHD and lower survival (p = 0,05).

To decrease the toxicity of the HSCT procedure, post-Cy doses were lowered for selected patients (25 mg/kg/d for Fanconi anemia and 40 mg/kg/d for the others) and the patients with low doses (n = 9) had similar GvHD rates but lower survival rates.

Of all the patients 20/33 (60%) were alive without any sign of primary disease. The ratio of grade 3-4 aGvHD was 33%. Sepsis was the most frequent cause of death (n = 8) and 85% of the deaths occurred in the first 6 months after HSCT.

Gender (F/M)	12/21
Median Age (months)	44 months (1-226 months)
Primary Disease(Immune Deficiency/Bone Marrow Failure/Metabolic Disease)	23/9/1
Comorbidity Score (0/1/2/3)	9/14/9/1
Conditioning (BU + FLU/CY + FLU/TREO + FLU)	4/11/18
Stem Cell Source (BM/PBSC/BM + PBSC)	17/4/12
Donor (Mother/Father/Sibling)	15/11/7
Median Donor Age (Years)	32
Grade 3-4 GvHD/Chronic GvHD	11/6
Outcome (Ex/Alive)	13/20

Conclusions: These results indicate that our comorbidity scoring could predict the success of haplo-HSCT regarding GvHD incidence and survival. Sibling donors and the young donor could

be preferred for decreasing the risk of severe GvHD. Haplo-HSCT could be a promising option in pediatric non-malign diseases, especially with selected donor types and performed before complications emerged.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P624

BELATACEPT: A PROMISING ALTERNATIVE TO TRADITIONAL GRAFT VERSUS HOST DISEASE PROPHYLAXIS IN CHILDREN AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

Mariah Wright[1], Hemalatha Rangarajan[1], Rolla Abu-Arja[1], Margaret Lamb[1], Joseph Stanek[1], Vinita Pai[1], Rajinder Bajwa[1]

[1]OH, Columbus, United States

Background: Calcineurin inhibitors are the standard of care for GvHD prophylaxis after HSCT, but adverse effects including hypertension, hypomagnesemia, and renal dysfunction are commonly seen. Incidence of acute and chronic GvHD is around 25-50% and frequent blood work is required to maintain therapeutic drug levels. Belatacept is a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor and is currently approved for prevention of adult renal transplant rejection. We studied belatacept for GvHD prophylaxis in children after HSCT at our institution.

Methods: For most patients, belatacept (10mg/kg/dose), IV, was started after neutrophil engraftment, weekly for 4 doses, then every 2 weeks for 2 doses and then every 4 weeks. Tacrolimus weaning was started after the 2nd dose of belatacept and weaned over subsequent 4-8 weeks. Belatacept, was continued for 6-9 months or 9-12 months in matched related donor and matched unrelated donor transplants respectively. Weaning was done by increasing the interval to 5, 6, 7 and 8 weeks for one dose each and then stopped. Data collection included patient demographics, HSCT details, treatment characteristics, treatment side effects, complications including development of aGvHD or cGvHD and viral reactivation. Univariate analyses were performed.

Results: A total of 12 patients underwent HSCT and received belatacept at our quaternary pediatric institution from 8/2018 to 9/2022; demographic data is shown in Table 1. Belatacept was started as a planned GvHD prophylaxis in all patients except 1 with MDS, who developed TA-TMA after which tacrolimus was discontinued and belatacept started as alternative GvHD prophylaxis. One patient (after haplo HSCT) developed early CMV reactivation, progressed to secondary graft failure, received only 4 doses of belatacept and was excluded from further analysis. Of the remaining 11 patients, with a median follow-up of 10 months (range 2-51 months), no patient developed posterior reversible encephalopathy syndrome, transplantation associated thrombotic microangiopathy, hypertension or hypomagnesemia. Acute GvHD was seen in 2 patients, (grade I in 1 patient while weaning belatacept, which responded to resumption of Q4 weekly doses) and grade III in 1 patient who had developed severe COVID infection leading to acute nephrotic syndrome followed by steroid refractory acute GvHD but responded to ruxolitinib. No patient developed chronic GvHD. Over 150 belatacept infusions have been performed in all 11 patients, with no reported allergic reactions, nausea, vomiting, diarrhea, azotemia, hepatic or other organ dysfunctions related to belatacept infusions. Two patients have come off belatacept and 2 others are near completion of therapy and there were no compliance issues.

Table 1

Characteristics	N = 11 (%)
Sex	
Female, male	4 (36%), 7 (64%)
Age at HSCT (years), Median (range)	8 (0.3-20)
Diagnoses	
Malignant, Non-malignant	1 (9%), 10 (91%)
HSCT type	
MSD (10/10 match)	4 (36%)
MUD, MMUD	7 (64%)
Graft Source	
Marrow, UCB	10 (91%), 1 (9%)
Conditioning Regimen	
Flu, Cytoxan	6 (55%)
Flu, Mel or Flu, Bu or Flu, Thiotepa	4 (36%)
Flu, Cytoxan, TBI	1 (9%)
GvHD prophylaxis	
Tacro, MTX or MMF, Belatacept	4 (36%)
Tacro, Belatacept	7 (64%)

Conclusions: Belatacept is a potentially safe and effective alternative to traditional GvHD prophylactic medications (calcineurin inhibitors, MMF and sirolimus) based our retrospective pilot study. Fewer clinic visits, no need of drug level monitoring, lesser daily number of total oral medications needed, and fewer side effects has also increased compliance. Belatacept has markedly decreased or similar rates of acute GvHD and chronic GvHD compared to abatacept and calcineurin inhibitors. Small sample size, lack of control group and relatively short duration of follow are some limitations of the study.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P625

PLASMA ST2 LEVELS ARE PREDICTIVE OF CHRONIC GVHD AFTER PEDIATRIC HSCT

Nakisa Kamari-Kany[1], Sarah Weischendorff[1,2], Christian Enevold[1], Marianne Ifversen[1], Katrine Kielsen[1], Klaus Müller[1,2]

[1]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [2]University of Copenhagen, Copenhagen, Denmark

Background: The outcome after allogeneic HSCT has improved significantly but is challenged by the risk of acute and chronic GvHD that contributes significantly to transplant-related morbidity and mortality.

The soluble IL-33 receptor, known as suppressor of tumorigenesis 2 (ST2), has been reported as a promising biomarker for aGvHD-related outcomes, but data of its value as a biomarker for cGvHD is sparse. In this time-course study, we investigated the value of plasma ST2 levels for prediction of cGvHD after pediatric HSCT.

Methods: We included 117 children undergoing HSCT between 2010-2020 in Denmark. Median age was 8.9 years (range: 1.1-17.9). Diagnoses included ALL (n = 29), AML (n = 18), other malignancies (n = 25), and benign disorders (n = 45). Donors were either MSD (n = 33) or MUD (n = 84). Bone marrow (n = 112) or

peripheral blood (n = 5) was used as stem cell source. All patients received a myeloablative conditioning regimen based on TBI (n = 23) or chemotherapy alone (n = 94), and 87 patients received ATG as part of the conditioning. GvHD prophylaxis consisted of cyclosporine A alone or in combination with methotrexate.

ST2 was measured by ELISA in plasma samples collected before conditioning and at day 0, +7, +14, +21, +30, +60, +90 and +180 post-transplant. Plasma samples from 17 healthy young adults were included for comparison.

Results: Plasma levels of ST2 in the patients were comparable to those in healthy controls (16760 pg/mL *vs*. 16323 pg/mL) before conditioning but increased early after transplantation reaching a maximum at day +30 (54301 pg/mL, $P < 0.0001$) and then gradually declined.

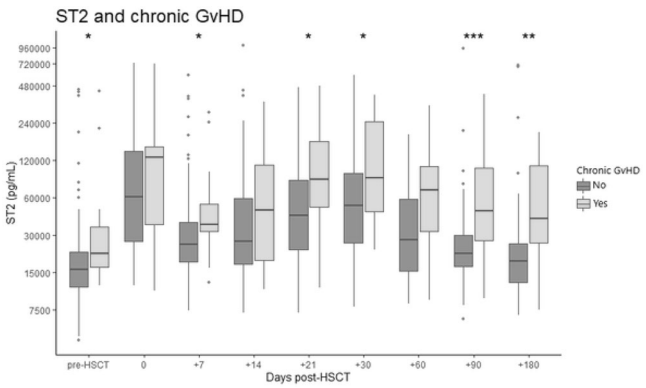
Patients with malignant diagnoses had significantly higher ST2 levels before conditioning compared to patients with benign diseases (18121 pg/mL vs. 14754 pg/mL, $P = 0.007$). Furthermore, busulfan-based conditioning was associated with elevated ST2 levels from day 0 to +21 (all $P < 0.05$).

Thirty-eight patients (32.5%) developed aGvHD grade II-IV (MAGIC criteria). These patients had significantly higher levels of ST2 from day +7 to +90 compared to patients with aGvHD grade 0-I. This was confirmed in a multivariable analysis adjusted for malignant diagnosis, donor type and busulfan-based conditioning (day +14: OR = 1.95 per doubling in ST2, $P = 0.0003$).

Nineteen patients (16.2%) developed cGvHD with median onset 6.7 months after transplantation (range: 3.7-114.9), of these 14 patients (73.7%) developed extensive and 5 patients (26.3%) developed limited cGvHD. Thirteen (68.4%) of the patients with cGvHD had previously been diagnosed with aGvHD, and 10 of these (76.9%) had aGvHD grade II-IV.

Patients developing cGVHD had significantly higher levels of ST2 before conditioning compared to patients without cGvHD (21502 pg/mL *vs*. 15876 pg/mL, $P = 0.01$). Furthermore, patients later developing cGvHD had significantly increased ST2 levels from day +7 to +180 compared to patients not developing cGvHD, and ST2 levels remained increased until 6 months post-transplant in these patients (Figure).

Conclusions: We demonstrate that ST2 levels before conditioning and during the early phase of HSCT are significantly increased in patients developing cGvHD. These findings support the use of ST2 as a prognostic biomarker for cGvHD as well as aGvHD after pediatric HSCT.



Disclosure: Nothing to declare.

18 - Paediatric Issues

P626

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA: A STUDY OF THE KOREAN BLOOD AND MARROW TRANSPLANTATION REGISTRY

Hyoung Soo Choi[1], Hyeon Jin Park[2], Hee Young Ju[3], Keon Hee Yoo[3], Chuhl Joo Lyu[4], Ho Joon Im[5], Min Kyoung Kim[6], Yeung-Chul Mun[7], Joon Ho Moon[8], Sung-Soo Yoon[9], Eunyoung Lee[2], Jae Hoon Lee[10], Je-Hwan Lee[11], So Young Chong[12], June-Won Cheong[4], Seunghyun Won[13]

[1]Seoul National University Bundang Hospital Seoul National University College of Medicine, Seongnam, Korea, Republic of, [2]National Cancer Center, Goyang, Korea, Republic of, [3]Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of, [4]Yonsei University College of Medicine, Seoul, Korea, Republic of, [5]Asan Medical Center Children's Hospital University of Ulsan College of Medicine, Seoul, Korea, Republic of, [6]Yeungnam University College of Medicine, Daegu, Korea, Republic of, [7]Ewha Womans University School of Medicine, Seoul, Korea, Republic of, [8]Kyungpook National University Hospital Kyungpook National University School of Medicine, Daegu, Korea, Republic of, [9]Seoul National University College of Medicine, Seoul, Korea, Republic of, [10]Gachon University Gil Hospital, Incheon, Korea, Republic of, [11]University of Ulsan College of Medicine and Asan Medical Center, Seoul, Korea, Republic of, [12]CHA Bundang Medical Center CHA University, Seongnam, Korea, Republic of, [13]Seoul National University Bundang Hospital, Seongnam, Korea, Republic of

Background: Chronic myelogenous leukemia (CML), BCR-ABL1-positive, is a myeloproliferative neoplasm in which granulocytes are the major proliferative component. CML in pediatric and young adult patients is uncommon, accounting for only about 3% of all leukemias and <10% of all reported CML. The introduction of tyrosine kinase inhibitors (TKIs) significantly improved treatment outcomes and reduced the number of allogeneic hematopoietic stem cell transplantation (HSCT) in CML. However, in some patients with advanced stage, TKI resistance, and difficulty taking TKI, HSCT is an important treatment option. This study was performed to investigate the status of allogeneic HSCT in Korean children, adolescents and young adults with CML.

Methods: We searched for patients enrolled in 2009-2019 in the Korean Blood and Marrow Transplantation Registry of the Korean Society of Blood and Marrow Transplantation. A total of 81 patients with CML underwent allogeneic HSCT, and among them, 36 patients under 40 years of age were retrospectively investigated. Patients were divided into two groups based on age of 20 years at the time of HSCT.

Results: Among 36 patients, 24 were male and 12 female. Fifteen patients were younger than 20 years of age at the time of HSCT (Group 1) and 21 were ≥20 years of age (Group 2). The median time from diagnosis CML to HSCT was 8.9 months (range 3.0 – 137.5). As for hematopoietic stem cells, 34 were peripheral blood stem cells and 2 were bone marrow. Myeloablative conditioning regimen was used in 19 patients (including total body irradiation in 6) (52.8%). At the time of HSCT, 29 patients were in complete remission and 7 had active disease. Acute GVHD occurred in 19 out of 36 patients (52.8%) and chronic GVHD in 13 patients (36.1%). Posttransplant DLI was used in 4 patients and TKI administration in one. Relapse occurred in 3 patients, second malignant neoplasm in one. Nine patients died at a median 38.9 months (range 0.7-133.1) after HSCT. In Group 1, one patient died from infection, and in Group 2, 3 patients died from infection, 2 from pneumonia, one from pulmonary toxicity, and 2 from relapse or progressive disease. Median follow-up duration from HSCT was 91.4 months (range 28.5 – 160.1). In 36 patients, 5-year overall survival (OS) and event free survival (EFS) were 73.1% and 63.9%. Five-year OS and EFS were 93.3% and 78.3% in Group 1 and 58.2% and 53.1% in Group 2, which were better in Group 1 than Group 2

#	Status before haplo-HSCT	Conditioning regimen	Engraftment	Status before immunotherapy	Therapy	Toxic complications/ infections	Therapy response	Status alive/ died
Pt 1	CR1 MRD+	Bu12Flu	primary graft failure, 0% donor chimerism	CR MRD+ after 15month	Blin №1	no/no	CR MRD-	alive 63 months
Pt 2	CR1 MRD+	Bu12Flu	>97% donor chimerism	CR MRD+ after 8month	Blin №1 + DLI Dose №1	no/no	CR MRD-	alive 39 months
Pt 3	Primary resistant	GIAC	>97% donor chimerism	CR MRD+ after 2month	Blin №1 + DLI Dose №1	no/no	CR MRD-	alive 8 months
Pt 4	Primary resistant	GIAC	>97% donor chimerism	Bone marrow + CNS relapse after 2month	Blin №4 + DLI Dose №4 after chemo	no/no	CR MRD +, persistence t (11;19)	alive 7 months

(P values = 0.04 and 0.08). In univariate and multivariate analysis, disease status at the time of HSCT was only a significant risk factor affecting outcome.

Conclusions: In allogeneic HSCT for CML, children and adolescents showed better outcomes than young adults. Disease status at the time of HSCT had a significant influence on the outcome. Allogeneic HSCT constitutes a reasonable therapeutic option, but requires careful monitoring for long-term effects, including 2nd malignant neoplasm, pulmonary toxicity, and potential gonadal toxicity. Future studies on pre-transplant treatment, optimal conditioning regimen, and indications of HSCT are needed.

Disclosure: None.

18 - Paediatric Issues

P627

COMBINED IMMUNOTHERAPY AFTER HAPLO-HSCT IN INFANTS ALL WITH KMT2A REARRANGEMENT

Olesia Paina[1], Liubov Tsvetkova[1], Zhemal Rakhmanova[1], Polina Kozhokar[1], Anastasia Frolova[1], Anna Osipova[1], Elena Dobrovolskaya[1], Evena Babenko[1], Natalia Ivanova[1], Ildar Barkhatov[1], Elena Semenova[1], Ivan Moiseev[1], Alexander Kulagin[1], Ludmila Zubarovskaya[1]

[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation, Saint Petersburg, Russian Federation

Background: Infant acute lymphoblastic leukemia (ALL) is characterized by a high incidence of KMT2A gene rearrangements (KMT2Ar +) and poor outcome with event-free survival of < 50% even after allogeneic HSCT because of high risk of relapse. Donor lymphocyte infusion (DLI) has been used as immunoadoptive therapy after allo-HSCT in B-ALL patients for prophylaxis or prevention of relapse. Considering low toxicity combination of blinatumomab and DLI maybe a promising immunotherapy for high risks infant ALL. Aim of this study was to evaluate the efficacy and safety concomitant use of blinatumomab and DLI for MRD+ or relapse therapy after haplo-HSCT in infants ALL with KMT2A r +.

Methods: We analyzed results of combined immunotherapy for high-risk KMT2Ar+ ALL with bispecific T-cell activator blinatumomab and DLI in 3 infants, and monotherapy with bispecific T-cell activator in 1 infant (Pt 1). Indications were combined relapse (BM + CNS) of disease after myeloablative (MAC) haplo-HSCT in 1 pt (Pt 4) and persistence of MRD+ in 3 pts after MAC haplo-HSCT. Two patients received 1 course of combined immunotherapy, 1 patient received 1 course of mono-blinatumomab (Pt 1) and 1 patient received 4 courses of combined immunotherapy (Pt 4) after cytoreduction chemotherapy. The doses of blinatumomab were: 2.5 μg/m^2/day for the first 7 days, from days 8 to 14 – 7.5 μg/m^2/day, from days 15 to 28 – 15 μg/m^2/day. DLI was administered on days 21 or 30 from blinatumomab infusion with started dose of $1.0x10^6$ CD3+ cells/kg.

Results: After one cycle of immunotherapy 3 pts achieved MRD negative remission and 1 pt achieved complete hematological remission with detectable MRD by PCR t(11;19). With the median follow up of 24 months (range, 8-63) 3 recipients had full donor chimerism and all patients were alive in CR. We did not observe any strong excess of toxicity and signs of acute GVHD.

Conclusions: This is the first report describing the results of concomitant use of blinatumomab and DLI in infant ALL with KMT2Ar+. Current evidence points toward the efficacy and manageable toxicity of combined immunotherapy in infants. This is specifically the case in the context of MRD-positive infant ALL after haplo-HSCT.

Disclosure: The authors declare no conflicts of interest.

18 - Paediatric Issues

P628

EFFECT OF GVHD PROPHYLAXIS AND SEROTHERAPY IN 58 PEDIATRIC HEMOGLOBINOPATHY PATIENTS CONDITIONED WITH TREOSULPHAN, FLUDARABINE AND THIOTEPA

Ysabel Schwietzer[1], Anne Kruchen[1], Johanna Schrum[1], Manon Queudeville[1], Matthias Bleeke[1], Ingo Müller[1]

[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Serotherapy and immunosuppression play an important role in allogeneic HSCT for hemoglobinopathies. We focused on a cohort with invariant conditioning as background to identify effects of evolving immunosuppressive strategies.

Methods: We collected data from 61 consecutive transplantations in 58 pediatric patients with hemoglobinopathies between 2011 and 2022 at our center.

Results: 31 children had sickle cell disease and 27 β-thalassaemia major. All patients were uniformly conditioned with treosulphan, fludarabine and thiotepa (TFT). With a median follow-up of 3.5 years, overall survival was 98.3% and disease-fee survival 96.6%. Engraftment of leukocytes was reached at day 14.5 and of platelets on day 17 on average.

39 patients received a graft from an MSD, all of which survived and all but one are disease-free. While the incidence of GvHD was low in this cohort (no grade III-IV, 8 grade I-II), 7 patients had mixed donor chimerism below 80% and two of them had to undergo re-transplantation from the same sibling to achieve complete donor chimerism. 29 of 39 patients displayed incomplete donor chimerism at some point after 10 days of engraftment, but showed increasing donor chimerism after reduction or cessation of immunosuppression. Last administration of an immunosuppressive drug posttransplant was as early as day +72 (median; range 12 – 267 days posttransplant). In 10 patients donor chimerism was 90% or less. 9 of these 10 patients

had received thymoglobulin, while CsA/MTX and CsA/MMF were equally distributed. Reactivation of CMV, HSV, HHV6 and BKV was equally distributed among the two serotherapy groups. However, EBV reactivation occurred more frequently in the thymoglobulin group as compared with the Grafalon® group (59% vs. 11%).

19 patients were transplanted from alternative donors, i. e. MUD (n = 9), 9/10 MMUD (n = 9) and 9/10 MMFD (n = 1). One SCD patient transplanted from a 9/10 MMUD rejected, was re-transplanted T-cell depleted from a haploidentical parent, but died from viral infections. All surviving patients except for one achieved complete donor chimerism. However, 11 patients developed aGvHD, which progressed to severe gut GvHD in seven cases. At last follow-up, all of these patients are GvHD- and disease-free. Interestingly, only one of the seven patients who had received Grafalon® as serotherapy and ptCy encountered transient GvHD, whereas all but one patient with severe aGvHD had received CsA/MTX, CsA/MMF or CsA/MMF/MTX without ptCy. In the patient cohort with severe GvHD more patients had received thymoglobulin than Grafalon®.

Mixed donor chimerism was a frequent observation in MSD transplants, while aGvHD grade III-IV was prevalent in unrelated donor transplants. In MSD transplants with declining chimerism, thymoglobulin was applied as serotherapy more often than Grafalon®. Dominating morbidity was severe steroid-refractory aGvHD of the gut in 7/20 unrelated donor transplants. However, in MUD as well as in 9/10 MMUD, Grafalon® and ptCy almost completely eliminated the occurrence of severe aGvHD.

Conclusions: In TFT-conditioned MSD transplants for hemoglobinopathies, Grafalon® in combination with short and low-dosed CsA/MMF has evolved as our favourite concept. For UD transplants with TFT-conditioning, immune suppression with Grafalon® and ptCy/CsA achieved most promising outcome in our hands.

Disclosure: IM served on an expert panel for Neovii and received travel support from Genzyme, medac and Riemser.

18 - Paediatric Issues

P629

LOW INCIDENCE OF RELAPSE AND GOOD SAFETY PROFILE IN CHILDREN WITH HIGH RISK AND RELAPSED LEUKEMIA ALLOGRAFTED WITH POSTTRANSPLANT CYCLOPHOSPHAMIDE (PTCY)

Francesca Gottardi[1,2], Davide Leardini[1,2], Tamara Belotti[1], Antonio Giacomo Grasso[1], Francesco Baccelli[1,2], Edoardo Muratore[1,2], Francesca Barnabe[2], Jessica Bandini[1], Domenico D'Amico[1], Korinne Di Leo[1], Arcangelo Prete[1], Riccardo Masetti[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [2]Università di Bologna, Bologna, Italy

Background: The use of posttransplant cyclophosphamide (PTCy) for graft-versus-host disease (GvHD) prophylaxis in haploidentical hematopoietic stem cell transplantation (haplo-HSCT) has become a valuable option for treatment of malignant diseases. Increasing evidences of safety and efficacy of this platform led to improving expertise of pediatric centers.

Methods: We retrospectively analyzed the outcome of consecutive PTCy haplo-HSCT performed for treatment of acute leukemia at the pediatric Transplant Unit of the IRCCS Azienda Ospedaliero-Universitaria di Bologna (Italy) from January 2016 to December 2022. Patients received non-stimulated bone marrow from haploidentical family donor. PTCy 50 mg/kg on days 3 and 4 was used as graft-versus-host disease (GvHD) prophylaxis along with cyclosporine, given for 3 to 6 months, started together with mycophenolate mofetil on day +5, the latter discontinued after 35 days. Conditioning was myeloablative in all based on busulfan, treosulfan or total body irradiation TBI (*Table I*).

Results: Seventeen patients with median age of 11 years (range 1-18) with HR or relapsed ALL and AML were included in the analysis, single-patient transplant characteristics are reported in *Table I*. Median CD34+ infused was $4{,}1x10^6$/kg (range 1,5-14) and median CD3 + $41{,}2x10^6$/Kg (range 19-81). 15/17 patients engrafted for neutrophil at a median time of 17 days (range 12-25), 1 patient (6%) died for septic shock during aplasia and 1 child (6%) experienced primary graft failure (GF), successfully rescued with a second haplo-HSCT performed at day +45. Cumulative incidence of any grade acute GvHD (aGvHD) was 49,2% (95% CI, 29,9-80,9) and grade II-IV acute aGvHD was 24,4% (95% CI, 10.4-57.4). Only 2 patients (13%) had grade III, both with gut involvement, no one grade IV. Cumulative incidence of cGvHD was 23,6% (95% CI, 8,7-64,3). Patients developing cGvHD presented moderate skin involvement, managed with steroids and ruxolitinib, and all are now disease free. No veno-occlusive disease cases were registered. There were 3 cases of bacteremia during aplasia, of which only one above-mentioned septic shock. Most frequent complications were non-severe viral infections (9 cases of CMV reactivations, 4 BK cystitis, 2 EBV reactivations without PTLD, and 2 HSV-1 reactivations). No fungal infections were registered. Two children relapsed (one was not in CR at HSCT) and later died for disease progression. Fourteen patients are alive in CR with a median time to HSCT of 553 days. With a median follow-up of 397 days, the overall survival rate is 75,5% (95% CI, 50,6-100,0), event-free survival rate is 74,3% (95% CI, 52,2-83,4), and transplant related mortality rate is 5,6% (95% CI, 8,7-64,3).

Table 1: Single-patient transplant characteristics.

#Case	Recipient sex	Disease	Age at HSCT (y)	Disease state at HSCT	Donor sex	Conditioning
1	M	B-ALL	14	CR2	F	Bu, Thio, Cy
2	M	AML	7	CR1	M	Treo, Thio, Flu
3	F	B-ALL	7	CR2	F	Bu, Thio, Flu
4	M	B-ALL	8	CR2	F	Bu, Thio, Flu
5	M	AML	15	Non CR	M	Bu, Thio, Flu
6	F	AML	15	CR2	F	Bu, Thio, Flu
7	M	ALL	18	Non CR	F	Treo, Thio, Flu
8	F	AML	1	CR1	F	Bu, Cy, Mel
8 rescue	F	AML	1	CR1	M	Thio, Flu, ATLG
9	F	T-ALL	12	CR1	F	Bu, Thio, Flu
10	F	AML, therapy related	11	CR1	F	Bu, Thio, Flu
11	F	AML	18	CR1	M	Treo, Thio, Flu
12	M	AML	17	CR1	M	Bu, Thio, Flu
13	M	AML	12	CR2	M	Bu, Thio, Flu
14	M	AML	8	CR2, MRD < 10^{-3}	M	Bu, Thio, Flu
15	M	B-ALL	5	CR2	F	TBI, Flu
16	F	AML, therapy related	7	CR1	F	Bu, Thio, Cy
17	M	ETP-ALL	13	CR1	F	TBI, Flu

ATLG Anti-T-LymphocyteGlobulin, *Bu* Busufan, *Cy* Cyclophosphamide, *Mel* Melphalan, *MRD* MinimalResidualDisease, *TBI* Total Body Irradiation, *Thio* Thiotepa, *Treo* Treosulfan, *Flu* Fludarabine.

Conclusions: PTCy haplo-HSCT is a safe and effective transplant platform for children with acute leukemia, with acceptable rates of

GF and GvHD, low rates of severe aGvHD and low burden of severe infections. Viral reactivations are most frequent complications. Low rates of relapse have been registered even with high proportion of heavily pre-treated patients. Expanding experience of pediatric centers may confirm the value of this transplant platform in pediatric acute leukemia.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P630

HEMATOPOETIC STEM CELL TRANSPLANTATION IN INBORN ERRORS OF METABOLISM - POLISH EXPERIENCE

Anna Fałkowska[1,2], Aleksandra Bachnacka[1], Monika Mielcarek-Siedziuk[3], Jowita Frączkiewicz[3], Joanna Bladowska[3], Maksymilian Deręgowski[4], Jolanta Goździk[5], Katarzyna Urbańska[2], Jacek Wachowiak[4], Krzysztof Kałwak[3], Katarzyna Drabko[1,2]

[1]Children's University Hospital, Lublin, Poland, [2]Medical University of Lublin, Lublin, Poland, [3]Wrocław Medical University, Wrocław, Poland, [4]Poznan University of Medical Sciences, Poznań, Poland, [5]Jagiellonian University Medical College, Kraków, Poland

Background: According to EBMT survey data in 2019, 5% of allo-HSCT in children were performed due to inborn errors of metabolism (IEM). Our Polish data indicate that out of 2392 allo-HSCT performed in our country in all pediatric centers only 75 (3%) were done for IEM. We aimed to analyze retrospectively the results of all reported 75 HSCT in 66 children with IEM performed in years 2001-2022 in four Polish transplantation centers.

Methods: The indications for HSCT included: adrenoleukodystrophy (25 patients), mucopolysaccharidosis type I (13 patients), osteopetrosis (11 patients), mucopolysaccharidosis type II (7 patients) and other (not standard) IEM (19 patients). The median of recipient's age at the moment of HSCT was 42 months. The conditioning regimen was myeloablative (busulfan based) in half of the cases and the other half received treosulfan based reduced toxicity conditioning with few non-myeloablative regiments used for second transplant in 7 procedures. In 52 cases stem cells were collected from matched unrelated donor (MUD), in 12 cases from matched sibling donor (MSD) and 6 donors were mismatched. The most common stem cell source was peripheral blood (40 procedures). The median number of transfused CD34 cells was 6,8 x 10^6 per kilogram of patient's bodyweight.

Results: The median of post-transplant follow-up in our study was 3 years (6 months – 17 years) Overall survival of entire group was 0,8 and was significantly higher in patients transplanted after 2010 ($n = 42$) as compared to children who had HSCT between 2001 and 2010 (0,88 vs 0,61 respectively, $p = 0,02$). There was a trend towards better OS in patients: transplanted for standard indications as compared to not standard (0,83 vs 0,72); receiving treosulfan based regimen as compared to full busulfan based or non-myeloablative and for bone marrow as the stem cell source as compared to peripheral blood or cord blood - however these differences were not statistically significant. Fourteen children died: 4 pts (X-ALD) form progression of disease and 10 pts (2 osteopetrosis, 1 MPS type I, 2 MPS type II, 5 non-standard indications) from transplant related complications.

Conclusions: Fewer patients with IEM, especially with indication considered as standard of care, are referred to transplantation in Poland as compared to majority European countries. Overall survival is comparable to published data especially in recent 10 years. All survived MPS patients do not require enzyme replacement therapy.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P631

USE OF LIVER POINT SHEAR WAVE ELASTOGRAPHY (PSWE) IN THE DIAGNOSIS OF SINUSOIDAL OBSTRUCTION SYNDROME IN CHILDREN

Blanca Molina[1], Teresa Cañas[1], Sara Vinagre[1], Olga Suarez[1], Isabel Rozas[1], Marta Escribano[1], Marta Gonzalez Vicent[1]

[1]Niño Jesus Hospital, Madrid, Spain

Background: Veno-occlusive disease or sinusoidal obstruction syndrome (SOS) is a potentially life threatening complication affecting patients undergoing hematopoietic stem cell transplantation (HSCT). Early treatment with Defibrotide has proved to increase survival. Therefore, an early diagnosis is essential. Ultrasound elastography are noninvasive techniques that measure tissue stiffness. They are used in the diagnosis of hepatic fibrosis in patients with chronic hepatopathy resulting from virus C and B, but nowdays we don't know the utitlity of liver point shear wave elastography (pSWE) in the diagnosis of pediatric SOS.

Methods: A retrospective study was carried out in Niño Jesus Hospital from Madrid between March 2018 and November 2021. We have reviewed the medical data of 127 patients under 21 years of age who underwent an HSCT. In 46 pediatric patients SOS were suspected. The median age was 8 years (1-20), 33 were male and 13 were female. Most of patients were diagnose with a malignant disease (35) and 11 patients had a non malignant disease. All patients except two, received an allogeneic transplantation. The diagnosis of SOS was confirmed in 31 patients, using the European Society for Blood and Marrow Transplantation diagnostic criteria for pediatric population. Abdominal ultrasound and liver pSWE were performed before the HSCT and after, when SOS was suspected.

Results: Liver stiffness in the suspicion moment was higher in the patients who were diagnosed of SOS, and these values increased compared to the pre-transplantation study (Table 1). A cut-off value of 1,37 m/s has been established for the diagnosis of SOS, with an area under the curve of 0,779 (IC 95% 0,61-0,93).

Patients with SOS		**Patients without SOS**	
Pretransplant elastography (median, range)	Postransplant elastography (median, range)	Pretransplant elastography (median, range)	Postransplant elastography (median, range)
m/s	m/s	m/s	m/s
1,20 (0,94-1,40)	1,25 (1,05-3,40)	1,14 (0,93-1,90)	1,43 (1,11-3,06)

Conclusions: In conclusion, liver pSWE type elastography is a useful technique for the early diagnosis of pediatric SOS that, being integrated into the ultrasound equipment, has the advantage that it allows two studies to be carried out in a single examination. SOS patients have higher VC values than patients without SOS and these values rise before ultrasound findings appear.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P632

SALVAGE TREATMENT OF PROGRESSIVE SEVERE CHRONIC GRAFT-VERSUS-HOST DISEASE BY IMMUNE ABLATION AND STEM CELL RESCUE IN 2 PEDIATRIC PATIENTS

Jaspar Kloehn[1], Anne Kruchen[1], Kerstin Schütze[1], Katharina Wustrau[1], Johanna Schrum[1], Ingo Müller[1]

[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Chronic Graft-versus-Host Disease (cGvHD) remains one of the leading causes of non-relapse mortality in patients after HSCT, for which there is no standard therapy.

Methods: We report 2 children with severe steroid-refractory (SR)-cGvHD in which several lines of immunosuppressive and biological treatment failed. However, we applied immunoablative therapy (IAT) with re-transplantation of purified $CD34^+$ donor stem cells to reset the aberrant immune system. The modified criteria of the National Institutes of Health were used to diagnose and score cGvHD. The concept of IAT with following stem cell rescue included mobilization with cyclophosphamide (1 x 2 g/m^2) and granulocyte colony-stimulating factor (5 x 15 µg/kg/d) in preparation for stem cell apheresis. After stem cell apheresis, we administered 3 further pulses of cyclophosphamide at a dose of 1.5 g/m^2 because of minor clinical improvement. The IAT consisted of antithymocyte globulin Grafalon® (4 x 15 mg/kg), cyclophosphamide (2 x 60 mg/kg) and fludarabine (4 x 40 mg/m^2). To assess the T cell receptor repertoire, Vβ spectratyping of peripheral blood T cells was carried out. V_β-Spectratyping was performed by PCR amplification of CDR3 regions followed by fragment analysis.

Results: Patient 1 represents an 8 years old girl with early relapse of B precursor ALL. She underwent HSCT from a matched sibling donor (Table 1). 13 months after HSCT, severe sclerodermatous SR-cGvHD was diagnosed. Different therapeutic approaches with methylprednisolone pulses, infliximab, adalimumab, ofatumumab, ruxolitinib, pentostatin, sirolimus and extracorporeal photopheresis remained ineffective. After the stem cell rescue, the patient showed stable engraftment on day 9. There was a complete response of cGvHD. The immune reconstitution proceeded well. Before IAT, V_β-Spectratyping of peripheral blood T cells showed oligoclonal V_β usage under active cGvHD and immunosuppressive therapy. After IAT, T cells developed polyclonal V_β usage (Figure 1). We could discontinue the immunosuppressive treatment on day 203. Only mild reactivation of cytomegalovirus occurred after IAT. As a side effect of long-term therapy with steroids, the patient developed osteonecrosis.

Patient 2 is a 16 years old boy with BCR/ABL positive common ALL who underwent HSCT from a matched unrelated donor (Table 1). He developed severe sclerodermatous SR-cGvHD 6 months after HSCT. Despite the application of methylprednisolone pulses, cyclosporine A, imatinib, ruxolitinib and extracorporeal photopheresis, the cGvHD progressed. After stem cell rescue, the patient engrafted on day 10 and showed partial response of cGvHD. Epstein-Barr virus reactivation occurred as an IAT-related complication. The patient remains limited but cGvHD progress has been stopped until today. Patient 2 has too few T cells for a meaningful V_β-Spectratyping.

Characteristics	Patient 1	Patient 2
Age (years)	12	16
Sex	female	male
Diagnosis	B precursor ALL	common ALL
Donor of initial HSCT	MSD (brother)	MUD
Stem cell source	bone marrow	peripheral blood
Conditioning	TBI, VP-16	TBI, VP-16, ATG
GvHD prophylaxis	cyclosporine A	cyclosporine A, methotrexate
cGvHD scoring before IAT	skin: 3, joints and fascia: 3, lungs: 2, eyes: 1	skin: 3, joints and fascia: 3, lungs: 2, eyes: 1
$CD34^+$ content of stem cell rescue	2.05 x 10^6/kg	2.4 x 10^6/kg
Engraftment after IAT	leucocytes > 10^9/l since day 9thrombocytes > 20 x 10^9/l since day 11	leucocytes > 10^9/l since day 10thrombocytes > 20 x 10^9/l since day 11
Response to IAT	complete response	partial response
cGvHD scoring after IAT	skin: 0; joints and fascia: 0; lungs: 2 (residuum of cGvHD); eyes: 0	skin: 2; joints and fascia: 2; lungs: 2; eyes: 0
Virus reactivation	CMV	EBV
Immunosuppression after IAT	discontinued on day 203	low dose methylprednisolone (0.1 mg/kg/d)
Last follow-up	day 759 after stem cell rescue	day 308 after stem cell rescue

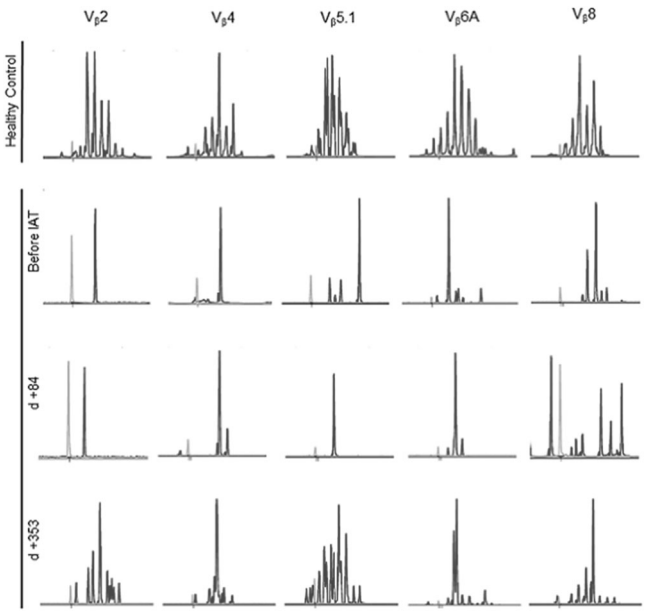


Figure 1: Vβ-spectratyping in patient 1

Conclusions: Two patients with life-threatening SR-cGvHD clearly benefitted from IAT with following re-transplantation of stem cells, while previous long-term immunosuppressive and biological treatment failed. Until now, this concept has only been a therapeutic option in some refractory autoimmune diseases. More data is needed to re-evaluate the usage in SR-cGvHD.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P633

SOLUBLE THROMBOMODULIN IS ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION AFTER PEDIATRIC MYELOABLATIVE HSCT

580

Denise Elbæk Horan[1,2], Katrine Kielsen[1,2], Marianne Ifversen[1], Claus H. Nielsen[2], Lars P. Ryder[1], Pär I. Johansson[1], Klaus Müller[1]

[1]Copenhagen University Hospital Rigshospitalet, Copenhagen OE, Denmark, [2]Institute for Inflammation Research, Copenhagen OE, Denmark

Background: Allogeneic HSCT is limited by acute toxicities including sinusoidal obstruction syndrome (SOS), capillary leak syndrome (CLS) and acute graft-versus-host disease (aGvHD). These complications are thought to be initiated by a dysfunctional vascular endothelium, although the pathophysiology remains poorly understood.

Soluble thrombomodulin (sTM) has been associated with development of SOS, CLS, sepsis and steroid refractory aGvHD after HSCT in minor cohorts of primarily adults. To further investigate the potential role of sTM in these non-infectious toxicities in children we investigated sTM levels in a large pediatric cohort.

Methods: We included 113 children undergoing myeloablative HSCT from 2010-2019 at the national transplantation center in Copenhagen, Denmark. Median age was 9.0 years (range: 1.1-17.6), and 61.1% were transplanted for malignant diagnoses. All patients received myeloablative conditioning based on either TBI ($n = 27$), busulfan ($n = 50$) or other chemotherapy ($n = 36$). Donors were matched siblings ($n = 33$) or matched unrelated donors ($n = 80$), and grafts were either BM ($n = 108$) or PB ($n = 5$).

Plasma levels of sTM were measured with ELISA prior to conditioning at the day of HSCT and at day +7, +14, +21, +30, +90 and +180 post-transplant.

Results: sTM levels increased significantly from pre-conditioning levels to day 0, peaked at day +30 and remained elevated until day +180 post-transplant (all $p < 0.05$). High sTM levels before the start of conditioning were associated with younger age (r = -0.2, $p = 0.05$). Patients receiving busulfan had significantly elevated sTM levels from day +7 to +21 compared with non-busulfan regimens (day +7: 5.0 ng/mL vs. 7.6 ng/mL, all $p < 0.05$).

Fifty-one children (45.1%) were diagnosed with SOS using the pediatric EBMT criteria at median day +7 (range: 2-58). Patients with SOS of any grade had significantly increased sTM levels at day +7 and +14. In a logistic regression analysis, high levels of sTM at day +7 (OR = 1.53, p = 0.019) and busulfan-based conditioning (OR = 5.75, $p = <0.0001$) were associated with SOS. In a multivariable analysis, high levels of sTM remained associated with SOS after adjustment for malignant diagnosis (OR = 1.43 pr. quartile, $p = 0.046$), but lost significance when adjusted for busulfan-based conditioning.

Fifteen patients (13.3%) diagnosed with CLS had increased sTM levels at day +7. In a logistic regression analysis, children with increasing levels of sTM had increased risk of CLS (OR = 1.88, $p = 0.025$), while no transplant characteristics including conditioning chemotherapy were associated with development of CLS.

sTM levels were significantly increased at day +14 in eight patients diagnosed with aGvHD grade III-IV vs. 0-II (6.7 ng/mL vs 6.3 ng/mL, $p = 0.05$). These results were confirmed in a multivariable logistic regression analysis with adjustment for ATG (OR = 2.71 pr. quartile, $p = 0.033$).

Conclusions: This study confirms that elevated levels of sTM early post-transplant are associated with SOS, CLS and aGvHD in a large single-center cohort of children undergoing HSCT. This suggests that conditioning-induced endothelial damage with activation of anti-thrombotic mechanisms play a key role in the pathogenesis of these complications. Further, the data suggest that sTM may prove useful as a biological marker for treatment-related complications and could help to guide treatment.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P634

REAL-TIME TREOSULFAN PHARMACOKINETICS FOR SCID INFANTS IDENTIFIED BY NEWBORN SCREENING

Sebastian Rosser[1,2], Christa Nath[2,1], Andrew McLachlan[1], Jason Chung[2,1], Peter Shaw[2,1], Melissa Gabriel[2], Steven Keogh[2]

[1]University of Sydney, Sydney, Australia, [2]The Children's Hospital at Westmead, Sydney, Australia

Background: The introduction of newborn screening (NBS) for identification of SCID in New South Wales, Australia, has allowed development of a platform for early HSCT based on treosulfan and fludarabine conditioning. A cumulative treosulfan exposure (AUC) of 4,800 (range 3,800 – 6,000) mg*h/L when combined with fludarabine has been proposed for this cohort, and we aimed to evaluate the feasibility of performing real-time treosulfan pharmacokinetics for SCID infants and determine the necessity of daily dose adjustment.

Methods: Five infants (ages 3 – 8 months) diagnosed with SCID by NBS underwent HSCT. Patients were conditioned with treosulfan (three doses once-daily, 10 – 12 g/m^2, subject to dose adjustment), fludarabine (cumulative 150 mg/m^2), and either alemtuzumab (cumulative 0.3 – 1 mg/kg) or ATG (Grafalon) (cumulative 15 mg/kg) prior to HSCT. Two infants with RAG1 deficiency also received thiotepa conditioning. Seven blood samples were collected at timed intervals after infusion and measured on the same day using high performance liquid chromatography. Treosulfan clearance and AUC was evaluated using Kinetica v4 non-compartmental analysis software and reported to clinical staff prior to preparation of the next dose.

Results: Table 1 provides details on daily and cumulative treosulfan AUC for five SCID infants in addition to an extrapolated cumulative AUC from a BSA-guided dose.

Infant A was 87 days old at transplant and received 10 g/m^2 treosulfan, with no requirement for dose adjustment. Infant A is currently 10 months post-transplant and D + 30 whole blood chimerism was 93%. Low T-cell chimerism at D + 100 was observed due to EBV reactivation, but recovered after rituximab.

Infant B was 121 days old at transplant and received an initial dose of 12 g/m^2 treosulfan, with dose adjustments on days 2 and 3. A BSA-guided dose of 10 g/m^2 would not have required dose adjustment. Infant B is currently 6 months post-transplant. D + 100 sorted chimerism was >83% for T, B, NK and granulocyte cell lines.

Infant C was 118 days old at transplant and received an initial dose of 12 g/m^2, with dose adjustments on days 2 and 3. A BSA-guided dose of 10 g/m^2 would achieve an extrapolated AUC > 6,000 mg*h/L, requiring dose adjustment. Infant C is currently 6 months post-transplant with complete donor T-cell chimerism and low B and granulocyte chimerism.

Infant D was 94 days old at transplant and received 10 g/m^2 treosulfan, with no requirement for dose adjustment. Infant D is currently 2 months post-transplant, with no chimerism data currently available.

Infant E was 241 days old at transplant and received 12 g/m^2 treosulfan with no requirement for dose adjustment. A BSA-guided dose of 10 g/m^{2}would have achieved an extrapolated AUC of <3,800 mg*h/L, requiring dose adjustment. Infant E is currently 1 month post-transplant, with no chimerism currently available.

Table 1

	Infant A	Infant B	Infant C	Infant D	Infant E
Conditioning regimen	Treosulfan/fludarabine			Treosulfan/ fludarabine/ thiotepa	
Day 1 dose (g) [1]	3.0	3.6	3.4	3.3	5.0
Day 1 clearance (L/h)	2.3	1.6	1.4	1.9	3.5
Day 1 AUC (mg*h/L)	1,304	2,223	2,512	1,740	1,428
Day 2 dose (g)	3.0	2.6	2.2	3.3	5.0
Day 2 clearance (L/h)	2.1	1.8	1.3	1.7	3.9
Day 2 AUC (mg*h/L)	1,406	1,468	1,645	1,913	1,281
Day 3 dose (g)	3.0	3.2	2.0	3.3	5.0
Day 3 clearance (L/h)	2.1	1.7	1.5	1.8	3.2
Day 3 AUC (mg*h/L)	1,406	1,869	1,346	1,804	1,552
Cumulative AUC (mg*h/L)	4,116	5,560	5,503	5,457	4,284
Cumulative AUC without dose adjustment	4,116	6,368	7,310	5,457	4,284
Dose if BSA-guided dosing was used (g) [2]	3.0	3.0	2.8	3.3	2.9
Extrapolated cumulative AUC for BSA-guided dosing (mg*h/L) [3]	4,116	5,261	6,138	5,457	3,589

[1]Initial treosulfan dose was based on an age-guided criteria: for patients <3 months: 10 g/m^2;≥3 months and <12 months: 12 g/m^2
[2]BSA-guided dosing criteria: BSA < 0.5 m^2: 10 g/m^2; ≥0.5 m^2 and <1.0 m^2: 12 g/m^2
[3]Extrapolated cumulative AUC was calculated by dividing the BSA-guided dose by the daily pharmacokinetic clearance and summing the values.

Conclusions: Treosulfan cumulative exposure was within the proposed therapeutic range for all infants, but dose adjustment was required in two cases. The current data shows significant intra-patient and inter-occasion variability in treosulfan pharmacokinetics that suggests pharmacokinetic monitoring may be needed to avoid high exposure, although optimisation of a weight or BSA-based dose may be sufficient.

Clinical Trial Registry: This study was registered with the Australian Clinical Trials Registry (registration number: ACTRN12615000038594)

Disclosure: Nothing to declare.

18 - Paediatric Issues

P635

THE EFFECT OF HLA B-LEADER, AND HLA DQ HETERODIMERS MATCHING IN PEDIATRIC HAPLOIDENTICAL STEM CELL TRANSPLANTATION IN ACUTE LEUKEMIA; RETROSPECTIVE SINGLE CENTER ANALYSIS

Mohammed Essa[1,2,3], Rodaina Abujoub[1], Abdulrahman Alsultan[4], Shahbaz Memon[1], Nada Alshaikh[1], Ali Hajeer[5,2]

[1]King Abdullah Specialist Children Hospital, Riyadh, Saudi Arabia, [2]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [3]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, [4]King Saud University, Riyadh, Saudi Arabia, [5]King Abdulaziz Medical City - MNGHA, Riyadh, Saudi Arabia

Background: Selection of family haploidentical donors is usually based on the patients' status of donor specific antibodies (DSA), Donors' age and gender, blood group matching, CMV status in addition to the degree of HLA matching disparity. The effect of DPB1 T-cell eptitope, HLA B-leader, KIR-Ligand, and HLA DQ heterodimers matching have been described and published in recent years. Our retrospective study aimed to identify the outcome of haploidentical HSCT including relapse and GVHD.

Methods: All pediatric patients less than 14 years of age with malignant diseases who underwent T cell replete HLA haploidentical HSCT using PT-CY approach were included and the data were retrieved and described including demographics, disease, conditioning regimens HLA typing, Gender, DPB1 T cell eptitope, HLA B-leader, KIR-Ligand, and HLA DQ heterodimers matching and their effect using the following website:https://www.ebi.ac.uk.

Results: A total of 19 patients (10 ALL and 9 AML/MDS/JMML) underwent HSCT. Patient and transplant characteristics are shown in the Table. All patients had no DSA,5 had ABO mismatch donor, 10 had gender mismatch donors and the median donor age was 20 years (4-40). The details of DPB1 T cell eptitope, HLA B-leader, KIR-Ligand, and HLA DQ heterodimers matching are demonstrated in the Table. All patients engrafted successfully 4 patients with ALL developed disease relapse, 2 of them received CART therapy. One patient with AML died from severe infections and cGVHD. 3 patients with ALL died from VOD, CMV infection and relapse respectively. Out of the population 2 patients developed aGVHD, 3 patients developed cGVHD and 1 patient developed developed both aGVHD and cGVHD. There was a trend towards Relapse in patients with (patient and donor) HLA DQ-G1G1 in contrast to patients who developed GVHD who had HLA DQ G1/G2 heterodimers and HLA-B leader mismatching containing M genotype. refer to the table for details.

Feature	**(n = 19) Median (range) or N (%)**	
Age (years)	8.25 (1.9-14)	
Gender (F/M)	6/13	
Diagnosis:ALL/AML or MDS or JMML	10/9	
Conditioning regimen: TBI /non-TBI based	12/7	
Relapse	4 (0.21)	
GVHD: Acute GVHD Grade I-IV/ Chronic GVHD	6 (4/3) (0.32)	
Outcome : Alive	15 (0.79)	
Follow up duration (days)	964 (245-2441)	
Donor	**Relapse/Total N (%)**	**GVHD/Total N (%)**
Patient: DQ G/ G		
G1/G1	**3/7 (0.42)**	1/7 (0.14)
G1/G2	1/9 (0.11)	**4/9 (0.44)**
G2/G2	0/3 (0)	1/3 (0.33)
Donor: DQ G /G		
G1/G1	**3/9 (0.33)**	2/9 (0.22)
G1/G2	1/10 (0.1)	**4/10 (0.4)**
G2/G2	0 (0)	0 (0)
B-leader Patient		
TT	3/12 (0.25)	4/12 (0.33)
MT	0/4 (0)	1/4 (0.25)
MM	1/3 (0.33)	1/3 (0.33)
B-leader Donor		
TT	1/6 (0.16)	1/6(0.16)
MT	2/8 (0.25)	**3/8 (0.37)**
MM	0/1 (0)	1/1 (1)
missing	1/4 (0.25)	1/4(0.25)
B leader Matching		
TTT	1/4 (0.25)	1/4 (0.25)

Feature	(n = 19) Median (range) or N (%)	
TMT	1/4 (0.25)	**2/4 (0.5)**
MTM	1/7(0.14)	2/7 (0.28)
missing	1/4 (0.25)	1/4 (0.25)
DPB1 T-Cell Epitope		
Permissive	2/8 (0.25)	2/8 (0.25)
Non-permissive	1/4 (0.25)	**2/4 – (0.5)**- 1 moderate
missing	1/7 (0.14)	2/7 – (0.28) - 1 severe
KIR MM GVH -B		
Matched	4/16 (0.25)	5/16 (0.31)
Mismatched	0/3 (0)	1/3 (0.33)
KIR MM GVH- C		
Matched	3/12 (0.25)	4/12 (0.33)
Mismatched	1/7 (0.14)	2/7 (0.28)

Conclusions: The outcome of haploidentical HSCT in our center is comparable to international data. Patients with AML had better disease free outcome compared to ALL patients. HLA DQ heterodimers and HLA B-leader mismatching had a trend towards influencing the rate of GVHD and relapse more than KIR-Ligand, and DPB1 T cell eptitope matching in this study however further studies and statistical analysis are needed in a larger population in our region to evaluate these findings.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare from all authors.

18 - Paediatric Issues

P636

ASSESSMENT OF KIDNEY FUNCTION USING DIFFERENT ESTIMATED GLOMERULAR FILTRATION RATES DURING PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Karin Melanie Cabanillas Stanchi[1], Jean Arturo Cabanillas Stanchi[1], Paul Grimm[1], Melanie Gansel[1], Veronika Schneider[1], Nora Rieflin[1], Stefanie Joachim[1], Judith Feucht[1], Sven Oberwegner[1], Nikolai Schleicher[1], Sebastian Michaelis[1], Michal Abele[1], Jana Dornhan[1], Lena Gruber[1], Antonia Däschle[1], Léa Thérond[1], Pia Glogowski[1], Christian Seitz[1], Michaela Gessner[1], Kathrin Buder[1], Markus Weitz[1], Peter Lang[1], Rupert Handgretinger[1], Michaela Döring[1]

[1]University Children's Hospital Tübingen, Tübingen, Germany

Background: Renal function is one of the major factors in decision making regarding the choice of regimen and dosage of conditioning chemotherapy during hematopoietic stem cell transplantation (HSCT). Accurate and reliable determination of renal function is therefore important to detect renal impairment at an early stage and to adjust the therapeutic regimen, if necessary. Estimated glomerular filtration rate (eGFR) equations commonly used are primarily based on the measurement of serum creatinine and cystatin C. However, these are inaccurate under certain circumstances, e.g. during malnutrition, muscle wastage or in certain age groups. Currently, there are few data on the course of renal function during pediatric HSCT.

Methods: In this monocentric prospective study, 130 pediatric patients who underwent allogeneic or autologous HSCT between 2018 and 2022 were enrolled and their data analyzed at the following observation days: at in-patient admission before the start of conditioning (baseline), day -5 before HSCT, day 0 (day of HSCT), day +7, +14, +21, +30, +60, +100, +150, and +200 after HSCT. We analyzed parameters for determination of renal function from urine (e.g. creatinine, α1-microglobulin, α2-macroglobulin, electrolytes), the serum (e.g. cystatin C, creatinine), creatinine-clearance (24h urine collection), and the eGFR as determined using different formulas: the updated Schwartz equation (considering patient height and serum creatinine), the updated Schwartz-III equation (considering patient height and gender, serum creatinine, serum urea, serum cystatin C) as well as the Schwartz-sCysC equation (considering serum cystatin only).

Results: A total of 130 pediatric patients with a median age of 8.0 years (range 0.1-17.8 years), 50% females, 102 allogeneic (78%) and 28 autologous (22%) HSCTs were studied. Patients received volume therapy between baseline and day +1 after HSCT at 3,000 mL/m^2 body surface area/day. A transient increase in α1-microglobulin (max day +21: mean 56.1 ± 8.2 mg/L), magnesium (max day +21: 3.2 ± 0.2 mmol/L), calcium (max day +21: 2.7 ± 0.2 mmol/L), and protein/creatinine quotient (max day +21: 152 ± 19.6 mg/mmol) was detected in urine. In serum, cystatin C (minimum day +7: 0.91 ± 0.03 mg/L), creatinine (min day +7: 0.36 ± 0.02 mg/dL), and uric acid (min day +7: 2.0 ± 0.7 mg/dL) transiently decreased, whereas urea increased (max day +14: 37.5 ± 3.7 mg/dL). The eGFR increased from baseline before the start of conditioning (e.g. eGFR-Schwartz-III: mean 120 ± 3 mL/min/1.73m^2) and peaked until day 0 (mean 131 ± 4 mL/min/1.73m^2) and then constantly decreased until day +200 (91 ± 4 mL/min/1.73m^2) significantly ($p < 0.0001$) below the baseline level. Creatinine clearance showed the same course (baseline: 104 ± 7; peak day 0: 112 ± 7; day +200: 73 ± 12 mL/min ($p < 0.0001$ vs. baseline)). Of all the eGFR equations used, the Schwartz-III equation showed the closest fit with the creatinine clearance.

Conclusions: The results suggest persistent impairment of the kidney function after conditioning therapy. The increase in renal function parameters around day 0 are consistent with the volume therapy. In the course thereafter until the end of the observation period, however, there is a deterioration of renal function below the baseline level. The Schwartz-III equation appears to describe renal function most reliably in this patient population.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare.

18 - Paediatric Issues

P637

DEVELOPMENT OF SEIZURES IN CHILDREN UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Iván López Torija[1], Eulalia Turón Viñas[1], Elisabet Coca Fernández[1], Pablo Escribano Sanz[1], Sara Redondo Velao[1], Montserrat Torrent Español[1], Isabel Badell Serra[1], Susana Boronat[1]

[1]Hospital Santa Creu i Sant Pau, Barcelona, Spain

Background: Neurological complications can reach from 11 to 59% of the patients under hematopoietic stem cell transplantation (HSTC), with consequences such ar death in 9 to 17% of the cases.

The objective of the present study is to describe the development of seizures in children under HSCT, their associated risk factors, etiology and prognosis.

Methods: A total of 178 HSCT in 155 pediatric patients (89 males, with an average age of 8.22 years) were included, in a retrospective observational study, between 2002 and 2018.

The 63,2% had neoplastic diseases and 36,8% of them non-neoplastic diseases. All HSCT were allogeneic; 37.6% were performed from related donors and 62.3% from unrelated donors. Only 25,8% were from HLA-identical related donors.

It should be noted that, 66,3% of the patients received myeloablative conditioning, and69 patients (44.5%) received busulfan (with phenytoin). The majority of children (98.7%) received cyclosporine at any point, either as prophylactic or treatment against GvHD.

We looked for the presence of a seizures during the study period, comprised between conditioning treatment period and 24 months after infusion. Patients with previous neurological involvement and those who underwent HSCT because of a symptomatic neurometablic disease were excluded. Seizures were diagnosed by means of clinical examination in most patients, and by ictal EEG if possible. A P-value ≤ 0.05 was considered statistically significant.

Results: Among the 155 patients, 27 (17.4%) developed seizures, of which 10 were consequently diagnosed with a central nervous system (CNS) infection, 5 with a vascular disease and 8 with drug toxicity. Three children were suffering, respectively, from a multiorgan failure, a hypertensive encephalopathy and a pre-engraftment syndrome, when they developed seizures. The last child was finally diagnosed with a febrile seizure.

Taking the total number of HSCT performed, prevalence of seizures in our series is 14.6%.

A statistically significant association was found between seizing and the type of HSCT performed (lower risk in familial identical donor, $p = 0{,}010$), the use of mycophenolate either in prophylactic or therapeutic use ($p = 0.043$ and 0.046, respectively), the use of steroids ($p = 0.023$), selective depletion of CD45RA+ ($p = 0.002$), the development of a pre-engraftment syndrome ($p = 0{,}007$), and the severity of the chronic GVHD ($p = 0{,}030$).

Children who developed seizures had a higher risk of CNS infection (odds ratio 37.25, IC95% 7.45-186.05) or vascular disease (odds ratio 12.95, IC95% 2.24-74.80).

Seizures predicted evolution to life-threatening complications and the need for admission to the Intensive Care Unit ($p < 0{,}001$) and higher mortality ($p = 0{,}023$). A statistically significant association was also found between seizures and sequelae in survivors ($p = 0{,}029$).

Overall survival was significatively lower in the group of patients who developed seizures $0.277 + 0.102$ while survival of the study population was $0.614 + 0.040$ at 10 years of follow-up.

Conclusions: Patients undergoing SCT from non-HLA-identical donors, especially if they suffer from chronic GvHD or pre-engraftment syndrome, have a statistically significant association with seizures in our series. These patients can develop life-threatening neurological conditions, as CNS infections (risk 37.25 times higher compared to children without seizures) or vascular disease (risk 12.95 times higher), and they can show greater morbidity and mortality.

Disclosure: No disclosure.

18 - Paediatric Issues

P638

NO DIFFERENCES IN EPIDEMIOLOGY AND IMPACT OF VIRAL INFECTIONS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION BETWEEN CHILDREN AND YOUNG ADULTS: A SINGLE CENTER EXPERIENCE

Manuela Spadea[1,2], Giulia Pruccoli[1,3], Raffaele Vitale[1], Valeria Ceolin[2,4], Vincenzo Apolito[2], Francesco Saglio[2], Franca Fagioli[1,2]

[1]University of Turin, Turin, Italy, [2]Regina Margherita Children's Hospital, Pediatric Oncohematology Stem Cell Transplantation and Cell Therapy Division, Torino, Italy, [3]Regina Margherita Children's Hospital, Infectious Diseases Unit, Torino, Italy, [4]Erasmus University MC, Rotterdam, Rotterdam, Netherlands

Background: Viral reactivations commonly occur after allo-HSCT and can cause severe complications. We aimed to explore any differences between children (< 12 y.o, C) and young adults (≥ 12y.o., AYA) in the epidemiology and impact of common opportunistic viral infections (CMV, EBV, BKV, adenovirus, HHV6, HSV-1) occurring within the first 100 days following allo-HSCT.

Methods: We retrospectively analyzed 96 (42M/54F) pediatric allo-HSCT, performed from January 2018 through August 2022, for infections with EBV, CMV, adenovirus, HSV-1, HHV-6, BKV. Median age at HSCT was 5,6y(IQR 18). 58C/38AYA were enrolled. Main indications for HSCT: acute leukemia (64%), myelodysplastic syndrome (20%). The remaining 15% covers other diseases of the hematopoietic system (severe aplastic anemia, hemoglobinopathies, inborn errors of metabolism, primary immunodeficiencies). Of the 81 patients suffering from malignant disease, 35.4% were in CR1, 19.8% in CR2. 14% of patients had an HLA-identical sibling donor (SIB); 67% an HLA-identical unrelated donor (MUD); 15% a haploidentical family member (HAPLO). The preferred stem cell source was bone marrow (BM, 60,5%), followed by peripheral blood stem cells (PBSC, 34.6%) and cord blood (CB, 5%). All patients received a myeloablative conditioning regimen (15% a RIC in the context of HAPLO). Serotherapy (ATG/ATLG) was administered in 68% of patients; all HAPLO underwent in vivo T-cell depletion by PT-CY. GVHD prophylaxis consisted mostly of cyclosporine (CSA) alone or with short-term MTX (SIB and MUD respectively); MMF and FK506 were used in HAPLO. All patients received acyclovir prophylaxis against CMV infection until discontinuation of immunosuppression, whereas none of them received letermovir (off label in our country for children). All patients but 4 engrafted. Cumulative incidence of acute GvHD was 31% (19% grade II-IV). Steroid therapy (PDN >1mg/kg/day) was administered in 50% of patients. OS of the entire population was 98% at 100 days, 94% at 1 year.

Results: We found 53/96 (55%) asymptomatic viral reactivations, 14/96 (15%) viral disease, 27/96 (28%) multiple viral infections. The viruses most encountered were CMV (42%), EBV (44%) followed by BK, HSV-1, adenovirus, HHV-6 for the remaining cases. Severe viral disease was rare (7/96); these patients died of PTLD (4/7) or MOF caused by systemic viral infection (3/7, adenovirus).

The overall survival for patients with multiple viral infections (OS 100%) and without multiple viral infections (OS 98%) at 100 days did not differ significantly.

No differences in epidemiology and impact between C and AYA were detected.

Ganciclovir/valganciclovir, foscavir, Rituximab, cidofovir/brincidofovir, immunosuppression withdrawal/tapering were the most employed therapies. None of our patients received cellular therapy.

Interestingly, higher age at HSCT, donor type, aGvHD, steroid therapy, in vivo T-cell depletion did not result as risk factors for viral infections in our population. However, patients who experienced asymptomatic viremia presented an earlier viral disease: 83 days [CI95% 74-91.5] *vs* 99 days [CI95% 97.5-100] (p.003) with 11.45 times higher global risk.

Conclusions: Our report highlights that viral infections do not differ between C and AYA for epidemiology and impact on transplant outcomes. Interestingly, this report strengthens the concept that MUD and haplo-HSCT are comparable with each other in the setting of all viral infections.

Clinical Trial Registry: not applicable

Disclosure: No conflict of interest to disclose.

18 - Paediatric Issues

P639

GRAFT FAILURE COMPLICATING ADENOVIRUS INFECTION: A UK NATIONAL EXPERIENCE

Shagun Shah[1], Kanchan Rao[2], Katharine Patrick[3], Oana Mirci-Danicar[4], Robert Wynn[1]

[1]Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust, Manchester, United Kingdom, [2]Great Ormond Street Hospital, London, United Kingdom, [3]Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom, [4]Bristol Royal Hospital for Children, Bristol, United Kingdom

Background: Reactivation of adenovirus is common in paediatric transplantation, especially when T-cell depleted and is an important cause of mortality. Treatment options include reducing immunosuppression and use of antiviral agents. We report graft failure as a previously little reported complication of adenovirus and its therapy in paediatric bone marrow transplant recipients.

Methods: This was a retrospective survey of all UK paediatric transplant centres in BSBMT. Paediatric patients who required a "top up" procedure for graft failure between 2010 and 2020 associated with adenoviraemia (greater than 10e3 copies/ml) were studied.

Results: There were 19 patients in total. Age at transplant ranged from 5 months to 19 years. Male:female ratio was: 1.7:1. 11 patients were transplanted for leukaemia, 4 for immunodeficiency, 2 for metabolic indications and 2 for non-malignant haematological conditions. They received FTT (Fludarabine, Treosulfan, Thiotepa) or TBI as myeloablative conditioning regimen and all had in vivo T-cell depletion with either Alemtuzumab or ATG. All patients had adenoviraemia within the first 3 months post-transplant. Of the total, 7 had primary graft failure and the remaining had secondary graft failure. 11 had adenovirus end organ disease involving gut (11), respiratory (5), bladder (1) or liver (1). All patients received cidofovir for their adenovirus treatment. 7 patients also had concurrent CMV reactivation and 3 had EBV reactivation.

All but one received CD34-selected top up grafts from mobilised PBSC. The CD34 cell count ranged from 3-15 x 10^6/kg. There was a persisting high level of adenoviraemia at the time of top up infusion in 4 patients, the rest had <1000 copies at the time.

Conclusions: Graft failure associated with invasive adenovirus is a significant problem in paediatric HSCT, especially in the T-cell depleted setting. Long term survival is possible with intensive antiviral therapy and with donor CD34 selected stem cells top up.

Disclosure: NOTHING TO DECLARE.

18 - Paediatric Issues

P640

MOBILISATION AND LEUKAPHERESIS FOR HAEMATOPOIETIC STEM CELL GENE THERAPY IN PAEDIATRICS INCLUDING INFANTS: A MULTIDISCIPLINARY STRATEGY FOR SUCCESS

Claire Horgan[1], Madeleine Powys[1], Kelly Watts[1], Jacques Diacono[1], Rebecca Sutton[1], Jayne Peters[1], Mercy Muzamhindo[2], Claire Donohue[1], Simon Jones[1], Robert Wynn[1]

[1]Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust, Manchester, United Kingdom, [2]NHS Blood and Transplant, Manchester, United Kingdom

Background: Autologous haematopoietic stem cell (HSC) gene therapy delivers supraphysiologic enzyme doses that better prevents disease progression than reverses established disease and can correct diseases refractory to allogeneic transplant. Early diagnosis and prompt access to gene therapy is imperative, especially in rapidly progressive diseases that involve the CNS such as metachromatic leukodystrophy (MLD) and mucopolysaccharidosis type IIIa (MPSIIIA), since there is a further obligate delay in enzyme-bearing cells reaching this compartment. Pre-symptomatic diagnosis is possible through newborn screening (NBS) but is only beneficial if autologous HSC can be harvested safely and successfully from young children as small as 5kg, and the genetically modified HSC infused before disease progression occurs.

Methods: A multidisciplinary team (MDT) comprised of experts in each of the steps necessary for the collection of adequate cells from children as small as 5kg is required to deliver a quality apheresate suitable for manufacturing a genetically modified HSC product. In our centre we have built an MDT that incorporates:

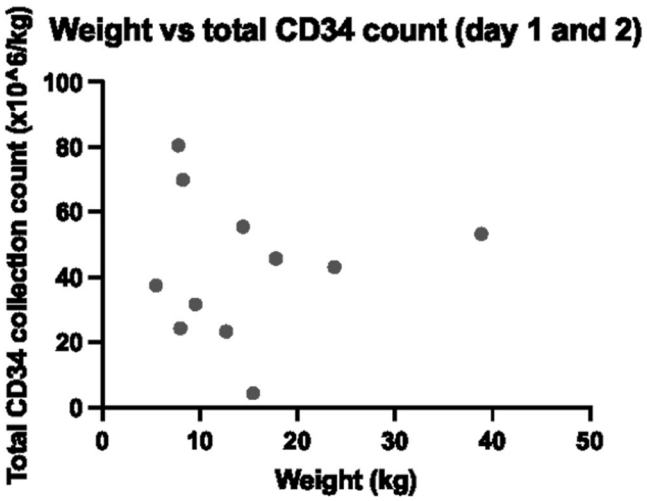
1. Metabolic diseases team- to identify suitable patients, including via NBS programmes
2. Transplant team- responsible for cell mobilisation protocols, and for the clinical care of the patient during mobilisation, leukapheresis, conditioning and reinfusion of the genetically modified HSC
3. An anaesthetic team- expert in the placement of temporary or permanent catheters and ensuring that these catheters permit adequate blood flow
4. A leukapheresis team- responsible for the collection of mobilised cells
5. A stem cell laboratory team- receives the apheresate, assesses its quality, cryopreserves as necessary the back-up cells, ships cells to the manufacturing facility, and receives back quality assured, genetically modified cells from that facility.

Results: 11 patients were apheresed for our stem cell gene therapy programme between (December 2018 and October 2022) including 6 patients with MPSIIIa, 2 with Gaucher's disease and 3 with MLD. Patient age ranged from 3.5 months to 11 years and weight from 5.52kg to 38.84kg (median 12.7kg, mean 20.8kg). The cohort included 5 patients who weighed less than 10kg at apheresis.

All patients were successfully mobilised with G-CSF and plerixafor (Table 1) and a suitable product for all patients was sent for gene therapy manufacturing. There was no correlation between weight and CD34 collection count (Figure 1) or age at mobilisation and CD34 collection count.

Table 1: Mobilisation and collection data

Indication	Baseline weight (kg)	Age at time of apheresis (years)	Day 5 (pre- 1st apheresis)		Total (over 2 days) CD34 collection (X10^6/kg)
			WCC (x10^9/l)	Abs CD34 count (viable cells) cells/ul	
MPSIIIa	17.8kg	2.41	37	166	45.68
MPSIIIa	9.54kg	1.32	48.7	212	31.68
MPSIIIa	8.25kg	0.57	48.1	332	69.89
MPSIIIa	12.7kg	1.81	37.9	306	23.37
MPSIIIa	7.8kg	0.38	61	620	80.57
MPSIIIa	15.45kg	1.68	39.1	100	4.37
Gaucher's	38.84kg	11.15	79	490	53.25
Gaucher's	14.4kg	2.89	64.7	285	55.45
MLD	7.66kg	1.02	48.4	240	24.4
MLD	5.52kg	0.30	106	500	37.51
MLD	23.78kg	6.72	70.1	145	43.16



Weight vs total CD34 count (x10^6/kg) over 2 day collection

Conclusions: We demonstrate and promote this successful multidisciplinary approach to mobilise, apherese and collect a CD34 stem cell product suitable for gene therapy manufacturing including very low weight and young individuals. Importantly, in this cohort of 11 patients, there were no significant issues with catheter dysfunction, and our data highlight that apheresis is feasible in very young and low weight children and is increasingly relevant as demand for such procedures is likely to increase in this evolving gene therapy era. This experience further strengthens the case for newborn screening programmes for diseases such as MLD, where stem cell gene therapy is licensed and efficacious, to ensure that patients can be diagnosed and treated in infancy before the onset of symptomatic clinical disease.

Disclosure: none of the authors have any conflict of interests related to this abstract.

18 - Paediatric Issues

P641

THE IMPACT OF RENAL ANOMALIES ON POST-HEMATOPOIETIC STEM CELL TRANSPLANTATION OUTCOME IN PEDIATRICS FANCONI ANEMIA

Amir Ali Hamidieh[1], Parisa Naji[1], Fahimeh Askarian[2,3], Nyasha Sandaramu[1], Leila Jafari[1], Fahimeh Jafari[1], Zeinab Nikfetrat[1], Maryam Behfar[1,4]

[1]Pediatric Cell and Gene Therapy Research Center, Gene, Cell and Tissue Research Institute, Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of, [2]Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of, [3]Pediatric Chronic Kidney Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of

Background: Fanconi anemia (FA), inherited bone marrow failure syndrome, affects not only the hematological system but also many other organs. The congenital abnormalities of the kidneys and the urinary tract (CAKUT) with 30% incidence amongst VACTERL-H association i.e., vertebral, anal, cardiac, tracheoesophageal fistula, esophageal atresia, renal, upper limb, and hydrocephalus, and PHENOS criteria i.e., skin pigmentation, small head, small eyes, nervous system, otology, and short stature, may influence hematopoietic stem cell transplantation (HSCT) outcomes, as the best potential treatment choice for hematologic manifestation; as well as raise renal complications possibilities post-transplant. Here, we aim to investigate the interrelations of CAKUT manifestation and renal complication i.e., acute kidney injury (AKI) within 30 days post-HSCT in a pediatric FA cohort.

Methods: We report on fifteen FA patients referred to Children's Medical Center from October 2020 to October 2022. The FA cytogenetic confirmatory was performed via chromosomal breakage analysis for all patients. HLA-matched sibling, other-related and unrelated donors were selected in five, seven, and three patients, respectively. Fourteen transplants utilized peripheral blood stem cell sources, while bone marrow in one case. A total body irradiation-free conditioning regimen consisting of oral Busulfan and Cyclophosphamide with or without rabbit Anti-Thymocyte Globulin was utilized. Patients received Cyclosporin A and a short course of Methotrexate as graft versus host disease (GvHD) prophylaxis regimen. All patients were examined in terms of CAKUT using an abdomen and pelvis computerized tomography scan pre-HSCT. Renal function was monitored pre- and during the first-month post-HSCT.

Results: The mean HSCT age of FA patients was nine years (range, 3 – 13) with nine females and six males. The mean age of donors was twenty-five years (range, 2 – 59). Eleven patients had normal kidneys and urinary tract, whereas four patients manifested CAKUT (ectopic kidney in two and horseshoe kidney in two). The mean number of injected MNC and $CD34^+$ was 7.2×10^8 cells/kg (range, 1.4 – 8.5) and 7.4×10^6 cells/kg (range, 2.5 – 10.3), respectively. All patients were efficaciously engrafted and ensued neutrophil and platelet in the median time of +11 (10 – 12) and +16 (15 – 20) days, respectively. The grade I-II and III-IV acute GvHD incidence rate was 45% and 18%, respectively. All CAKUT patients experienced grade I-II acute GvHD. Pre-HSCT median eGFR in patients without and with CAKUT was 98.21 ml/min/1.73m^2 (68.35 – 198.8), and 106.83 ml/min/1.73m^2 (90.75 – 128.33), respectively. Median eGFR in patients without and with CAKUT were 107.25 ml/min/1.73m^2 (85 – 147.12), and 99.99 ml/min/1.73m^2 (87.14 – 108.09) + 30 days post-HSCT.

Conclusions: There was a slight decrease in the median eGFR of the FA patients with CAKUT, but they had surprisingly clinically acceptable eGFR levels, showing that none of them had clinical manifestations of AKI. These data indicate that FA patients with CAKUT withstood the total body irradiation-free conditioning regimen resembling those without CAKUT and had similar successful HSCT outcomes.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P642

PEDIATRIC AUTOLOGOUS STEM CELL TRANSPLANTS: A SINGLE CENTRE EXPERIENCE

Ashutosh Walawalkar[1], Rajesh Patil[1], Ratna Sharma[1], Pranoti Kini[1], Amit Jain[1], Girish Chinnaswamy[2], Maya Prasad[2], Ram Gollamudi[2], Kalyani Patil[1], Sriraksha Ganiga[1], Krisha Shah[1], Mamta Manglani[1]

[1]MCGM - Comprehensive Thalassemia Care, Pediatric Hematology - Oncology & Bone Marrow Transplant Centre, Mumbai, India, [2]Tata Memorial Hospital, Mumbai, India

Background: Autologous Stem Cell Transplants (ASCT) is indicated in hematological malignancies such as relapse/refractory lymphomas and solid tumors e.g. High-risk Neuroblastoma (HR-NBL). We present the data on ASCT in pediatric patients at our centre.

Methods: We reviewed charts of 76 patients who underwent autologous transplants at our centre from August 2018 to December 2021. Age, gender, stem cell mobilization technique with processing (cryopreservation done with 10% DMSO), remission status pre-ASCT, conditioning regimens, toxicities and outcomes in these patients were analyzed. Survival was plotted using a Kaplan-Meier curve.

Results: Out of 76 patients evaluated, 52 (68.5%) were HR-NBL, 20 (26.3%) were relapsed/refractory lymphoma, 2 (2.6%) Relapsed Acute Promyelocytic Leukemia and 1 (1.3%) each of Ewing's Sarcoma and Metastatic Choriocarcinoma. The mean age was 3 years 9 months at the time of referral for HSCT (15 months – 18 years) with M:F ratio of 1.8:1. Peripheral blood was the graft source in all patients. Stem cell mobilization was done using a combination of GCSF + Plerixafor in 49 (64.4%) patients, GCSF alone in 25 (32.9%) patients, while 2 (2.7%) patients required chemo-mobilization. Busulfan + Melphalan was the conditioning regimen used in the majority of [47 (90.3%)] cases of HR-NBL, while in 5 (9.7%) patients Treosulfan + Melphalan was used. BEAM conditioning protocol was the standard protocol used in all cases of relapse/refractory lymphoma except 1 patient in whom TBC (Thiotepa, Busulfan, Cyclophosphamide) protocol was used in view of CNS Lymphoma. Busulfan + Cyclophosphamide was used for patients with Relapsed APML, Carboplatin + Etoposide was used for patient with metastatic choriocarcinoma and Treosulphan + Melphalan was used for patient with Ewing's Sarcoma. The median viability of cryopreserved stem cells before the infusion was 83% (55-99%). The Median CD34+ cell dose infused was 6.5 x 10^6 cells/kg (4.7-19.5). The median time to neutrophil engraftment was day+12 (10-16) and platelet engraftment was day+16 (6-36) Median time of follow-up was 18 months (1-39 months). Sinusoidal Obstruction Syndrome was noticed in 4 patients who improved on treatment and 1 patient developed status epilepticus with Acute Kidney Injury. A total of 40 patients from the cohort were alive and well post ASCT, while 3 patients relapsed after a median follow-up of 10 months (1–19 months) & were advised palliative care, remaining 33 patients expired. Relapse rates were as high as 36.8% in patients of HR-NBL and were the most common cause of death noticed in these patients.

Outcomes in HR-NBL			
Total N	**N of Events**	**N**	**Percent**
52	31	21	EFS: 40.4%
52	29	23	OS: 44.2%
Outcomes in Relapsed/Refractory Lymphoma			
Total N	N of Events	N	Percent
20	2	18	EFS: 90%
20	1	19	OS: 95%

Conclusions: ASCT is an option to improve outcomes in certain childhood malignancies like HR-NB and relapsed/refractory lymphomas. Combined treatment modalities along with targeted immunotherapy can achieve better results in future. Larger study with long-term follow-up will prove beneficial to know the impact of ASCT in such childhood cancers.

Clinical Trial Registry: None

Disclosure: Nothing to declare.

18 - Paediatric Issues

P643

CASE REVIEW OF NUTRITION MANAGEMENT FOR WOLMAN DISEASE DURING ADMISSION FOR HSCT

Rebecca Fisher[1], Kerryn Chisholm[1], Melissa Gabriel[1]

[1]The Children's Hospital at Westmead, Sydney, Australia

Background: Wolman disease is a rare congenital lysosomal storage disorder, characterized by an impaired metabolism of lipids with an incidence rate of less than 1 in 100,000 births. A minimal fat diet is required to prevent intracellular accumulation of cholesteryl esters and triglycerides that can result from the deficiency of lysosomal acid lipase. Left untreated, infant mortality is likely within the first year of life.

Potter et al (2021) reported 5 Wolman disease cases receiving Enzyme Replacement Therapy (ERT), minimal fat diets then HSCT. These patients all presented to HSCT with severe gastrointestinal (GI) involvement with 3 of the 5 patients experiencing significant ongoing GI symptoms during HSCT including both vomiting and diarrhoea. Despite their ongoing GI disturbances normal growth was still achieved with weight and length for age Z scores being within -1 to +1.

Methods: An 8 month old male with Wolman Disease and secondary HLH was admitted to The Children's Hospital at Westmead for HSCT (MSD marrow conditioning: Treosulfan, Fludarabine, Thiotepa and Alemtuzumab). He had been treated with ERT and a minimal fat diet prior to admission.

He presented for HSCT with minimal gastrointestinal issues however demonstrated growth delay. The patient's growth prior to his transplant admission was weight between the 3rd-15th centile z-score -1.64 and length < 3rd z-score -2.50.

The patient's diet prior to admission was predominantly a high osmolality, low fat elemental formula diluted to 0.85kcal/ml with of caramel flavouring added to improve palatability and 2ml of walnut oil per day. At home 2 small puree meals consisting of fruit or vegetables were offered.

To help address the risk of the patient being given oral, enteral or parenteral lipids whilst an inpatient an allergy alert for fats and PN lipids was entered in the electronic medical records and an age appropriate fat free diet code was ordered.

Results: The patient's total length of stay was 50 days (41 days post-transplant) with minimal complications. The patient was able to consume his usual formula orally throughout the admission, despite the high osmolality (providing on average of 54% of caloric and 40% of protein requirement). Parenteral nutrition without lipids was commenced on day -6 to address the risk of metabolic decompensation from suboptimal nutrition and ceased 34 days later, providing on average 40% of caloric and 37% of protein requirements. A nasogastric tube was inserted 22 days post-transplant for enteral feeds (providing an average of 21% of caloric and 25% of protein needs). Growth on discharge had improved from admission, however the patient still had growth delay with weight between the 3rd-15th centile, z-score for age -0.91 whilst length remained < 3rd centile, z-score for age -2.29.

Conclusions: Meeting nutrition requirements whilst achieving a minimal fat diet and minimal gastrointestinal complications was challenging but achievable.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P644

ORAL MICROBIOME IN PEDIATRIC AND YOUNG ADULT PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION: A SINGLE CENTER PROSPECTIVE STUDY

Maura Faraci[1], Carola Bonaretti[1], Gianluca Dell'orso[1], Filomena Pierri[1], Stefano Giardino[1], Francesca Angiero[2], Sergio Blasi[2], Gianpietro Farronato[3], Eddi Di Marco[1], Andrea Trevisol[2], Loris Ruffino[2], Roberto Biassoni[1]

[1]*IRCCS - Istituto G. Gaslini, Genova, Italy, University of Genoa, Genova, Italy, University of Milan, Milano, Italy*

Background: The role of intestinal microbiome in Hematopoietic Stem Cell Transplantation (HSCT)has been recognized and reported in many studies. In contrast, oral microbiome has been described in a few patients and its role is not yet defined. This prospective study aimed to evaluate oral microbiome in a cohort of children and adolescents receiving allogeneic HSCT.

Methods: Between 2019 and 2022, we studied 17 patients (median age 5 years, range 0.7-24.7) undergoing allogeneic HSCT for non-malignant (n = 9) and malignant diseases (n = 8). Eight patients received stem cells from haploidentical donor, 5 from alternative donor, and 4 from matched related donor. The conditioning regimen (CR) was myeloablative in 14 of them. Oral microbiome samples were longitudinally collected before HSCT, at the engraftment, and 30 and 100 days after HSCT.

Results: Eleven patients developed toxic oral mucositis (grades >2 in 3/11 patients). The analysis of oral microbiome includes16S mapped reads per sample analyzed from the 98 oral microbiome samples was 194521 +/−57929.

The analysis of the 5 most relevant phyla in microbial community in oral samples of patients ≥2 yrs of age demonstrated that *Firmicutes* increase their abundance over four time-points (pre-HSCT, engraftment, +30 days, and +100 days after transplant), specifically from 46% pre-HSCT to 72% at the last collection. In contrast, *Proteobacteria* and *Bacteroidetes* decreased from 20% to 10% and from 17 to 19% respectively. *Firmicutes/Bacteroidetes* (F/B) and *Firmicutes/Proteobacteri*a (F/P) ratios increased along the four observations, with F/B ranging from 2.7 to 8.0 and F/P from 2.3 to 7.2. Furthermore, the alpha diversity profiling indices analyzed showed their lowest values at engraftment, with a later increase in diversity profiling indices reaching higher values than before HSCT.

The analysis of sparse metagenomic data based on different algorithms to compare microbiome between patients affected by oral mucositis with patients without mucositis, showed that *Atopobium*, *Campylobacter*, *Fusobacterium periodonticum*, and different *Prevotella* species were all associated with mucositis. In addition, the supervised Random-Forest and the sparse correlation for compositional data (SparCC) analyses showed that *Prevotellaceae* and *Fusobacteriaceae*, but not the *Micrococcaceae family and Kingella genus*, among the principal microbial taxa associated with severe oral mucositis (grades >=2).

Conclusions: Overall, oral microbiome variability is influenced by the transplant procedure as demonstrated by alpha diversity indices showing their lowest values at engraftment. The oral microbiome analysis showed differences at the species level. *Mycoplasma* and *Prevotella oris* taxa show the best statistical correlations with severe oral mucositis (grade >=2) in oral swabs samples. Improved knowledge of oral microbiome behavior in HSCT setting could lead to specific approaches in order to reduce incidence of oral mucositis.

Disclosure: no conflict of interest.

18 - Paediatric Issues

P645

EXPERIENCE OF HAPLOIDENTICAL STEM CELL TRANSPLANTATION FOR CHILDREN WITH ACUTE LEUKEMIA, MYELODISPLASTIC SYNDROME IN BELARUS

Dmitry Prudnikau[1], Nataliya Kirsanava[1], Yulia Mareika[1], Mariya Naumovich[1], Nina Minakovskaya[1], Pavel Yanushkevich[1], Yanina Isaykina[1]

[1]*Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Minsk, Belarus*

Background: Today, haploidentical transplantation receive more and more children, especially when alternative donors are not available.

Methods: We analyzed outcomes of patients (n = 28) with acute leukemia (n = 23, 82%), myelodisplastic syndrome (n = 5, 18%), who underwent haploidentical stem cell transplantation (HSCT) in our center in 2012-2022 yy.. All patients with acute leukemia were in complete remission (CR) at the time of HSCT. The conditioning was myeloablative in all cases. Some patients (n = 13) received haploidentical transplantation with TCRab depletion, 15 received PTCy 50 mg/kg on day +3 and +4 for graft-versus-host disease (GVHD) prophylaxis in combination with low dose ATG, tacrolimus or cyclosporine and mycophenolate mofetil. As source of stem cells, 21 patients received peripheral stem cells (PSC), 7 – bone marrow (BM).

Results: 2-year overal survival (OS) and 2-year event free survival (EFS) after PTCy HSCT was 79,1%, and 73,0% respectively. Acute GVHD 2-4 was seen in 3 patients, chronic in 6. In contrast, 2-year OS and 2-year EFS for patients who underwent haploidentical transplantation with TCRab depletion were 69,2% (p = 0,04) and 46,2% (p = 0,05) respectively. 3 patients developed acute GVHD 2-4, 7 – chronic. Median follow-up of patients after TCRab depletion was 2,14 year (0,3-8,97), after transplantation with PTCy - 1,79 year (0,23-3,09). 5 of 13 children after haploidentical transplantation with TCRab depletion have relapsed (2-year CIR = 30,8%), 5 - transplant-related mortality (2-year TRM = 23,1%). After transplantation with PTCy have relapsed 2 patients (2-year CIR = 14,9% (p = 0,44)), without TRM (p = 0,03).

Conclusions: Outcomes of haploidentical transplantation for patients with acute leukemia and myelodisplastic syndrome are not bad, especially after PTCy HSCT. But, we need more patients, longer follow-up for better assessment of results.

Disclosure: No conflict of interest.

18 - Paediatric Issues

P646

CENTRAL NERVOUS SYSTEM INVOLVEMENT IN POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A PEDIATRIC CASE

María Pérez Raya[1], Jorge Díez Pastor[1], Antonia Pascual Martínez[1], Javier Carrillo Checa[1], Ángeles Palomo Bravo[1]

[1]*Hospital Regional Universitario de Málaga, Málaga, Spain*

Background: Post-transplant lymphoproliferative disorder (PTLDs) are infrequent complications with negative impact that usually

develop in the first 6 months after transplant in relation to profound cellular immunosuppression.

They are mostly due to uncontrolled proliferation of B cells originating from donor lymphocytes and frequently associated with EBV infection. Other risk factors include total body irradiation (TBI) or graft-versus-host disease (GVHD).

Clinical course is characterized by fever and adenopathies, but also involvement GI tract, liver and central nervous system (CNS). The treatment consists of lowering immunosuppression, with the possibility of associating Rituximab. Others would be use of chemotherapy in case of severity, up to EBV-specific T cell immunotherapy. In cases with CNS involvement, the options include systemic or intrathecal Rituximab associated with Methotrexate and Cytarabine based schemes, specific cell therapy and/or radiotherapy.

Methods: We report a case of PTLDs with CNS involvement in a pediatric patient.

Results: We present the case of a 12 years old male patient, diagnosed with grade II aplastic anemia with telomere shortening. Allogeneic HSCT from an identical unrelated donor after GETMON regimen, which included CTI was performed. Prophylaxis against GVHD was corticotherapy and cyclosporine (CsA).

In early post-transplant he developed hepatosplenic candidiasis solved with antifungals. Subsequently he was readmitted at hospital on day +90 due to intestinal aGVHD (MAGIC III), requiring broad-spectrum antimicrobial coverage in addition to deepening immunosuppressive treatment, with association of up to 3 lines of inmunosuppressive treatment. However, due to torpid clinical course, infusion of mesenchymal cells was requested, in addition to Infliximab and extracorporeal photopheresis.

Other complications included respiratory infection of probable fungal origin, hemorrhagic cystitis due to BK virus, reactivation of cytomegalovirus and gram-positive bacteremia. On day +113 he met the Jodele 2015 criteria for atypical thrombotic microangiopathy, CsA was discontinued and he received eculizumab with improvement.

In this context of profound immunosuppression, on day +176 he suffered tonic-clonic crisis. Moreover, a submandibular adenopathy was observed. Multiple parenchymal focal lesions were visualized in brain CT and MRI, with dilatation of the contralateral herniated right lateral ventricle, compatible with probable lymphoproliferative syndrome. He started treatment with dexamethasone and antimicrobial coverage until the infectious cause was ruled out. The extension study with abdominal ultrasound, spinal cord study and microbiological isolations was negative.

Due to severe and rapidly progressive neurological symptoms, an urgent ventriculoperitoneal shunt was performed.

CNS and submandibular biopsies confirmed high-grade B CD20 positive lymphoma with positive EBV. Blood tests showed an increase up to 904 UI/mL EBV viremia.

Given its severity, urgent chemotherapy with Metotrexate at 5g/m^2/24h, Rituximab and Cytarabine at high doses was considered, but the treatment was not fully completed due to worsening with signs of interlocking and surgical dismiss, resulting finally in death.

Conclusions: - PTLDs with CNS involvement is an infrequent complication with unfavorable prognosis that requiries an agile diagnosis and treatment with Rituximab and urgent chemotherapy as well as withdrawal of immunosuppression, if feasible.

- Active surveillance should be performed in patients with known risk factors and profound immunosuppression, as in our case.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P647

CLINICAL PHARMACEUTICAL CHALLENGES OF A BONE MARROW TRANSPLANT (BMT) PATIENT WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV): A PAEDIATRIC PHARMACISTS PERSPECTIVE

Poonam Lumb[1], Neil Tickner[1]

[1]Imperial College Healthcare NHS Trust, London, United Kingdom

Background: Patient X, was admitted for matched sibling bone marrow transplant (BMT) for beta thalassaemia in the paediatric BMT unit. Key challenges included pre-existing acquired HIV infection and a learning disability. This case focuses on the clinical pharmaceutical management and interventions from a paediatric pharmacist's perspective to ensure;

- Antiretroviral (ARV) therapy remained effective during mucositis and managing oral to IV switches, including therapeutic drug monitoring (TDM).
- HIV viral load remained undetectable (< 20 copies/ml) throughout the transplant, to limit risk of viral resistance.
- Drug-drug and drug-feed interactions were avoided, to avoid dolutegravir chelation with polyvalent cations enterally.
- Appropriate adherence support for safe administration of complex BMT medication on discharge, in view of learning disability.

Methods:

Timeline of Events	Challenges and Pharmacist Actions	Measure of Action
D-8. Admitted for BMT. Pharmacist-led ARV management plan in place within the conditioning protocol, with MDT approved recommendations if; • Mucositis develops to reduce enteral absorption • Nasogastric (NG) feeding or oral electrolytes required	Management plan created liaising with HIV team. Patient continued on current ARV regimen: Triumeq® (dolutegravir 50mg/abacavir 600mg/lamivudine 300mg) 1 tablet orally once daily.	• Monitor HIV viral load weekly.
D-1. Patient developed painful mucositis with increased frequency and stool output of >20ml/kg/day.	NG tube inserted. Triumeq® switched to individual components; • dolutegravir 50mg film-coated tablet: crushed and dispersed in water • abacavir and lamivudine suspensions NG feeding commenced as patient experienced pain on swallowing and increased stool output. **Interaction actions:** • ARV timing changed to 10am and feeding schedule modified (dolutegravir administered 2 hours before or 6 hours after NG feeds). • Requested clinicians to correct electrolyte disturbances via IV route.	• Monitor HIV viral load weekly. • Dolutegravir TDM taken (trough level 30 minutes before and peak level 2 hours after dose). • Blood biochemistry

Timeline of Events	Challenges and Pharmacist Actions	Measure of Action
D + 2. Worsening mucositis and parenteral nutrition initiated	• ARV therapy switched to IV zidovudine 250mg BD and IV enfuvirtide 90mg BD. • Prescribing and administration guidance provided to medical and nursing teams for off-label IV enfuvirtide • Drug interaction identified between enfuviritide and mycophenolate mofetil (MMF)	• Monitor HIV viral load and MMF level weekly.
D + 42. Patient improving and engrafted, Triumeq® recommenced. Discharge preparation.	Liaised with learning disability specialists to design medication chart outlining dosing, timing and administration instructions via visual aid.	• Monitor HIV viral load weekly • Self-medication observed by nursing team

Results: The management plans allowed the seamless transition of ARV therapy throughout the mucositis episode. Throughout transplant the weekly HIV viral load remained undetectable, dolutegravir TDM results were within acceptable range for therapeutic effect (tested twice during the mucositis phase) and the patient understood their discharge medication appropriately and safely post discharge.

Conclusions: This case highlights the role a clinical pharmacist has in the pharmaceutical management of BMT patients with HIV and learning difficulties. Implementing monitoring plans, understanding the pharmacokinetic principles of drug absorption and risks associated with drug-drug and drug-feed interactions were critical to the ongoing management of the patient's HIV, alongside routine BMT care.

Disclosure: Nothing to declare.

18 - Paediatric Issues

P648

REVIEW OF NUTRITION SUPPORT PRACTICES IN PEDIATRIC HSCT RECIPIENTS: A NEWLY ESTABLISHED CENTER

Fatma SE Ebeid[1], Yasmin Gamal[1], Sara Makkeyah[1], Safa Matbouly[1], Nihal Hussein Aly[1], Alaa Taha Mousa[1], Noura Bahaa[1], Haya E Ibrahim[1], Nayera HK Elsherif[1]

[1]Ain Shams University, Cairo, Egypt

Background: Malnutrition can suppress the immune system and delay engraftment, and associated with increased risk of complications, prolonged length of hospital stays, and hematopoietic stem cell transplantation (HSCT), mortality and morbidity particularly in low to middle income countries. **Our objective** is to illustrate the nutrition support practices over a period of 1-year in a newly developed Pediatric HCT program at Ain Shams University in Cairo, Egypt.

Methods: Prior to the start of the first transplant, the nutritional strategic plans were developed and implemented as a part of the standard of care. All patients underwent full nutritional and anthropometric assessments.

Results: Fifteen children undergone transplant, four autologous and 11 allogeneic transplantation (10 matched siblings and one matched family donor). In addition, two patients received immunosuppressive therapy for aplastic anemia. The main diagnosis for allogeneic transplantation was aplastic anemia (33.3%), β-thalassemia major (20%), one patient with ALL, one with AML and one with HLH. Three patients had autologous transplant for neuroblastoma and one for refractory Hodgkin disease. The mean baseline Z scores of weights and BMI were (-0.86 ± 1.2 and -0.27 ± 1.4 respectively). All patients received high protein formulas(1-1.5kcal/ml) throughout the transplant course with poor acceptability in 33.3%. Nasogastric feeding was used in only one 2-year-old girl who underwent autologous transplantation, 4 patients required TPN (2 allogeneic and 2 autologous transplant patients) at day+10 to 14 for an average of 6 days without adverse events. The mean time to reach full oral intake (9.06 ± 6.8 days). The mean pre-engraftment Z scores of weights and BMI were (-0.3 ± 4.27 and -0.3 ± 1.56 respectively). Moderate mucositis was reported in 8 patients (53.3%). Four children had acute GVHD (3 had skin GVHD stage 2 and one had upper gastrointestinal GVHD stage 2) and 2 suffered from Veno-occlusive disease. The mean Z scores of weights & BMI showed improvement during the post engraftment period in most of the patients. Seven patients maintained full chimerism after a year follow-up, with no reported deaths.

Conclusions: Although we could not use all the available nutritional tools like the nasogastric tube feeding, most of our patients were able to tolerate their daily caloric requirements.

Disclosure: Nothing to declare.

30 - Solid Tumours

P649

CELL-FREE THERAPY BY DACTINOMYCIN LOADED INTO THE BONE MARROW MESENCHYMAL STEM CELLS-DERIVED EXOSOMES

Zahra Sadat Hashemi[1], Mahdieh Shokrollahi Barough[1], Saeed Khalili[2], Ardeshir Ghavamzadeh[3], Ramin Sarrami Forooshani[1]

Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran, Islamic Republic, Shahid Rajaee Teacher Training University, Tehran, Iran, Islamic Republic of, [3]Cancer and Cell Therapy Research Center, Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of

Background: bone marrow mesenchymal stem cells (BM-MSCs) are the most common MSC source and widely studied MSC type. These cells recruit into the tumor sites by following chemokines, cytokines, and growth factors secreted by tumor cells. Therefore, targeted chemotherapeutic drug delivery is one of the applications of BM-MSC cells and BM-MSC-derived exosomes (Exos). In fact, these derivatives are considered as their parent cells and can be used as means of the vehicle with low adverse effects for other healthy organs. We investigated the delivery of Dactinomycin (DACT) to breast cancer spheroids by BM-MSC-Exos.

Methods: Human mononuclear cells (MNCs) were separated from the donor's healthy bone marrow by the high-density gradient centrifugation using Ficoll solution (Written informed consents were obtained according to the national ethical guidelines for research on stem cells and regenerative medicine). After two weeks, adherent BM-MSCs were grown to 70%–80% confluency and incubated for 48h in serum-free media. The media were harvested and passed through 0.22μm filter membranes and concentrated by using an Amicon filter (100kDa). MSC-Exos were finally precipitated by PEG following a 10000g centrifuge for 40min at 4°C. DACT was loaded into the MSC-Exos via the ultrasonication method. The cytotoxic effect of DACT-Exos in human breast cancer spheroids (3D culture of MDA-MB-231 cells) was monitored.

Results: The spindle shape morphology of BM-MSCs was observed and characterized by CD marker expression (Flow cytometry analysis for CD105+ and CD45- and their multipotent differentiation capacity into osteocytes. The morphology of the isolated MSC-Exos was confirmed by the TEM microscope and the size distribution was reported by DLS (dynamic light scattering) as 130nm. The efficacy of DACT loading into the lipid bilayer membrane of Exos was calculated as 52% (encapsulated/ total). All viability assays confirmed the more inhibitory effects of DACT-Exos compared to the free DACT (MTT: Apoptosis: Acridine Orange/ Ethidium Bromide: The live cells were stained in green but DACT-Exos have increased orange manifestations in spheroids, which then altered to the red, and Real-Time PCR). The results indicated that DACT-Exos selectively reduced tumor cell viability and spared fibroblasts as noncancerous cells. The remarkable effect of DACT-Exos in reducing invasion was maintained for a long time in a transwell assay.

Conclusions: Exosome-based therapy as cell-free therapy along with the cargo of chemotherapy drugs showed a potent inhibitory effect on proliferation and induced apoptosis on human breast cancer mass (as the tumor mimic). They can be used as drug carriers with selective toxicity to normal cells to reduce the side effects of chemotherapeutic drugs. Also, the new combined formula provides an additive effect and a more severe reduction in cell viability and could effectively be taken up by receptor-mediated endocytosis, or direct fusion with the plasma membrane of MDA-MB-231 spheroids. The mild and stable release indicated that the lipid bilayer of Exos could directly target and fuse cell membranes, enhancing the cellular internalization of the drug. It opens up hope for a new generation of treatments but further in vivo study is needed.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

30 - Solid Tumours

P650

OUTCOMES OF BUSULFAN VERSUS TREOSULFAN BASED REGIMENS FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANT IN CHILDREN WITH HIGH RISK EWING SARCOMA

Amit Dotan[1], Hila Rosenfeld Keidar[1], Rachel Shukrun[1], Sabina Edelman[1], Ronit Elhasid[1]

[1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Background: The role of consolidation high-dose chemotherapy in high risk Ewing sarcoma (ES) is still controversial. The high dose regimens used consist of either busulfan and melphalan or treosulfan and melphalan followed by autologous stem cell rescue (ASCR).

The goal of our study was to compare the efficacy and toxicity of both regimens.

Methods: We conducted a retrospective analysis of all the children who received high dose chemotherapy followed by ASCR for high risk ES in Tel Aviv Sourasky medical center, Israel. High risk ES was defined as: relapsed ES, ES with lung metastasis or localized high risk ES (tumor volume at diagnosis ≥ 200 ml or poor histologic response defined as viable cels ≥ 10%).

Treosulfan-based regimen (TBR) was given to patients with abdominal, pelvic or spinal masses with planned radiation therapy to the area. The rest of the patients received Busulfan-based regimen (BBR).

Overall survival (OS), relapse free survival (RFS), and the incidence of complications (Bacteremia, Fungal infections, VOD and mucositis) were compared between the two groups.

Results: Between November 2010 and December 2021 26 children received high dose chemotherapy followed by ASCR for high risk ES. 18 were treated with BBR (10 with lung metastasis, 5 with relapsed disease and 3 with localized high risk disease) and 8 were treated with TBR (6 with lung metastasis and 2 with localized high risk disease).

The average age for the entire cohort was 14.4 years (range 3.5-23.7 years).

The median follow up time for the entire cohort was 3.6 years (range 0.9-11.6 years), 3 years (range 0.2-11.1 years) for the BBR group and 1.6 years (range 0.6-4.3 years) for the TBR group.

At the time of data analysis the OS of the TBR group was superior to the BBR group, 87.5% (7/8) versus 66.7% (12/18), but that was not statistically significant (p-0.26). The RFS was also superior in the TBR group (62.5%,5/8) compared to the BBR group (50%, 9/18) again without statistical significance (p-0.55).

There was increased incidence of bacteremia events in the BBR group (4/18, 22.2%) compared to the TBR group (0/8, 0%) that was not statistically significant (p value – 0.27).

There was statistically significant (p value – 0.02) increased incidence of mucositis in the BBR group (18/18, 100%) compared to the TBR group (5/8, 62.5%).

There were no events of veno-occlusive disease (VOD) nor fungal infections in both groups.

Conclusions: Our single center cohort showed no statistically significant differences in OS and RFS between the BBR group and the TBR group, mostly due to small cohort size.

Both regimens were relatively safe as shown by low incidence of major complications (i.e. no events of VOD) with statistically significant lower incidence of mucositis in the TBR group.

A larger cohort, using larger, multicenter database is required to better explore the difference in outcomes and toxicity between BBR and TBR.

Disclosure: Nothing to declare.

30 - Solid Tumours

P651

CLINICAL CHARACTERISTICS, TREATMENT AND OUTCOME OF CHILDREN WITH HIGH-RISK NEUROBLASTOMA IN MALAYSIA: A SINGLE CENTRE EXPERIENCE

Sie Chong Doris Lau[1], Hamidah Alias[1], C-Khai Loh[1]

[1]Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Background: High-risk neuroblastoma (HRNB) is a childhood malignancy with poor prognosis. The use of high-dose chemotherapy with autologous stem cell transplantation (ASCT) and immunotherapy have improved their overall survival to as high as 70% in developed nations. However, in developing countries with limited resources, these treatments may not be available to all HRNB patients.

Methods: Data of HRNB patients who were diagnosed and treated at our centre between 2016 to 2021 were extracted from their medical records. Patients were treated using HR-NBL-1/ SIOPEN protocol, consisting of intensive chemotherapy (Rapid COJEC), surgery, ASCT with BuMel myeloablative therapy, radiotherapy to the primary/metastatic sites, and maintenance treatment with cis-retinoic acid.

Results: A total of 13 patients (9 boys and 4 girls) were diagnosed with Stage IV neuroblastoma. Median age at diagnosis was 2.8 years (IQR 1.5; 5.3). The primary site of tumour was suprarenal (n = 8), retroperitoneal (n = 3) and thorasic (n = 2). Five patients achieved partial response and underwent primary tumour resection followed by ASCT within 4.8 months from diagnosis. Another two patients had mixed response and received additional chemotherapy [either one or combination of the following: topotecan/vincristine/doxorubicin (TVD) or ifosfamide/carboplatin/etoposide (ICE)]. One successfully underwent ASCT 1 year from diagnosis while another will be undergoing the procedure soon (duration of 14 months from diagnosis). Among the 6 patients who had ASCT, stem cells were obtained via bone marrow harvest – mean CD34 cell count was 10.38 x 10^6/kg (SD 9.18). Median time for neutrophil engraftment (> 0.5 x 10^9/L) was 13.5 days (IQR 12.0; 21.2) while platelet recovery (> 20 x 10^9/L) took 15.5 days (IQR 10.5; 27.7). Out of the 13 patients, three died during induction phase due to progressive disease, one defaulted midway while another two patients returned to their home country for continuation of care. Three-year overall survival for our centre was 30.5% with 4 patients died from relapse after ASCT.

Conclusions: The outcome of HRNB patients remained poor with high relapse and mortality rate. Efforts should be made to allow incorporation of immunotherapy in developing countries to improve the overall survival of these patients.

Disclosure: Nothing to declare.

30 - Solid Tumours

P652

AUTOLOGOUS TRANSPLANTATION OF HEMATOPOIETIC STEM CELLS FOR MALIGNANT NEOPLASMS IN CHILDREN: EXPERIENCE OF THE N.N. BLOKHIN

Teymur Aliev[1], Irina Kostareva[1], Karina Sergeenko[1], Elena Machneva[1], Nataly Burlaka[1], Nara Stepanyan[1], Ravil Fatkhullin[1], Yury Lozovan[1], Tatyana Potemkina[1], Konstantin Mitrakov[1], Garik Sagoyan[1], Amina Suleymanova[1], Olga Kapkova[1], Alexander Temny[1], Lana Kudaeva[2], Marina Rubanskaya[1], Olga Romantsova[1], Timur Valiev[1], Nataly Batmanova[1], Anatoly Kazantsev[1], Vladimir Polyakov[1], Kirill Kirgizov[1], Svetlana Varfolomeeva[1]

[1]Lev Durnov Research Institute of Pediatric Oncology and Hematology of N.N. Blokhin National Medical Research Centre of Oncology, Moscow, Russian Federation, [2]Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russian Federation

Background: Autologous hematopoietic stem cell transplantation (aHSCT) is a method of consolidative therapy in pediatric cancers. One of the key aspects is the improvement of results with less organ toxicity. Big groups of pts. require to be analyzed.

We aimed to represent experience of aHSCT for children with malignancies in our center and estimate safety and tolerability of the method.

Methods: Overall, 159 pts. received 185 aHSCT in 2021-2022 (during 23 months). Diagnosis: Hodgkin disease (HD), non-Hodgkin lymphoma (NHL), neuroblastoma (NB), Wilms' tumor (WT), germ cell tumor (GCT), Ewing sarcoma (ES), retinoblastoma (RB), pleuropulmonary blastoma (PPB) and CNS tumors. HD/NHL – 17 pts., NB – 85 pts., WT – 16 pts., GCT – 8 pts., ES – 26 pts., RB – 3 pts., PPB – 1 pt., CNS – 3 pts. M/F = 86/73. Age median – 9.2 y.o. (0.9 – 17) y.o. Conditioning regimens: HD/NHL – CEAM, NB/ES – Treo/Mel, GCT – MAKEI-based with thiotepa (tandem aHSCT), WT – melphalan, PPB – treo/mel, RB/CNS – thiotepa based regimens. Median of CD34+ pos. cells re-infused – 8.3x10^6 /kg (1.9 - 36).

Results: All pts. engrafted. Median day of engraftment – 9 (7-17). At the median follow-up of 13 months (1-23) OS for all group is 87.3%, EFS – 78.4%. Main cause of death – relapse/progression. TRM was quite low, only 1 pt. died due to therapy toxicity. No relapses were found in GCT group. Main toxicities: oral mucositis 2-4 gr. was found in 73.2% of pts., febrile neutropenia – 81.7%, enterocolitis 2-4 gr. – 43.5%, toxicodermia 2-4 gr. – 40.8%.

Conclusions: aHSCT in children with malignant disorders is a good option of consolidative therapy. Toxicity and TRM seems to be feasible. Long-term follow-up required.

Disclosure: Nothing to declare.

30 - Solid Tumours

P653

PRESENCE OF SOLID TUMORS DOES NOT PREVENT AUTOLOGOUS STEM CELL TRANSPLANTATION IN REFRACTORY/RELAPSED NHL

Ismail Arslan[1], Aynur Ugur Bilgin[1], Osman Ilhan[1]

[1]Koru Ankara Hospital, Ankara, Turkey

Background: In this clinical abstract, the patient diagnosed with multiple neoplasms such as marginal zone lymphoma (MZL), non-small cell lung cancer, and prostate adenocarcinoma was transplanted with the LEAM autologous hematopoietic stem cell transplantation protocol with the permission of the Stem Cell Council of the Ministry of Health.

Methods: Our patient, a 65-year-old man, was diagnosed with splenic marginal zone B-cell lymphoma after histopathological and immunohistochemical evaluation. The patient was hospitalized in the hematology department and treated once according to the R-CHOP protocol. After five months of remission, he was diagnosed with non-small cell lung cancer incidentally during a routine exam. He had thoracic surgery for a right upper lung lobectomy, according to the oncology council's decision. Four years after the remission, a recurrence of lymphoma was detected with imaging tests and pathology. He was treated five times with the R-CHOP protocol, with the hematology council's approval, due to R-CHOP sensitivity. After one year of the second remission, he was incidentally diagnosed with prostate adenocarcinoma during a routine exam, and he had radical prostatectomy surgery with the oncology council's decision. Two years after the second remission, the R-GEMOX protocol was given four times to the patient for a second recurrence. Despite multiple neoplasms, the patient was evaluated in the hematology department of Private Koru Ankara Hospital and decided to undergo autologous transplantation after a third remission. By submitting an application to the Ministry of Health's Stem Cell Council, we were given permission for the transplant.

Results: Splenic marginal zone B-cell lymphoma is a more rare lymphoma found in the blood, bone marrow and spleen. As with other types of MZL, it tends to grow and spread slowly, so treatment may be safely delayed unless symptoms or other problems arise. Herein, we present a patient with marginal zone lymphoma who was diagnosed with secondary neoplasms of non-small cell lung cancer and prostate adenocarcinoma after remission. However, since the prognosis is poor in refractory/relapsed MZL, autologous HSCT is appropriate. In our case, the presence of two different solid tumors, which are rare in the literature, caused hesitation about transplantation.

Conclusions: In conclusion, patients with non-Hodgkin's lymphoma (NHL) are at increased risk for second cancers. [1] The patients who developed secondary malignancies, significantly more than the endemic rate. [2] Reviewing the literature, there are a few clinical cases of non-Hodgkin lymphoma patients with multiple neoplasms. There is lung cancer after treatment for non-Hodgkin lymphoma [3] and non-Hodgkin lymphoma with prostate cancer [4] but there is no case of autologous hematopoietic stem cell transplantation for non-Hodgkin lymphoma with prostate adenocarcinoma and non-small cell lung cancer. In this case, we present a high-risk, low-survival patient diagnosed with multiple neoplasms such as marginal zone lymphoma (MZL), non-small cell lung cancer and prostate adenocarcinoma who was transplanted with the LEAM autologous hematopoietic stem cell transplantation protocol. Physicians should be aware of the probability of multiple neoplasms in the routine hematologic examinations of non-Hodgkin lymphoma. Autologous HSCT was successfully performed in our patient, and the patient is being followed in complete remission.

Disclosure: Nothing to declare.

10 - Stem Cell Donor

P654

GLOBAL TRENDS IN DEMAND FOR MISMATCHED UNRELATED DONOR TRANSPLANTS HAVE POSITIVELY IMPACTED RACIALLY AND ETHNICALLY DIVERSE CANDIDATES FOR HEMATOPOIETIC CELL TRANSPLANTATION

Steven Devine[1], Stephanie Fingerson[1], Erica Jensen[1], Stephen Spellman[1]

[1]National Marrow Donor Program, Minneapolis, United States

Background: Reliance on fully HLA-matched unrelated donors (URDs) creates a gap in access to hematopoietic cell transplantation (HCT) for racially/ethnically diverse (ED) patients. The National Marrow Donor Program (NMDP) is committed to bridging this gap by improving outcomes in recipients of HLA-mismatched unrelated donor (MMUD) HCT, as recent studies report encouraging outcomes.

Methods: We sought to assess the potential impact of recent favorable MMUD studies published in 2021 on global demand by comparing the number of MMUD transplants facilitated by NMDP operations in fiscal year 2022 (FY22), Oct '21-Sept '22, compared to the three prior FYs (2019-2021). NMDP Bioinformatics Research then simulated searches in US recipients of haploidentical related (HRD) HCT reported to the CIBMTR from 2013-2020. The cohort consisted of 8,281 HRD HCT recipients. A search simulation was run on each patient to estimate counts of possible 8/8 and 7/8 matches on the NMDP registry. This process queries a database of pre-imputed donor HLA genotypes and counts any donor matching at 8/8 and 7/8 at high resolution.

Results: During FY19-21, the NMDP facilitated a mean of 840 MMUD transplants annually. The majority were 7/8 (93%) with 7% matched at 4-6/8 loci. In FY22 the number of MMUD facilitated globally was 1,040, representing a 24% increase relative to the FY19-21 mean. Of note, the number of <7/8 MMUD HCTs increased from a mean of 60 annually to 109 in FY22, an increase of 82%. The impact of this overall growth in MMUD transplants for ED recipients was substantial. In FY21, NMDP facilitated 240 MMUD transplants for US ED patients while in FY22 that number increased to 340, an annual growth rate of 46%. The majority of the growth in the US has been due to increased use of post-transplant cyclophosphamide (PTCy)-based GVHD prophylaxis, based on CIBMTR data. Similar proportional increase in MMUD transplants facilitated by NMDP was observed in donor grafts provided for both domestic and international recipients. To assess the potential for growth, NMDP Bioinformatics Research simulated searches for US recipients of HRD HCT reported to the CIBMTR between 2013 and 2020 using the currently available donors on the NMDP registry (N = 24.3M). While <16% of the US HRD HCT recipients had an existing 8/8 donor on the registry, >84% had at least one 7/8 URD and 64% percent had five or more 7/8 donors, the majority <35 years old.

Conclusions: NMDP has observed substantial growth in global demand for MMUD donor HCT in FY22, positively impacting our ability to facilitate HCT for ED patients. Most US recipients of HRD HCT have multiple MMUD options as well, indicating potential for sustained growth. This trend will enable NMDP and other global donor registries to close the current gap in access to HCT for all patients, particularly those with diverse ancestry. MMUD existence could also have a positive impact on all patients currently considered for HRD HCT who have developed donor specific antibodies. This approach is being tested in the ongoing NMDP sponsored multi-center ACCESS trial of MMUD HCT (NCT04904588).

Clinical Trial Registry: ClinicalTrials.gov: NCT04904588

Disclosure: All authors are NMDP employees.

10 - Stem Cell Donor

P655

YOUNGER DONORS MIGHT BE PREFERRED FOR THE ELDERLY MDS/AML RECIPIENTS OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION-RETROSPECTIVE ANALYSIS ON BEHALF OF THE POLISH ADULT LEUKEMIA STUDY GROUP (PALG)

Alicja Sadowska-Klasa[1], Anastazja Szlauer-Stefańska[2], Anna Łojko-Dankowska[3], Maciej Majcherek[4], Patrycja Mensah-Glanowska[5], Ksenya Kviatkouskaya[6], Ewa Karakulska-Prystupiuk[7], Anna Czyż[4], Jan Maciej Zaucha[1]

Medical University of Gdansk, Gdansk, Poland, Maria Sklodowska-Curie Institute - Oncology Centre, Gliwice Branch, Gliwice, Poland, Poznan University of Medical Sciences, Poznan, Poland, Wroclaw Medical University, Wroclaw, Poland, Jagiellonian University medical College, Krakow, Poland, Jagiellonian University Medical College, Krakow, Poland, Oncology, and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

Background: With the aging of the European population, the number of elderly patients with MDS-EB2/AML (myelodysplastic syndrome with an excess of blasts/acute myeloid leukemia) is increasing. The introduction of novel therapies allows for achieving more complete responses and subsequent consolidation with allogeneic hematopoietic cell transplantation (allo-HCT) which remains the only curative option in the long-term perspective. Here, we asked what are the outcomes of the Polish elderly patients subjected to allo-HCT.

Methods: We retrospectively identified all consecutive elderly patients (age above 60) with the diagnosis of MDS-EB2/AML who were treated with myeloablative (MAC), reduced intensity (RIC) or non-myeloablative (NMA) conditioning followed by allo-HCT in the PALG allied centers between 2014-2020.

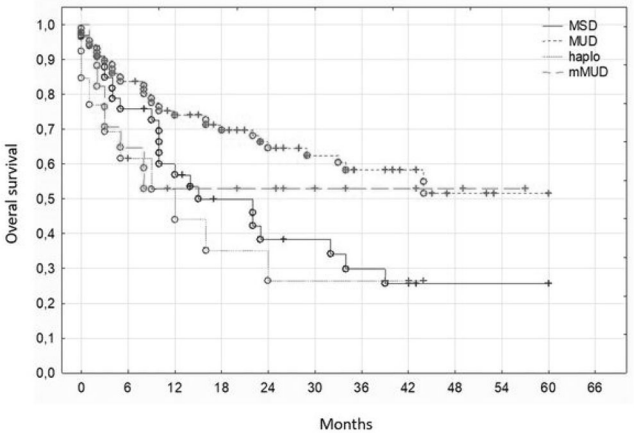
Results: A total of 150 patients were included in the analysis, with a median age of 63 years (range 60-72) at the time of allo-HCT, including 36% of patients over 65 years. Almost one quarter (22%) were transplanted in active disease. They received MAC with TCI score≥3,5 (67;45%), RIC with TCI score in the range

between 2,5-3,0 (46;31%) or NMA conditioning with TCI score ≤2 (32;21%), and graft from matched unrelated donor (MUD; 87;58%), matched related donor (MRD, 33;22%), mismatched unrelated (mMUD, 17;11%) or haploidentical donor (13;9%). ATG was used in all 103 patients who were transplanted with unrelated donor and in 6 transplanted with MRD. The median time to engraftment was 18 days with no difference by donor type. Acute and chronic GvHD were observed in 38 (25%) and 43 (28%) of patients, respectively. The basic characteristic of the study group is summarized in table 1.

Non-relapse mortality rate at day 100 was 11% (17pts). In univariate analysis, NRM rate was significantly correlated with donor type, conditioning intensity, aGvHD, and infectious complications. In multivariate analysis, early NRM was significantly negatively affected by mMUD HR 6,32 (95%CI 1-32), and TCI ≥ 3,5 HR 2,46 (95%CI 0,7-7,9), and positively by MUD with HR 0,15 (95% CI 0,02-0,87).

The median follow-up time for surviving patients was 17 months (range: 0,5-100). The median time of estimated overall survival (OS) was 33 months. The estimated 3-year OS was 48% for all patients, with the best OS for MUD (58%) and mMUD (52%), whereas only 30% for MRD and haploidentical group (Figure1). In univariate analysis, donor type (MRD vs MUD), donor age above 50 years, no ATG in GvHD prophylaxis, and active disease status negatively affected OS. In multivariate analysis, the only factors affecting OS were active disease status HR 2,24 (95%CI 1,35-3,74); haploidentical donor HR 6,57 (95% CI 1,57-27,44) and older (> 50years) donor HR 5,33 (95% CI 1,6-17,8).

	TOTAL	MSD	MUD	haplo	mMUD	P value
Study group	150 (100%)	33 (22%)	87 (58%)	13 (9%)	17 (11%)	
Median age	63 (60-73)	63 (60-73)	63 (60-72)	64 (60-70)	63 (60-68)	NS
Age>65	55 (36%)	8 (24%)	33 (38%)	6 (46%)	8 (47%)	NS
Donor age >50	36 (24%)	33 (100%)	2(2%)	1 (8%)	0 (0%)	P < 0.05
Female/Male	70 (47%)/ 80 (52%)	20 (61%)/ 13 (39%)	41 (47%)/ 46 (53%)	4 (31%) / 9 (69%)	5 (29%) / 12 (71%)	NS
CR	117 (78%)	23 (70%)	67 (77%)	10 (77%)	17 (100%)	NS
Active	33 (22%)	10 (30%)	20 (23%)	3 (23%)	0 (0%)	
TCI ≥ 3,5	67 (45%)	17 (52%)	43 (49%)	4 (31%)	3 (17%)	P < 0.05
TCI 2,5-3	46 (31%)	7 (21%)	22 (25%)	5 (38%)	12 (70%)	
TCI ≤ 2	32 (21%)	9 (27%)	18 (20%)	4 (31%)	1 (6%)	
No data	5 (3%)	-	4 (4%)	-	1 (6%)	
ATG	109 (73%)	6 (18%)	87 (100%)	N/A	17 (100%)	P < 0.05
Comorbidities						
Diabetes	21 (14%)	3 (9%)	12 (14%)	3 (23%)	3 (18%)	NS
Hypertension	93 (62%)	20 (61%)	53 (62%)	9 (69%)	11 (65%)	NS
Coronary Artery Disease	29 (19%)	6 (18%)	16 (18%)	3 (23%)	4 (24%)	NS
Severe infections	50/144 (35%)	9 (28%)	24 (29%)	11 (85%)	6 (40%)	P < 0.05
	6 no data	1	3	0	2	
aGvHD	38/150 (25%)	6 (18%)	16 (18%)	8 (62%)	8 (50%)	P < 0.05
cGvHD	42/146 (28%)	12 (36%)	25 (29%)	1 (8%)	4 (29%)	NS
mild	17 (41%)	4 (12%)	13 (15%)	0 (0%)	0 (0%)	NS
moderate	16 (38%)	4 (12%)	10 (12%)	0 (0%)	2 (14%)	NS
severe	8 (19%)	4 (12%)	2 (2%)	1 (8%)	1 (7%)	NS
score unknown	1 (2%)	-	-	-	1 (7%)	
Early death tox	17 (11%)	3 (9%)	5 (6%)	4 (31%)	5 (29%)	P < 0.05
Relapse	50 (34%)	14 (45%)	29 (34%)	5 (38%)	2 (13%)	NS
Death relapse	38 (25%)	12 (39%)	22 (26%)	3 (23%)	1 (6%)	NS
Non-relapse mortality	33 (22%)	10 (32%)	11 (13%)	6 (46%)	6 (38%)	P < 0.05
Total deaths	72 (48%)	22 (67%)	33 (38%)	9 (69%)	8 (47%)	P < 0.05
Median follow-up	17months	14 (0-95)	20 (0-100)	9 (0-43)	10 (0-59)	NS
Median OS	33 months	15 months	Not reached	12 months	Not reached	



Conclusions: The donor selection for elderly patients seems to play an important role due to the negative impact of mismatched donors on early NRM. The better long-term OS for MUD compared to MRD may result from younger donor age leading to better immune graft function and less NRM; however, no use of ATG could significantly negatively affect the OS in the MRD group.

Clinical Trial Registry: N/A

Disclosure: nothing to disclose.

10 - Stem Cell Donor

P656

IDENTIFYING PERMISSIBLE HLA MISMATCHES IN PEDIATRIC SCT USING HLA-EMMA

Erik G. J. Von Asmuth[1], Fleur Hiensch[1], Sebastiaan Heidt[1], Alexander B. Mohseny[1], Dave L. Roelen[1], Cynthia S. M. Kramer[1], Frans Claas[1], Arjan C. Lankester[1], Adriaan A. van Beek[1]

[1]Leiden University Medical Centre, Leiden, Netherlands

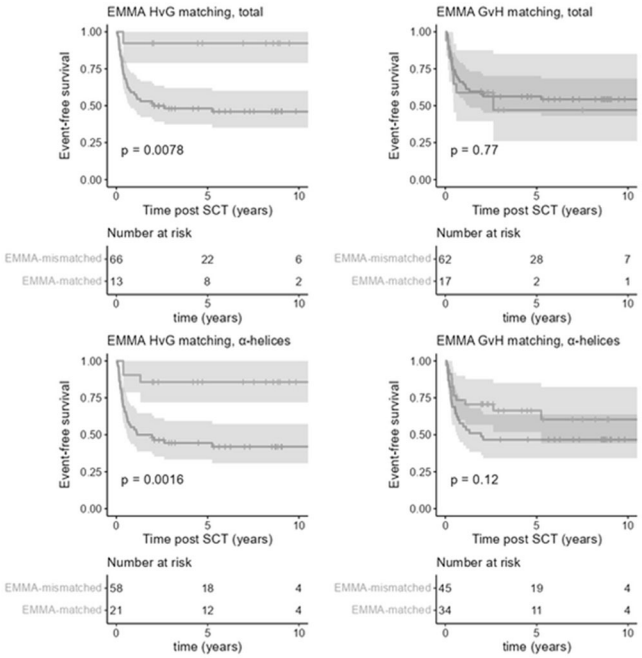
Background: HLA mismatched unrelated donor (MMUD) transplants have inferior clinical outcome compared to 10/10 matched unrelated donor transplants (MUD). Tools to identify permissible mismatches may enhance clinical outcome by improving donor selection.

Methods: To identify permissible HLA mismatches for MMUD transplants, we used HLA-EMMA, a computer algorithm that can define all amino-acid (AA) sequence mismatches in case of a HLA mismatched donor-recipient combination. We used HLA-EMMA version 1.06 beta, and analyzed the clinical impact of AA mismatches at the α-helix, β-sheet, or at any location in the HLA molecule in both the Host versus Graft (HvG) and Graft versus Host (GvH) direction.

In total, 79 pediatric patients with MMUD transplants were studied, which all had at least second field typing available. Mismatches were analyzed for HLA-A, B, C, DRB-1, and DQB-1 loci, to allow for fair comparisons with 10/10 MUD transplants.

The primary endpoint was event-free survival (EFS), defined as relapse-free subsequent transplant-free survival, as this was the main determinant of clinical outcome within this cohort, and also analyzed grade II-IV acute Graft versus Host Disease (aGvHD). We defined matched as the absence of any AA mismatches.

Results: In the HvG direction for HLA-EMMA, we identified 21 patients without an AA mismatch in the α-helix, 32 patients without a mismatch in the β-sheet, and 13 patients without any AA mismatch. For the GvH direction, these were 34, 36 and 17, respectively.



Both HvG AA mismatches on the α-helix and all HvG AA mismatches were strongly associated with decreased EFS ($p = 0.002$ and 0.008, respectively, figure 1), while β-sheet mismatches were not ($p = 0.08$). MUDs ($N = 157$) had similar EFS as MMUDs matched at the α-helix and those without any AA mismatches ($p = 0.30$, 0.23 respectively).

For acute GvHD, HLA-EMMA HvG α-helix, β-sheet and any location matching all trended to less aGvHD without reaching significance (5 vs 24%, $p = 0.06$, 9 vs 26%, $p = 0.07$ and 0 vs 23%, $p = 0.06$ respectively).

GvH-direction matching was not associated with EFS, both on the α-helix ($p = 0.12$), β-sheet ($p = 0.34$), or any location ($p = 0.77$), or with aGvHD ($p > 0.3$ for all evaluated approaches).

We also evaluated the PIRCHE HSCT module, which predicts the number of mismatched peptides derived from host HLA molecules that could theoretically be presented in donor MHC-I (PIRCHE-I) and MHC-II (PIRCHE-II) but did not find significant associations with EFS or aGvHD ($p > 0.1$ for all cutoffs and outcomes).

Conclusions: Using HLA-EMMA in the HvG direction, 21 out of 79 MMUD transplants had no AA mismatches on the α-helix. They had superior event-free survival compared to those with AA mismatches, and performed similar to 10/10 MUDs. When counting AA mismatches at any location on the HLA molecule, a similar effect was seen, but fewer patients were classified as permissibly mismatched.

Using the current approach, we could identify a subgroup of approximately 25% of MMUDs with a permissible mismatch, which performed similar to MUDs. If future donor selection is based on the identification of such permissible mismatches, this will enhance the clinical outcome in recipients for whom no MUD transplant is available.

Disclosure: Nothing to declare.

10 - Stem Cell Donor

P657

OUTCOME COMPARISON BETWEEN HLA-MATCHED SIBLING DONOR ALLOGENIC HSCT AND MATCHED RELATED NON-SIBLING DONOR ALLOGENIC HSCT IN PEDIATRIC PATIENTS; SINGLE CENTER RETROSPECTIVE STUDY

Sarah Alghazwani[1], Rodaina Abujoub[1], Shahbaz Memon[1], Abdulrahman Alsultan[2], Mohammed Essa[1,3,4]

[1]King Abdullah specialist Children Hospital, Riyadh, Saudi Arabia, [2]King Saud University, Riyadh, Saudi Arabia, [3]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [4]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

Background: Due to high rate of consanguinity in the local community, an extended donor search within the family may yield a suitable donor such as one of the parents or a cousin. There is paucity in the literature in regards to the outcome of patients who are transplanted from matched related non-sibling donors including engraftment and Graft versus host disease (GVHD). in this study, we compared the outcome between Matched Sibling Donor (MSD) HSCT and Matched Related Non-Sibling Donor (MRN-SD) HSCT.

Methods: Data were collected for all patients who were transplanted from MRN-SD from January 2015 till December 2020 then they were controlled with MSD who were transplanted in the same periods with matching diagnosis, age, gender, conditioning, cell dose and stem cell source performed during the same time period. Both groups received the same conditioning regimens and GVHD prophylaxis based on diagnosis. Variables including demographic details such as age, gender, diagnosis, source of stem cell, HLA matching 10/10 and 9/10, conditioning regimen, GVHD prophylaxis, acute GVHD, chronic GVHD, viral Infection (CMV), chimerism tests and Survival. T-Test, Wilcoxon rank sum test, and Chi-Square test were used for analysis.

Results: A total of 76 patients were reviewed during study period. 30 patients (39.5%) in MRN-SD arm and 46 patients in MSD (60.5%) were identified after matching in age, disease, and conditioning regimens. All patients received similar approach including stem cell source and GVHD prophylaxis (CNI + 2nd agent). Out of the MRN-SD group, 18 patients (59%) had one of their parents as a donor and the rest as 2nd degree relatives. Both groups were equally distributed and were homogeneous. Both groups have no statistical significant difference in outcome including engraftment, GVHD and Chimerism tests results. All patients remain alive with median follow up of 884 days (66-3160).

Patient or Transplant Characteristics - N = 76	**MRN-SD group :N: 30 Median (range) or N (%)**	**MSD group (Control): N = 46 Median (range) or N (%)**
Donor relation to patient	Mother 10 (0.33) Father 8 (0.26) 2nd degree: 12 (0.4)	Sibling : 46 (1.0)
HLA matching: 10/10:9/10	26 (0.87): 4(0.13)	46 (1.0)
Age (years)	5.5 (3-10)	6(3-9)
Gender (F/M)	16/14	12/34
Diagnosis:		
Hemoglobinopathy	18	27
Fanconi Anemia	3	5

Patient or Transplant Characteristics - N = 76	MRN-SD group :N: 30 Median (range) or N (%)	MSD group (Control): N = 46 Median (range) or N (%)
Aplastic anemia	2	5
HLH	3	3
Primary immunodeficiency	4	6
Conditioning regimen:		
Thiotepa/Busulfan/Fludarabine	15	21
Busulfan/Fludarabine/ATG	5	4
Fludarabine/Cyclophophamide/ATG	5	10
Fludarabine/melphalan/ATG	1	3
Busulfan/Fludarabine	1	3
Busulfan/Cyclophosphamide/ATG	2	3
No Conditioning	1	2
Infused nucleated cell dose (X 108/kg)	5.9(4.27-7.67)	4.3(2.84 -5.29)
Infused CD34 cell dose (X 106/kg)	6.0(4.83 -7.82)	8.1(6.32 -11.60)
Successful engraftment	29 (0.96)	44 (0.96)
Disease Free	29 (0.96)	45(0.98)
Mixed Chimerism (donor cells < 90%)	9 (0.30)	11 (0.24)
GVHD	4 (0.13)	5 (0.11)
CMV reactivation	16 (0.53)	21 (0.46)

Conclusions: This study showed no significant difference in allogenic HSCT outcomes between matched sibling donors and matched non-sibling related donors despite using the same management approach in terms of conditioning therapy, serotherapy and GVHD prophylaxis, Larger registry studies are needed to confirm out findinings.

Clinical Trial Registry: Not Applicable.

Disclosure: Nothing to declare from authors.

10 - Stem Cell Donor

P658

COMPARABLE CLINICAL OUTCOMES AFTER CORD BLOOD TRANSPLANTATION IN THE US AND JAPAN: RESULT FROM A COLLABORATIVE STUDY

Mizuki Watanabe[1,2,3], Laurel A Thur[2], Junya Kanda[1], Ayumu Ito[3], Takashi Tanaka[3], Yoshihiro Inamoto[3], Sung-Won Kim[3], Yasuyuki Arai[1], Chisaki Mizumoto[1], Toshio Kitawaki[1], Ann Dahlberg[2,4], Colleen Delaney[4], Akifumi Takaori-Kondo[1], Takahiro Fukuda[3], Filippo Milano[2]

[1]Kyoto University Hospital, Kyoto, Japan, [2]Fred Hutchinson Cancer Center, Seattle, United States, [3]National Cancer Center Hospital of Japan, Tokyo, Japan, [4]University of Washington School of Medicine, Seattle, United States

Background: Outcomes after cord blood transplantation (CBT) have been reported to be affected by different transplant strategies adopted in different centers. Herein, we conducted a collaborative retrospective analysis to compare clinical outcomes between the US and Japan, and to identify different prognostic factors in adult patients undergoing CBT.

Methods: Between 2006 and 2022, 252 patients received a first CBT (single CBT (sCBT), n = 26; double CBT (dCBT), n = 226) at Fred Hutchinson Cancer Center (FH) and 246 (only sCBT) at two Japanese institutions (National Cancer Center Hospital of Japan, Kyoto University Hospital). Overall survival (OS) and relapse free survival (RFS) were assessed using the Cox proportional hazard multivariate model, using variables selected manually in the preceding univariate analysis.

Results: Table summarizes the patient characteristics in each cohort. Median follow-up for survivors was 3.9 years for the FH and 4.6 years for the Japanese cohorts. Patients with lymphomas (24.8% vs 4.4%), high/very high revised disease risk index (rDRI) (29.7% vs 9.5%) and over 50 years of age (51.6% vs 42.5%) were more frequently observed in the Japanese cohort while total nucleated cell dose and CD34+ cell dose were significantly higher in the FH group regardless of the number of the CB units received. All patients at FH received TBI containing regimens and cyclosporine with mycophenolate mofetil (MMF) for GVHD prophylaxis, while 20% of patients in the Japanese cohort received non-TBI regimens and methotrexate with calcineurin inhibitor for GVHD prophylaxis.

Five-years OS and RFS were 52.0% and 49.6% for the FH cohort, and 56.4% and 47.2% for the Japanese cohort. The frequency of aGVHD grade II-IV and grade III-IV were significantly higher among patients at the FH than in Japan (68.3% vs 49.6% and 16.7% vs 10.2%, respectively), while the incidence of cGVHD was comparable between the 2 cohorts. In both cohorts, patients with high/very high rDRI (vs. low-intermediate DRI) had a poorer OS (FH: HR 1.98 $p = 0.060$; Japan: HR 1.99, $p = 0.003$) and RFS (FH: HR 1.77, $p = 0.045$; Japan: HR 2.75, $p < 0.001$) with higher relapse risk (FH: HR 2.44, $p = 0.031$; Japan: HR 3.15, $p < 0.001$). Reduced intensity conditioning showed a negative impact on relapse in both groups (FH: HR 1.93, $p = 0.048$; Japan: HR 1.67, $p = 0.049$). The presence of grade II aGVHD showed a positive impact on OS in both cohorts (vs grade 0-I, FH: HR 0.43, $p = 0.002$; Japan: HR 0.45, $p = 0.008$), whereas limited cGVHD had a positive impact only in the Japanese cohort (HR 0.21, $p = 0.035$). Grade III-IV aGVHD was associated with poor OS only in the Japanese group (HR 3.15, $p < 0.001$).

		Fred Hutch, Single CBT		Fred Hutch, Double CBT		Japan	
		n = 26	%	n = 226	%	n = 246	%
Age at CBT		42 (17-72)		45 (17-73)		51 (17-70)	
Gender	Female	15	57.7	112	49.6	104	42.3
	Male	11	42.3	114	50.4	142	57.7
Ethnicity	Caucasian	10	38.5	116	51.3	0	0
	Asian	3	11.5	33	14.6	246	100
	Hispanic/Latino	7	26.9	29	12.8	0	0
	Others/ Unknown	6	23.1	48	21.2	0	0
Disease type	AA/MDS/CML	6	23.1	43	19.0	33	13.4
	AML	8	30.8	50	22.1	24	9.8
	ALL	10	38.5	87	38.5	109	44.3
	Lymphoma/ATL	0	0.0	10	4.4	75	30.5
	Others	2	7.7	36	15.9	5	2.0
DRI	Low/ Intermediate	20	76.9	141	62.4	122	49.6
	High/Very high	3	11.5	21	9.3	73	29.7
TNC / kg		3.6 (2.3 - 4.6)		4.2 (2.3-8.4)		2.7 (0.0 - 6.3)	
CD34+ count / kg		0.29 (0.14-0.71)		0.27 (0.03-2.20)		0.7 (0.0 - 4.4)	
HLA-MM	0-1	11	42.3	52	23.0	41	16.7
	2-	15	57.7	170	75.2	132	53.7

Conclusions: In this large comparative study, we demonstrated similar clinical outcomes in patients receiving CBT at the FH and in Japan. Some of the differences observed between the 2 cohorts, such as the incidence of aGVHD, could be explained by different clinical practices between US and Japan. The presence of grade II aGVHD had a positive impact on OS in both groups, contrary to the previous reports and importantly, 5-year OS and RFS were similarly good.

Disclosure: Nothing to declare.

10 - Stem Cell Donor

P659

ACCESS: A MULTI-CENTER, PHASE II TRIAL OF HLA-MISMATCHED UNRELATED DONOR HEMATOPOIETIC CELL TRANSPLANTATION WITH POST-TRANSPLANTATION CYCLOPHOSPHAMIDE FOR PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Monzr M. Al Malki[1], Brian Shaffer[2], Steven M. Devine[3], Bronwen E. Shaw[4], Larisa Broglie[4], Muna Qayed[5], Sung Won Choi[6], Stephen R. Spellman[3], Craig Malmberg[3], Eric Ndifon[3], Brent Logan[4], Jeffery J. Auletta[3,7], Heather E. Stefanski[3], Janelle A. Olson[3], Antonio Jimenez Jimenez[8]

[1]City of Hope Cancer Center, Duarte, United States, [2]Memorial Sloan Kettering Cancer Center, New York, United States, [3]CIBMTR® (Center for International Blood and Marrow Transplant Research), National Marrow Donor Program/Be the Match, Minneapolis, United States, [4]CIBMTR® (Center for International Blood and Marrow Transplant Research), Medical College of Wisconsin, Milwaukee, United States, [5]Aflac Cancer and Blood Disorders Center, Emory University and Children's Healthcare of Atlanta, Atlanta, United States, [6]The University of Michigan, Ann Arbor, United States, [7]Nationwide Children's Hospital, Columbus, United States, [8]Division of Transplantation and Cellular Therapy, University of Miami Miller School of Medicine, Maiami, United States

Background: Despite more than 40 million donors registered globally, many patients with hematologic malignancies who need unrelated donor (URD) hematopoietic cell transplantation (HCT) cannot identify an 8/8 matched URD. The use of mismatched unrelated donors (MMUD) could alleviate this problem if survival rates are equivalent. The National Marrow Donor Program (NMDP) sponsored ACCESS study is currently evaluating the use of MMUD PBSC in adults while exploring the safety and efficacy of MMUD BM in pediatrics.

Methods: ACCESS (NCT04904588) is an ongoing multi-center phase II study with three strata – 2 adult strata based on conditioning intensity [Stratum 1 - myeloablative (MAC), or Stratum 2 -reduced intensity (RIC)] and a pediatric stratum. All patients receive GVHD prophylaxis using post-transplant cyclophosphamide (PTCy) on days 3 and 4 post-HCT, tacrolimus, and MMF beginning day 5.

Key exclusion criteria include a suitable HLA-matched related or 8/8 high resolution matched URD and presence of donor-specific HLA antibodies to any mismatched allele/antigen with mean fluorescence intensity > 3000. URD must be 18-35 years old and matched at 4/8-7/8 alleles (HLA-A, -B, -C, and -DRB1).

The primary endpoint is one-year OS. Select secondary and exploratory endpoints include GVHD-Free Relapse Free Survival (GRFS) and event-free survival (EFS) at 1-year, incidence of patient-reported toxicities and symptoms, OS in the pediatric stratum, and the prioritization of URD selection characteristics. HLA loss of heterozygosity will be assessed on peripheral blood samples from relapsed patients. Patient-reported outcome data are also being collected at baseline, 100, 180 and 365 days post-HCT.

The study will accrue 300 subjects (260 adults; 40 pediatrics) to determine whether OS at one year is 75% in the adult strata.

Results: 35 of 42 planned study sites are open to enrollment, 22 of which have enrolled at least one subject. Adult accrual is over 150% of projected accrual, while pediatric accrual is behind target.

Consistent with the aim of improving access to HCT for all patients in need, 47% of enrolled patients to date are racially/ethnically diverse. AML has been the most common diagnosis (Table 1). TBI-based conditioning has been used most frequently in the MAC Stratum 1 (45%) and Fludarabine/Melphalan on Stratum 2 (60%). 85% of the reported infused products to adult patients have been cryopreserved. Unrelated donor HLA match score has included 7/8 (64%), 6/8 (29%), 5/8 (5%), and 4/8 (< 1%) matched donors, with 15 study sites selecting a donor that is <7/8 matched. Registry models conducted in support of the study suggest all patients will have multiple ≥ 5/8 donor options with age ≤35 years available.

Table 1. Demographics/Baseline characteristics of enrolled patients and unrelated donors in the ACCESS trial as of 12/02/2022

Characteristic	STRATUM 1	STRATUM 2	STRATUM 3
No. of patients	47	88	5
No. of centers	12	14	5
Age at HCT - no. (%)			
Median (min-max)	42 (21-65)	65 (24-77)	10 (9-20)
Sex - no. (%)			
Male	29 (62)	44 (50)	3 (60)
Female	18 (38)	44 (50)	2 (40)
Primary diagnosis - no. (%)			
ALL	15 (32)	6 (7)	2 (40)
AML	17 (36)	45 (51)	2 (40)
MDS	7 (15)	21 (24)	1 (20)
Other Acute Leukemia	1 (2)	2 (2)	0 (0)
CLL	0 (0)	1 (1)	0 (0)
CML	0 (0)	2 (2)	0 (0)
Lymphoma	0 (0)	7 (8)	0 (0)
Not yet reported	7 (15)	4 (5)	0 (0)
Donor age - no. (%)			
Median (min-max)	25 (19-34)	25 (19-35)	29 (23-33)

Conclusions: Accrual has been brisk and site participation broad, suggesting ACCESS addresses an unmet patient need. Adult accrual is anticipated to complete in mid-2023. Planning for the next NMDP-sponsored MMUD study is underway, focusing on mitigating risks of NRM, GVHD, and relapse.

Clinical Trial Registry: Trial registration number: NCT04904588 ClinicalTrials.gov

Disclosure: Monzr M. Al Malki: Consultancy and Research Funding: Gilead; NexImmune; Miltenyi Biotec; Incyte; CareDx: Membership on an entity's Board of Directors or advisory committees; Hasna Biopharma

Steven M. Devine: Consultancy: Orca Bio

Bronwen E. Shaw: Consultancy: Orca Bio

Brian Shaffer: Consultancy: Hansa Biopharma; Gamida Cell: Research support: Miltenyi

Larisa Broglie: Nothing to declare

Muna Qayed: Honoraria and membership on an entity Board of Directors or advisory committees: Novartis: Honoraria: Vertex

Sung W. Choi: Nothing to declare

Stephen R. Spellman: Nothing to declare

Craig Malmberg: Nothing to declare

Eric Ndifon: Nothing to declare

Brent Logan: Nothing to declare

Jeffery Auletta: Membership on an entity's Board of Directors or advisory committees: AscellaHealth

Heather E. Stefanski: Ad Board: Novartis

Janelle A. Olson: Nothing to declare

Antonio Jimenez Jimenez: Research funding: AbbVie

10 - Stem Cell Donor

P660

BLUSTAR – A PROJECT TO RECRUIT NON-CAUCASIAN HEMATOPOIETIC STEM CELL DONORS RESULTING IN MORE THAN 8,000 DONORS AND MORE THAN 10 PBSC APHERESES SO FAR

Lambros Kordelas[1,2], Christian Binder[1,3], Karin Gebhardt[1], Carlos Jiménez Klingberg[3], Joana Siepmann[1], Daniel Weichert[1], Johannes Fischer[4], Thomas Zeiler[3], Peter A. Horn[2]

[1]WSZE, Ratingen, Germany, [2]University Hospital Essen, Essen, Germany, [3]German Red Cross Blood Service West, Breitscheid, Germany, [4]University Hospital Düsseldorf, Düsseldorf, Germany

Background: Approximately 19 million people with a non-Caucasian genetic origin live in Germany. The majority of these people descend from regions where the population has a genetically different distribution of HLA antigens when compared to the most common HLA frequencies in Central Europe. In severe hematological diseases, allogeneic stem cell transplantation might offer the only curative therapeutic option. However, finding HLA-compatible hematopoietic stem cells (HSC) donors in case a related donor is lacking, continues to be a major challenge in the non-Caucasian population as there are only few unrelated donors with a similar genetic background registered in HSC donor registries.

Methods: The "BluStar" project was initiated to recruit healthy individuals with a non-Caucasian background as potential donors for HSC. The non-Caucasian donors were registered and typed by the Westdeutsche SpenderZentrale (WSZE), Ratingen, Germany. Several dedicated recruiting events, multi-lingual flyers, and intensive interactions with relevant social stakeholders have been employed to attract potential non-Caucasian HSC donors. We analysed the gender and age distribution of donors recruited in the BluStar project. Besides, we documented the "work-ups" (i.e. requests for a potential HSC donation) resulting out of the BluStar cohort per country and compared the apheresis probability and cancellation rate of work-ups in the BluStar cohort with that in the non-BluStar WSZE donor cohort.

Results: Since December 2017, in total more than 8,000 non-Caucasian HSC donors have been recruited and HLA-typed in this project. 5,312 (66%) donors were male (m), the remaining 2,705 (34%) donors were female (f). The age distribution was as follows: < 30 years: 1,651/1,377 (21%/17%, m/f); <40 years: 1,311/457 (16%/6%, m/f); <50 years: 1,237/462 (15%/6%, m/f); >50 years: 1,116/412 (14%/5%, m/f). Since the beginning of the project, 23 work-ups were initiated. Eleven work-ups were eventually cancelled; however, eleven peripheral blood stem cells (PBSC) and one DLI were collected and administered to patients. The PBSC/DLI were delivered to Germany, USA, France, Spain, UK and Australia. Interestingly, the apheresis probability is exactly twice as high compared with the apheresis probability in the non-BluStar WSZE donor cohort (0.14% vs. 0.07%), indicating the medical need for non-Caucasian HSC donors. On the other hand, the cancellation rate of work-ups in the BluStar cohort is also twice as high as in non-BluStar WSZE donor cohort (48% vs. 25%).

Conclusions: This project describes the successful registration of more than 8,000 non-Caucasian donors in a registry for unrelated HSC donors. The high recruiting numbers gives testimony of the willingness of this cohort of potential donors to be registered and HLA-typed. The exactly twice-fold apheresis probability in this non-Caucasian donor cohort, translating in eleven PBSC and one DLI apheresis in this short time period, pinpoints the lack of non-Caucasian HSC donors. However, the high cancellation rate might indicate higher logistic hurdles in this cohort. Obviously, there is serious medical need to increase the number of non-Caucasian HSC donors to enable more allogeneic stem cell transplantations in the non-Caucasian patient population.

Disclosure: No potential conflict of interest.

The European Development Fund 2014-2020 (ERDF) and the European Union funded this project.

10 - Stem Cell Donor

P661

RETROSPECTIVE REVIEW OF DONOR LYMPHOCYTE REQUESTS TO ANTHONY NOLAN REGISTRY SHOW EXCELLENT DONOR AVAILABILITY AND VERY LOW RATES OF DONOR ATTRITION AND MEDICAL CLEARANCE FAILURE

Angharad Pryce[1], Ruta Maniusyte[1], Ann O'Leary[1], Catherine Burlton[1], Paul Johnson[1], Julia Lee[2], Rachel Pearce[2], Antonio Pagliuca[3], Chloe Anthias[1], Jane Apperley[4], Robert Danby[3]

[1]Anthony Nolan Donor and Transplantation Services, London, United Kingdom, [2]British Society of Blood and Bone Marrow Transplantation and Cellular Therapy, London, United Kingdom, [3]Anthony Nolan Research Institute, London, United Kingdom, [4]Imperial College London, London, United Kingdom

Background: Relapse is the commonest cause of treatment failure after haematopoietic cell transplant (HCT).[1] Donor lymphocyte infusions (DLI) remain an important strategy in both the prevention and treatment of relapse.

Access to and availability of DLI, therefore, remain crucial to transplant centres (TCs) and their patients, with some TCs storing DLI pre-emptively from the initial harvest. Ability to do so however depends on stem cell laboratory capacity, adequate cell count so as not to compromise optimal CD34+ cell dose for transplant, and donor consent/registry agreement for storage. Otherwise, standard procedure is for additional lymphocyte apheresis to be requested and collected from the original HCT donor. However, there is limited data on DLI request completion rates and availability of donors to help inform TC decision making.

Methods: This was a retrospective review of subsequent donation request for DLI received by Anthony Nolan registry (Jan 2015 to Jan 2022) to assess completion rates and donor availability. This included requests from UK and International TCs for UK and international donors. We also compared UK TC unrelated donor lymphocyte requests to the number of UK transplant patients receiving unrelated donor DLI as reported to BSBMTCT in order to estimate frozen cell availability stored from first collection.

Results: There were 1148 DLI requests during the study period, with 968 completed collections (84.3%). The commonest indication was AML accounting for 47% of all requests. 66 (5.7% total requests) were cancelled for donor reasons; the commonest reason being donor unavailability (1.9%). 1.3% of donors were not committed or contactable and only 1.5% were cancelled due to the donor failing medical clearance.

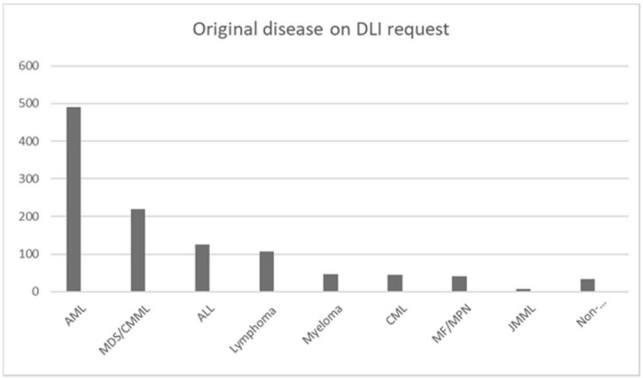
Between Feb 2017 and July 2021 there were 747 UK unique patients who received an unrelated DLI as reported to BSBMTCT compared to 537 unrelated DLI requests from UK TCs to AN registry in this period, estimating 28% had stored DLI available from previous collections. Corresponding audit of the DLI request forms during this period showed 15% documenting previous stored and subsequently infused DLI from time of first PBSC harvest, (information not provided in 18%).

Table 1.

Total DLI requests	**1148**
Total Complete	**968 (84.3%)**
Cancelled Donor	**66 (5.7%)**

• Not available	22
• Not contactable/committed	15
• Failed medical clearance	18
• Other	11
Cancelled Patient	**104 (9%)**
• Patient died	18
• Health deteriorated	52
• Health improved	24
• Other	10

Fig 1.



Conclusions: DLI remain an integral strategy to both reduce risk of relapse and treat relapse post HCT often used alongside pharmacological approaches. Therefore, availability and access to this cellular therapy is an important consideration for TCs and limited data exits to provide reassurance in the unrelated donor setting. This retrospective review shows the relatively common practice of storing DLI off the back of the initial PBSC collection. However, there is considerable TC variability, of particular interest given the difference between conventionally collected versus G-CSF primed DLI has not been extensively established.[2-3]

For TCs without storage capacity or unwilling to compromise on cell count this provides reassurance of high completion rates of DLI requests, and high levels of donor availability, with only 5.7% of requests not being facilitated for donor reasons. This aids TC decision making and highlights to registries that good donor experience, follow up and methods to maintain engagement are likely crucial to ensure high completion of subsequent donation rates.

Disclosure: Nil to disclose.

10 - Stem Cell Donor

P662

POSTTRANSPLANT CYCLOPHOSPHAMIDE BASED T CELL REPLETE HAPLOIDENTICAL STEM CELL TRANSPLANTATION IN PEDIATRIC HEMATOLOGICAL MALIGNANCIES: A SINGLE CENTER EXPERIENCE

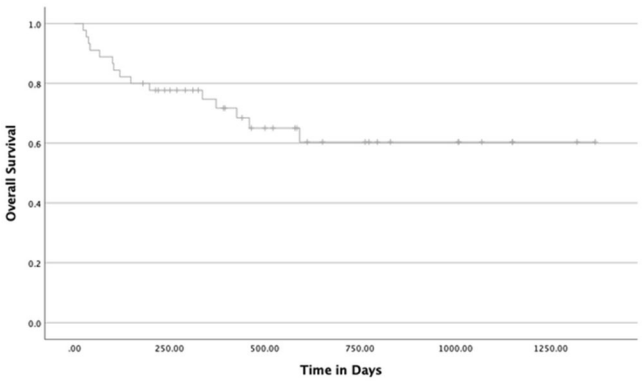
Rajesh Patil[1], Ratna Sharma[1], Pranoti Kini[1], Amit Jain[1], Ashutosh Walawalkar[1], Akanksha Chichra[2], Shyam Srinivasan[2], Kalyani Patil[1], C. Muralidharan[1], Srishti Srivastava[1], Sriraksha Ganiga[1], Santosh Khude[1], Mamta Manglani[1]

[1]MCGM - CTC, PHO & BMT Centre, Mumbai, India, [2]Tata Memorial Hospital, Mumbai, India

Background: Haploidentical stem cell transplantation as a treatment option for various high risk hematological malignancies is on the rise due to limited availability of matched allogenic donors. We share our experience of T cell replete haploidentical stem cell transplantation (Haplo HSCT) with posttransplant cyclophosphamide (PTCY) in our cohort of pediatric hematologic malignancies.

Methods: This is a retrospective analysis of children with various high risk hematological malignancies who underwent haplo HSCT at our center from February 2019 to June 2022. Besides standard conditioning regimen, all received PTCY 50 mg/kg on day 3 and 4 as GVHD prophylaxis along with tacrolimus/cyclosporine and mycophenolate mofetil.

Results: This analysis included 45 patients. Median follow up was 584 days (180 – 1357 days). Median age was 8 years (3 years -18 years) with male to female ratio of 3 : 1. Out of 45 patients, 10 (22.2%) were ALL-CR1, 12 (26.6%) were ALL CR2, 3 (6%) were AML CR1, 10 (22.2%) were AML CR2 while remaining 10 (22.2%) patients were of various other high risk hematologic malignancies like MPAL, CML BC, MDS and high risk lymphomas. All patients received myeloablative conditioning, TBI based conditioning used in 86.3 % patients with ALL. A median of 9. 2 millions (6 millions -10 millions) of CD34/Kg cell dose was infused. Successful engraftment (at day 28) was observed in 41/45 patient (91.1%). Incidence of grade II-IV & III-IV acute GVHD was 29.2 % & 17% respectively. Mild chronic GVHD was seen in 37% of patients while 13% of patients developed moderate chronic GVHD. One patient developed severe chronic GVHD in form of bronchiolitis obliterans and succumbed. Event free survival (EFS) and overall survival (OS) of this cohort was 62.2 % (28/45) and 66.6% (30/45) at 584 days (19.3 months) of median follow up. Out of 15 patients expired post haplo HSCT, 6 (40%) were lost due to disease relapse while engraftment failure and infections were causes of mortality in 4 patients (26.6%) each. CMV viremia was detected in 46.6% patients while 9% patients had CMV disease. Symptomatic BK viruria was noticed in 7% patients while only one patient (2%) had adenoviremia.



Conclusions: Haploidentical stem cell transplants with PTCY is an efficacious strategy in the treatment of pediatric hematological malignancies. Further improvement in supportive care can lead to better outcomes following this approach.

Disclosure: Nothing to declare.

10 - Stem Cell Donor

P663

CURRENT DEMAND AND PROVISION OF UNRELATED DONOR LYMPHOCYTES TO UK TRANSPLANT CENTRES FROM ANTHONY NOLAN UK STEM CELL REGISTRY

Angharad Pryce[1], Ruta Maniusyte[1], Ann O'Leary[1], Paul Johnson[1], Antonio Paglicuca[2], Chloe Anthias[1], Jane Apperley[3], Robert Danby[2,2]

[1]Anthony Nolan Donor and Transplantation Services, London, United Kingdom, [2]Anthony Nolan Research Institute, London, United Kingdom, [3]Imperial College London, London, United Kingdom

Background: Donor lymphocyte infusions (DLI) are an integral strategy in both prevention and treatment of relapse following haematopoietic cell transplantation (HCT). With advancement in cellular therapy techniques, there is potential for further refinement of DLI strategies in the future. This review aims to understand current practice in UK transplant centres (TC), evaluate demand and provision, and review donor safety of this procedure.

Methods: This was a retrospective review of UK transplant centre (TC) completed DLI requests received by Anthony Nolan registry for UK donors between February 2017 and July 2020. Data was collected from DLI request forms from the TC, as well as data on the donor experience, achievement of target cell request, and procedure related complications.

Results: There were 506 UK transplant requests for DLI during this period, of which 200 were for UK donors, and 193 were complete and available for review.

Commonest indication was pre-emptive for mixed chimerism (42%) followed by relapse (33%), MRD-positive (10%) and prophylactic (5%). Underlying disease was most commonly AML. There was large TC variation in CD3 dose requested from 10-300x 10^6 CD3 cells/kg. Median time to DLI collection from first transplant was 261 days. 15% of patient had stored DLI from first transplant and had received at least one dose ahead of subsequent request. 30% of patients had previous or current GVHD, 7% continued on immunosuppression.

Over 75% of collections were accommodated within 3 weeks of first choice dates. Requested cell target was achieved in 45%. However, only 5 donors (3%) needed to donate DLI more than once. In all cases TC reported cryopreserving additional aliquots. 34 (17.6%) discarded additional excess cells (> 10% of total volume collected).

The DLI donors were male (74%), median age of 28.4 (range 18-62 years). Complications were rare with no overnight admissions needed. There was one vasovagal (< 0.5%) and one extravasation (< 0.5%). 12 donors (6.2%) required central lines of which 5 were unplanned. Approximately one third of donors required treatment for hypocalcaemia. Post-procedural full blood count showed one grade 1 thrombocytopenia of <100. Mild reduction in platelets count 100-150 was seen in 15.5%.

DLI requests from UK TC for UK donors	Number (%)
Total UK Transplant centre requests	506
UK donors	200
Completed requests available for review	193
Original disease	
AML	65 (34%)
MDS/CMML	37 (19%)
Lymphoma	21 (11%)
ALL	15 (8%)
Myelofibrosis	11 (6%)
Multiple Myeloma	9 (5%)
CML	8 (4%)
Non-malignant	3 (1.5%)
Other/Not known	24 (12.5%)
Indication	
Mixed chimerism	42%
Relapse	33%
MRD positive	10%
Prophylactic	5%
Not known	10%
Initial donation	
PBSC	166 (86%)
BM	9 (5%)
Not documented	18 (9%)
PBSC Median dose	5.21 x 10^6/kg
BM Median dose	3.72 x 10^8 TNC/kg
Median time from 1st transplant to DLI	261 days (range 1 month to 13.5 years)
Previous DLI	
Stored DLI at time of initial transplant	30 (15%)
Infusion of one or more doses of stored DLI	30 (15%)
GVHD and concurrent immunosuppression	
Diagnosis of GVHD made post-transplant	30%
Current immunosuppression	7%

Conclusions: DLI remain an important strategy to reduce risk of relapse and treat relapse post HCT. This review shows the majority of UD-DLIs provided to UK TCs are for pre-emptive treatment of mixed chimerism. The majority of patients are weaned from immunosuppression with only 7% remaining on systemic immunosuppression. Variability in cell dose request was marked between TCs as was the practice of storing DLI at the time of first harvest.

Donors can be counselled that if asked to donate DLI it is most likely to occur within the first year. Donor lymphocyte collections are a well-tolerated and safe procedure with mild and easily treated side effects such as hypocalcaemia. Although donors may not reach the target CD3 dose requested only very few will be required to donate again suggesting the vast majority achieved adequate CD3+ve yield. The high discard rate of excess cells raises possibility of diverting such cells for ethically approved research provided appropriate donor consent.

Disclosure: Nil to disclose.

10 - Stem Cell Donor

P664

OVERVIEW OF MATCHED UNRELATED DONOR SEARCH - LIMITED EXPERIENCE WITH THE ROMANIAN NATIONAL VOLUNTARY STEM CELL DONOR REGISTRY (RNDVSCH)

***Zsofia Varady*[1]**

[1]Romanian National Voluntary Stem Cell Donor Registry, Bucharest, Romania

Background: Background: Stem cell donor registries have two primary objectives in their activity: (1) to increase the numbers of registrations for voluntary stem cell donors, and (2) to link the patient's need for a timely unrelated compatible transplant with a stem cell donation through donor centers, laboratories, transplant centers, apheresis facilities and cell transport.

The objective is to bild a network in one's own country and to connect with others internationally in order to select the best potential unrelated donor through a standardised procedure.

Methods: In recent years, the NGS technique has proven to best meet the needs, such as obtaining high-resolution HLA typing with minimal ambiguity in a single test, defininig regional genetic diversity more precisely, and increasing workload.

In the last 3 years (2019-2021) 5300 whole blood EDTA samples have been tested for HLA-A, B, C, DRB1, DQB1 and DPB1 alleles using NGS Long-Range PCR – Holotype HLA kit, Omixon and MiniSeq platform (Ilumina). The HLA Twin software was used for data analysis. The rare alleles defined in the Twin application were taken into account. All rare alleles, including those confirmed by family study, were also tested by a second method: SSP and HLA Score software (CareDx Olerup), SBT SeCore kit and uTYPE software (Thermo Fisher One Lambda). We identified rare HLA alleles in 46 unrelated donors, 3 patients and 3 relatives of different patients. The distribution of rare alleles per locus was: 12 HLA-A, 19 HLA-B, 8 HLA-C and 13 HLA-DRB1.

Case Presentation: Male, 20 years old, with acute myeloblastic leukemia M4 AML1-ETO in second complete remission requiring a stem cell transplant. In February 2019 we identified a potential 9/10 matched unrelated donor, but he refuse to donate, so, the decision was made to an haploidentical transplant. The lab identified that HLA-A*02:819 did not exist in the IMGT 3.32 allelic database until March 2019. This allele was confirmed in the patient's father and sister. The haploidentical transplant was performed în 11th December 2019 from his sister with Fludarabin/Thiothepa/Melphalan conditioning and graft versus host disease prophylaxis with post-transplant cyclophosphamide/tacrolimus/mycophenolate. Engraftment was on day+16 with complete chimerism on day+30. Three years after the transplant, he is in complete molecular remission with the exception of herpetic keratitis in June 2020.

Results: In Romanian National Voluntary Stem Cell Donor Registry (RNDVCSH) (ION 1372) we have a total of 61351 donors enrolled, 99,5% are typed in HLA-A, B, DRB1. The first stem cell graft came in 10th January 2013. Since then we imported 397 stem cell grafts and 42 donor lymphcytes and we exported 18 stem cell grafts and two donor lymphocytes.

Conclusions: According to preliminary data, the Romanian population contains 0,98% rare alleles. Until this moment, 72% of identified rare specificities were detected only once. The identified rare HLA specificities were found and confirmed for the first time in the Romanian population. Continued use of NGS technology in routine testing will help facilitate high-resolution HLA typing for patients and donors, as well as contribute to a better understanding of regional genetic diversity.

Disclosure: Zentiva - Funding.

10 - Stem Cell Donor

P665

TRENDS IN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION OVER THE PAST 21 YEARS – A SINGLE CENTRE ANALYSIS

Pavel Jindra[1], Michal Karas[1], Kateřina Steinerová[1], Daniel Lysák[1], Jiří Šrámek[1], Alexandra Jungová[1], Marcela Hrabětová[1], Veronika Bergerová[1], Tereza Dekojová[1], Tomáš Procházka[1]

[1]University Hospital, Pilsen, Czech Republic

Background: Allogeneic Haematopoietic cell transplantation (alloHCT) has achieved significant advances in recent years, which have enabled its extension to other diseases and, above all, made it feasible even for elderly patients. On the other hand, the availability of innovative treatment significantly changes the utilization of alloHCT for some diseases. We evaluated how these changes were reflected at our center.

Methods: The file consists of 855 patients who underwent 1st alloHCT during 2001-2021. For the analysis we divided the file into three 7-years periods: 2001-2007(A = 257 pts), 2008-2014 (B = 304 pts) and 2015-2021 (C = 294 pts).

Results: A significant gradual increase in the median age of patients was evident for the consecutive periods– 50y (range 20-68) vs. 53y (19-71) vs. 55y (20-74), $p < 0.0001$. Likewise, the proportion of patients over 70 increased from 0% in period A to 23 (8%) in period C, $p < 0.0001$. This was reflected in a decline in the use of the myeloablative regimen (43% in A compared to 24% and 28% in periods B and C, respectively, $p < 0.0001$). Bone marrow use increased from 11% to 20% in period B ($p = 0.0049$), then remained the same for C (18%, $p = 0{,}943$). Fundamental changes were observed in the type of donors when, as expected, a large increase in haploidentical donors was recorded in the C period: 27% vs. 1% in B vs. 0% in A ($p < 0.0001$). This was at the expense of siblings (from 41% to 26% and 9%, respectively, $p < 0.0001$), as the proportion of unrelated donors remained essentially the same (60% vs.73% vs. 64%). Regarding GVHD prophylaxis, CNIs/MTX remained the mainstay for all types of transplantation except for haploidentical donors, where PTCY was exclusively used. However, administration of ATG as an adjunct to CNIs increased significantly (from 22% through 30% to recent 55%, $p < 0.0001$).

In all periods, the main indication was myeloid malignancies (AML/MDS), the proportion of which even rose steadily (from 39% in A to 62% in C, $p < 0.0001$). On the other hand, there was a significant decrease in transplants for CML (11%, 4% and 1%, $p < 0.0001$) and for CLL (14, 13 and 3%, $p < 0.0001$). The share of other indications - ALL, NHL, MM, MH, MPN - remained essentially the same with insignificant variations during periods (e.g. ALL 9%, 13% and 9%, $p = 0.1608$).

Conclusions: Our summary of a single centre transplant activity over the past 21 years surprisingly closely mirrors the EBMT&CIBMTR data. It documents a continuing trend towards transplantation of increasingly older patients and unrelated and haploidentical donors as the currently predominant donor type. Myeloid malignancies remain the predominant indication (which is also reflected by the increasing age of transplant recipients), while in response to the advent of new drugs, some diagnoses (namely CML and CLL) have decreased substantially. The onset of CAR-T treatment in lymphoid malignancies has not yet been reflected in the last period. In contrast to the EBMT data, there has been no decline in the bone marrow utilization in our centre, as its indisputable benefits in certain situations (outside of SAA) are supported by solid evidence.

Disclosure: Nothing to declare.

10 - Stem Cell Donor

P666

EXPERIENCES OF PARENTS WHO CONCEIVED SAVIOR SIBLINGS FOR BEING HEMATOPOIETIC STEM CELL DONORS TO THEIR SICK CHILDREN AND SUCCESSFULLY COMPLETED THE PROCESS: A QUALITATIVE STUDY

İbrahim Eker[1], Hamide Nur Çevik Özdemir[2], Fırat Yılmaz[3], Akif Yeşilipek[4], Alphan Küpesiz[5], Vedat Uygun[6], Gülsün Karasu[7], Funda Tayfun Küpesiz[8], Orhan Gürsel[9], Barış Kuşkonmaz[10], Serap Aksoylar[11], Fatma Visal Okur[12], Gülcihan Özek[13], Musa Karakükcü[14], Başak Adaklı Aksoy[15], Özlem Tüfekçi[16], Zühre

Kaya[17], Barış Malbora[18], Ahmet Emin Kürekçi[19], Ali Bülent Antmen[20]

[1]Afyonkarahisar Health Science University, Afyonkarahisar, Turkey, [2]Afyonkarahisar Health Science University, Afyonkarahisar, Turkey, [3]Qualitative & Mixed Method Researcher, Istar Soft Consultant Research Center, Ankara, Turkey, [4]Medical Park Antalya Hospital, Antalya, Turkey, [5]Akdeniz University School of Medicine, Pediatric Hematology Oncology Unit, Antalya, Turkey, [6]Istinye University, Medical Park Antalya Hospital, Antalya, Turkey, [7]Medicalpark Göztepe Hospital, Istanbul, Turkey, [8]Akdeniz University, Antalya, Turkey, [9]University of Health Sciences, Gülhane Training and Research Hospital, Ankara, Turkey, [10]Hacettepe University, Bone Marrow Transplantation Unit, Ankara, Turkey, Ege University, Izmir, Turkey, [12]Hacettepe University, BMT Unit, Ankara, Turkey, [13]Ege University Medical School, Pediatric BMT Center, Izmir, Turkey, Division of Pediatric Hematology and Oncology, Erciyes University KANKA Pediatric Hematology, Oncology & BMT Center, Kayseri, Turkey, [15]Altunbaş University, School of Medicine, Medical Park Bahçelievler Hospital, Pediatric Stem Cell Transplantation Unit, Istanbul, Turkey, [16]Dokuz Eylul University Pediatric Hematopoietic Stem Cell Transplantation Unit, Izmir, Turkey, [17]Gazi University School of Medicine, Unit of Pediatric Hematology, Ankara, Turkey, [18]Yeni Yüzyil University Gaziosmanpaşa Hospital, Pediatric Bone Marrow Unit, Istanbul, Turkey, [19]Lösante Hospital, Pediatric Hematology/Oncology and Stem Cell Transplantation Center, Ankara, Turkey, [20]Turkish Pediatric Bone Marrow Transplantation Study Group (TPBMT-SG), Acibadem Adana Hospital, Pediatric BMT Unit, Adana, Turkey

Background: Preimplantation genetic diagnosis (PGD) by using human leukocyte antigen (HLA) matching together, offers preselection of a potential HLA-genoidentical healthy donor, in other words savior sibling, for an affected sibling, who requires Hematopoietic Stem Cell Transplantation (HSCT). Unfortunately ethical, religious, legal and financial discussions on this subject are continuing, but the experiences and opinions of the parents who have gone through this process. were not included in these discussions. Evaluating the experiences and opinions of these parents will provide a more accurate and more realistic perspective to discussions on this issue, which is not applied much in the world because of these dilemmas. It will also provide valuable contributions to families who decide to experience this treatment modality.

Methods: The research is designed as phenomenological qualitative research. A total of 16 parents, who conceived savior siblings for being HSCT donors to their sick children and successfully completed the process, from 10 different pediatric transplant centers in Türkiye were included, using purposive sampling. Qualitative interviews were conducted by video teleconference method between August and December 2022, with the parents who agreed to participate. Demographic data, introductory information and semi-structured interview forms were used to collect data. The views of the participants were analyzed with Maxqda data analysis software and Colaizzi's seven-step method and thematic coding was created by the researchers

Results: Within the scope of the research, 4 themes were created. These are; Disease Stage, HSCT, Recovery Phase and Social Family. In Disease Stage Theme; Learning the Diagnosis, Treatment Method, Decision Phase, Religious and Cultural Factors, Coping Strategies and Recommendation categories were included. In HSCT Theme; Emotional Condition of Parents, Difficulties and Caring for a Sick Child After HSCT categories were included. In Recovery Theme; Meaning Attributed to the Savior Sibling and Change in Mood categories were included. In Social Family Theme; Family Members' Perspective, Having a Savior Sibling, Support Systems, Image and Suggestions categories were included. The codes that come to the fore in these themes and categories are compatibility with religious and ethical values, not feeling regret, determination to live the same process if necessary, the joy of both having a new healthy child and helping the sick child survive, trust to the responsible physician, the burden of the process being on the mothers to a great extent, the need for psychosocial support, the emphasis of resoluteness even though there are difficulties.

Conclusions: Our qualitative study demonstrate that, PGD and HLA matching process for savior sibling is very difficult and should be followed and supported from the beginning, to the end of HSCT by a large team that includes, primarily the responsible transplant physician as the team leader, as well as branches such as psychologists, pedagogues, social and financial services. In addition, families experiencing this process in Turkey do not have a negative religious or ethical opinion about the issue, and they recommend families to try this treatment opportunity with the support mentioned above, who need to go through these processes for their sick children.

Clinical Trial Registry: There is no Clinical Trial registry number and website

Disclosure: "Nothing to declare".

10 - Stem Cell Donor

P667

ALTERNATE DONOR TRANSPLANTATION USING SINGLE-ANTIGEN MISMATCHED GRAFTS – THE IRISH EXPERIENCE

Alanna Allen[1], Catherine Flynn[1]

[1]St James Hospital, Dublin, Ireland

Background: Human leukocyte antigen (HLA)-matched allogeneic stem cell transplant (SCT) is a curative treatment for haematologic malignancies (1). Approximately 1/3 of eligible patients have a HLA-matched sibling (2). For the remainder, the chances of finding a 10/10 HLA-matched donor in the unrelated registry vary according to ethnicity. Due to smaller family size, ineligibility of older sibling donors, and our increasing ethnic diversity, an increasing number of potential transplant candidates lack a fully-matched donor. Alternate donor strategies provide an avenue to transplant for these patients but historically are associated with poorer outcomes (3).

Our favoured alternate donor platform in Ireland has been the use of single-antigen mismatched donors and the objective of this study was to report the outcomes in this patient cohort over the last decade.

Methods: We retrospectively assessed all patients who underwent HLA-mismatched SCT for a haematological malignancy between January 2015 and August 2021. Data was retrieved from the electronic patient record in St James's Hospital. The CIMBTR disease risk index was used to grade disease risk pre-transplant, GVHD was graded according to Glucksberg grade (I-IV). Survival analysis was performed using the Kaplan-Meier model.

Results: Forty-five patients were identified. The diagnoses were varied; acute myeloid leukaemia or precursor lymphoid neoplasms accounted for the majority (60%). CIBMTR disease risk assessment showed over 90% of patients had intermediate/high-risk disease. Patients had a median Karnofsky score of 80% and the majority (80%) had a low HCT-CI score of 0-1. Stem cell sources included peripheral blood (66%) and bone marrow (34%). Conditioning regimes were myeloablative in 44% and reduced-intensity in 56%. Most patients received GVHD prophylaxis with a combination of a

calcineurin inhibitors (CNI) and ATG (70 %) while the remainder received CNI in combination with MMF or Methotrexate. The median time to neutrophil engraftment was 23 and platelet engraftment was 23 and 25 days respectively. All patients reached neutrophil engraftment but 4 required the use of GCSF, 5 patients failed to achieve platelet engraftment and 3 had delayed platelet engraftment.

Acute Graft Vs Host Disease GVHD occurred in 60% (n = 27); 18% (n = 8) developed grade 3-4 GVHD. Chronic GVHD was recorded in 40% (n = 18) patients, 14 of whom had prior Acute GVHD or acute engraftment syndrome.

At the time of censoring, 21 deaths recorded; 12 (57%) were due to relapse and the remainder were due to treatment-related mortality. The median time to relapse was 190 days (Mean =330 days). The estimated OS at 2 years was 60%.

Conclusions: Increasing demand for alternate donor transplantation warrants continued optimisation of available platforms. Our survival outcomes are comparable to those seen in fully-matched donor transplants, which may be due to the selection of patients with good performance status and low co-morbidities for this higher-risk platform. Despite the use of ATG we continue to see significant GVHD. Novel GVHD-prevention strategies such as the use of post-transplant cyclophosphamide may improve outcomes further and extend the possibility of mismatched or haploidentical transplantation to those who lack fully-matched donors.

Disclosure: I have nothing to disclose.

2 - Stem Cell Mobilization, Collection and Engineering

P668

PERIPHERAL BLOOD STEM CELL PRE HARVEST XN-HPC COUNT AS AN EFFECTIVE SURROGATE FOR CD34+ CELL COUNT IN A MAJOR HAEMOPOIETIC STEM CELL TRANSPLANTATION CENTRE

Siew Lian Chong[1], Asral Wirda Ahmad Asnawi[2,1], Sen Mui Tan[1]

[1]Hospital Ampang, Ampang, Malaysia, [2]Universiti Sains Islam Malaysia, Bandar Baru Nilai, Malaysia

Background: CD34+ haemopoietic cell count is used to define cell harvest goals. Successful peripheral blood stem cell transplantation depends on the infusion of an appropriate number of HPCs to achieve rapid and durable haematologic recovery. In this study, we evaluated the use of the Hematopoietic Progenitor Cell count programme on the Sysmex XN-3000 haematology analyser as an effective parameter for the enumeration of CD34+ cell count.

Methods: Two hundred and one peripheral blood samples were collected from 144 subjects who were scheduled to undergo peripheral blood stem cell collection. CD34+ enumeration was performed using FACS Calibur flow cytometry as per standard protocol. The same sample was used for XN-HPC enumeration. To compare both methods, cell counts were reported as the number of cells in $x10^6$/L. Passing-Bablok analysis was used to estimate the slope and intercept with 95% confidence interval (CI) while agreement between the two methods were analysed using Bland-Altman difference plot. Spearman's rank correlation coefficient, *r* with 95% CI was calculated followed by the calculation of the receiver operating characteristic (ROC) curve to identify the XN-HPC value that could effectively predict the cutoff of ≥10 $x10^6$/L and 20 $x10^6$/L CD34+ cell.

Results: The correlation between two methods was high ($r = 0.766$; 95% CI: 0.702-0.818). The regression equation was defined as XN-HPC = 3.45 + 0.78 (CD34+). Results from the Passing Bablok show that the intercept at 3.45 (2.54 to 4.74) with the slope at 0.78 (95% CI 0.69 to 0.89). The residual analysis of this model indicates no significant deviation from linearity ($p = 0.360$). The ROC curve demonstrated the area under curve to be 0.88 (0.82 to 0.92) with a positive predictive value of 80.3%.

Conclusions: Correlation of CD34+ and XN-HPC showed strong correlation and good agreement with minimal bias. XN-HPC showed good analytical performance. With the increasing prevalence of stem cell transplantation and its high costs per year, XN-HPC appears to be suitable, rapid and sustainable alternative for CD34+ cell enumeration.

Clinical Trial Registry: www.nmrr.gov.my
NMRR-20-2585-57209 (IIR)

Disclosure: The authors (Siew Lian, Chong; Asral Wirda, Ahmad Asnawi; Sen Mui, Tan) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

2 - Stem Cell Mobilization, Collection and Engineering

P669

AUTOLOGOUS PERIPHERAL BLOOD STEM CELL MOBILISATION TECHNIQUES, CELL YIELDS AND PRACTICE VARIATION-BY-COUNTRY IN MYELOMA PATIENTS UNDERGOING FIRST AUTOLOGOUS STEM CELL TRANSPLANTS IN EBMT CENTRES (2012-2021)

Patrick Hayden[1], Diderik-Jan Eikema[2], Linda Koster[3], John Snowden[4], Denis Caillot[5], Gwendolyn van Gorkom[6], Laimonas Griskevicius[7], William Arcese[8], Charles Crawley[9], Maurizio Musso[10], Claude Eric Bulabois[11], Murray Martin[12], Tanja Netelenbos[13], Andrew McDonald[14], Johan Maertens[15], Matteo Parma[16], Arpad Illes[17], Cecilia Iasksson[18], Claudia Sossa[19], Joanna Drozd-Sokolowska[20], Kavita Raj[21], Meral Beksac[22], Stefan Schönland[23], Donal McLornan[21], Ibrahim Yakoub-Agha[24]

[1]Trinity College Dublin, Dublin, Ireland, [2]EBMT Statistical Unit, Leiden, Netherlands, [3]EBMT Leiden Study Unit, Leiden, Netherlands, [4]Sheffield Teaching Hospitals NHS Trust, Sheffield, United Kingdom, [5]Hopital d'Enfants, CHU de Dijon, Dijon, France, [6]University Hospital Maastricht, Maastricht, Netherlands, [7]Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania, [8]Tor Vergata University of Rome, Rome, Italy, [9]Addenbrookes Hospital, Cambridge, United Kingdom, [10]Ospedale La Maddalena - Dpt. Oncologico, Palermo, Italy, [11]CHU Grenoble Alpes - Université Grenoble Alpes, Grenoble, France, [12]Leicester Royal Infirmary, Leicester, United Kingdom, [13]Haga Hospital (Leyenburg), The Hague, Netherlands, [14]Alberts Cellular Therapy, Pretoria, South Africa, [15]University Hospital Gasthuisberg, Leuven, Netherlands, [16]Ospedale San Gerardo, Monza, Italy, [17]University of Debrecen Clinical Center, Debrecen, Hungary, [18]Umea University Hospital, Umea, Sweden, [19]FOSCAL-UNAB, Floridablanca, Colombia, [20]Central Clinical Hospital, The Medical University of Warsaw, Warsaw, Poland, [21]University College London Hospitals NHS Trust, London, United Kingdom, [22]Ankara University, Ankara, Turkey, [23]Medizinische Klinik u. Poliklinik V, University of Heidelberg, Heidelberg, Germany, [24]CHU de Lille, Univ Lille, INSERM U 1286, Lille, France

Background: The techniques employed to mobilise autologous peripheral blood stem cells in patients with myeloma have evolved over time and vary between countries. The most common methods are (1) Cyclophosphamide and Granulocyte - Colony Stimulating Factor (G-CSF), (2) G-CSF only, (3) G-CSF and Plerixafor, and (4) Other. In general, chemotherapy, usually Cyclophosphamide, is used in Europe and single agent G-CSF in North America.

Methods: We performed a retrospective analysis of the EBMT database to analyse stem cell mobilisation techniques in patients undergoing a first ASCT for myeloma over the last decade. This data was available on a select cohort of patients for whom Med B form data had been submitted.

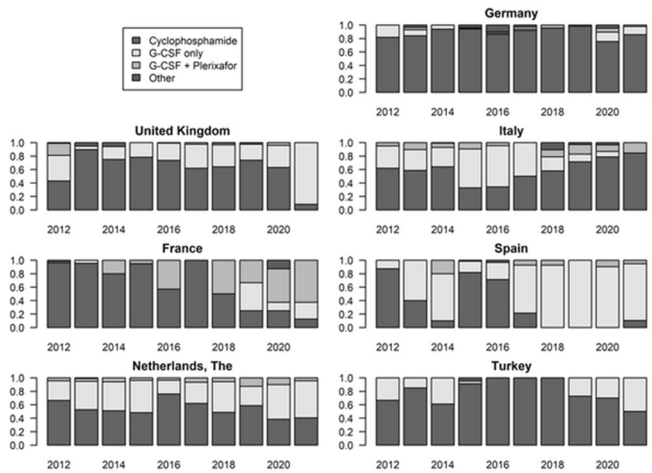
Results: A total of 76,923 patients received a first autologous stem cell transplant for myeloma in 501 EBMT-affiliated centres between 2012 and 2021. Detailed Stem cell mobilization data including CD34 results were available on 4,710 (M 58%: F 42%) patients from 87 centers. The Median (IQR) age was 61.3 (54.7-66.1) years. MM subtypes were IgG, IgA, Light Chain and Other in 56.6%, 19.2%, 20.8% and 3.4%, respectively.

The frequency of use of each of the stem cell mobilization techniques were as follows: Cyclophosphamide (n = 3,017, 67.1%), G-CSF only (n = 1,207, 26.9%), G-CSF + Plerixafor (n = 222, 4.9%) and Other (47, 1.0%).

The comparative median annual CD34 yields (x10e6/kg) reveal that the yields following Cyclophosphamide-based mobilization were consistently higher (6.14-7.8) than those following either G-CSF (4.46-6.1) or G-CSF and Plerixafor (2.5-5.6). The median (IQR) stem cell yields (x10e6/kg) following Cyclophosphamide, G-CSF, G-CSF and Plerixafor, and Other were 7.32 (4.9-10.14), 5.25 (3.88-7.38), 4.94 (3.42-6.85) and 4.9 (3.82-7.54), respectively.

We next analyzed the median annual CD34 yields (x10e6/kg) by induction regimen (no. of pts): CTD (Cyclophosphamide, Thalidomide, Dexamethasone) (n = 712) 7.56, Other (n = 623) 5.86, PAD (Bortezomib, Adriamycin, Dexamethasone) (n = 256) 5.8, VAD (Vincristine, Adriamycin, Dexamethasone) (n = 172) 5.03, VCD (Bortezomib, Cyclophosphamide, Dexamethasone) (n = 1,735) 6.21, VD (Bortezomib, Dexamethasone) (n = 603) 5.97, VRD (Bortezomib, Lenalidomide, Dexamethasone) (n = 811) 5.42 and VTD (Bortezomib, Thalidomide, Dexamethasone) (n = 3,192) 7.12 ($p < 0.001$), the highest yields being collected following CTD and VTD (< 0.001).

We finally examined mobilization trends in the seven largest countries in the dataset (France, Germany, Italy, the Netherlands, Spain, Turkey, and the United Kingdom) over time (see Figure). Data was available for between 9.6% and 22.8% of patients in 6 of the 7 countries; however, it was only available in 2.9% of patients from Germany. There were wide national variations in clinical practice both over time and between countries, as shown below.



Conclusions: Over the last decade, two-thirds of patients in EMBT centres underwent autologous stem cell collection following Cyclophosphamide and G-CSF, one quarter following single agent G-CSF and 5% following G-CSF and Plerixafor. Yields were consistently higher following chemotherapy-based mobilization. However, we have no data on associated morbidity such as the incidence of infection, the need for hospital admission or costs. The highest yields were seen in patients who had received either CTD or VTD induction. Finally, limited data on trends in practice shows considerable variation between countries combined with significant changes in some countries over the last decade.

Disclosure: **Hayden:** *Amgen:* Other: Participation in Advisory Board.

Snowden: *Novartis:* Speakers Bureau; *Mallinckrodt:* Speakers Bureau; *Gilead:* Speakers Bureau; *Janssen and Jazz:* Speakers Bureau; *Medac:* Membership on an entity's Board of Directors or advisory committees; *Kiadis:* Other: clinical trial IDMC membership.

Griskevicius: *Miltenyi Biomedicine:* Membership on an entity's Board of Directors or advisory committees.

Drozd-Sokolowska: *Servier:* Honoraria, Speakers Bureau; *AbbVie:* Honoraria, Speakers Bureau; *Janssen:* Honoraria; *Roche:* Consultancy; *Sanofi:* Honoraria.

Beksac: *Oncopeptides:* Consultancy, Honoraria, Other: Advisory Boards, Speakers Bureau; *Amgen:* Consultancy, Honoraria, Other: Advisory Boards, Speakers Bureau; *Sanofi:* Consultancy, Honoraria, Other: Advisory Boards, Speakers Bureau; *Takeda:* Consultancy, Honoraria, Other: Advisory Boards, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Other: Advisory Boards, Speakers Bureau.

Schönland: *Pfizer:* Honoraria; *Takeda:* Honoraria, Other: Travel Support; *Janssen:* Honoraria, Other: travel support, Research Funding; *Prothena:* Honoraria, Other: Travel Support, Research Funding.

McLornan: *CELGENE BMS:* Research Funding, Speakers Bureau; *ABBVIE:* Speakers Bureau; *NOVARTIS:* Honoraria, Research Funding, Speakers Bureau; *JAZZ:* Honoraria, Speakers Bureau.

Yakoub-Agha: *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Kite, a Gilead Company:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Support; *Janssen:* Honoraria; *Bristol Myers Squibb:* Honoraria.

2 - Stem Cell Mobilization, Collection and Engineering

P670

EFFICACY AND SAFETY OF THE G-CSF BIOSIMILAR FILGRASTIM-AAFI COMPARED TO FILGRASTIM: A REPORT FROM THE NATIONAL MARROW DONOR PROGRAM

Joseph Maakaron[1], Katie Picotte[2], Kevin Tram[2], Ruth Bakken[2], Jason Oakes[2], Meghann Cody[2], John Miller[2], Steven Devine[2], Heather Stefanski[2]

[1]University of Minnesota, Minneapolis, United States, [2]National Marrow Donor Program, Minneapolis, United States

Background: The regulatory pathway for approval of biosimilars is less rigorous than that of original compounds and only requires demonstrating similar safety, purity, and potency. The National Marrow Donor Program (NMDP) recently amended the current IRB approved IND protocol to allow fligrastim biosimilars as mobilization agents for peripheral blood stem cells. We started using filgrastim-aafi (Nivestym, NV) instead of filgrastim (Neupogen, NP) for mobilizing stem cells in March 2022. We herein present a comparative analysis of the two drugs.

Methods: The NMDP routinely collects data about donors and grafts. In March of 2022, the G-CSF product was switched from NP to NV. We compared donor safety, product quality, and adverse events between March - July of 2021 where donors received NP and March - July 2022 where donors received NV.

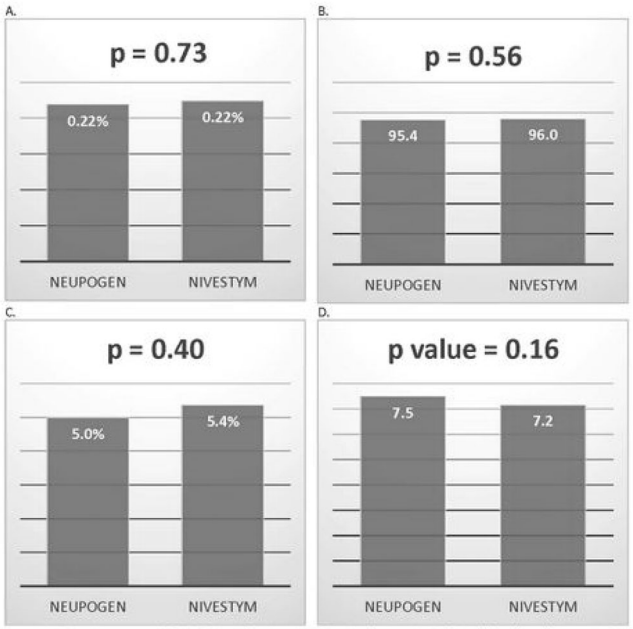


Figure 1. A. Average CD34 Distribution in Pre-Apheresis white blood cell count; B. Average CD34 cells/μL in Pre-Apheresis white blood cell count; C. Occurrence of 2-Day Collections; D. 95% Trimmed Average transplant center reported cell dose.

Results: There were 801 and 913 healthy donors who underwent stem cell mobilization with NP and NV respectively. Average donor weight was similar between the groups (85 kg for NP vs 83 kg for NV). Day +5 pre-apheresis peripheral blood CD34 count and percentage did not differ between groups (95.4 cells/μL for NP vs 96.0 cells/μL for NV, $p = 0.56$; 0.22% vs 0.22%, $p = 0.73$). Median liters of blood processed was similar (16.2 for NP vs 15.8 for NV; $p = 0.92$) as was requirement for 2-day collections (5.0% for NP vs 5.4% for NV; $p = 0.40$). The product met NMDP quality cell dose metric level (4.5x10^6 Cd34+ cells/kg recipient weight) in 89% and 88% of cases for NP and NV respectively. Main outcomes are summarized in Figure 1. Adverse events (grades 3 and higher) were comparable or even less in the biosimilar group with 28 in the NP group and 23 in the NV group. The most common AEs were headache, fatigue and bone pain. There were two grade 4 AEs in the NP group (fatigue and HA) and one in the NV group (subdural hemorrhage); all have been reported previously and expected.

Conclusions: Mobilization and apheresis of an adequate cell dose with a normal graft composition while maintaining donor safety remains critical for the success of transplant programs across the world. These data provide reassurance that mobilization of volunteer unrelated donors with Nivestym results in comparable safety and efficacy compared to Neupogen.

Disclosure: HES Novartis, Ad board.
SMD Orca Bio: Consultancy, Other.

2 - Stem Cell Mobilization, Collection and Engineering

P671

OPTIMIZING BONE MARROW HARVEST MANIPULATION FOR RBC REDUCTION IN PEDIATRIC ALLOGENIC STEM CELL TRANSPLANTATION: A SINGLE CENTER EXPERIENCE

Walid Almashaqbeh[1,2], Sami Jammah[3,1], Saad Almalki[3,1], Rodaina Abujoub[2], Shahbaz Memon[2], Abdulrahman Alsultan[4], Mohammed Essa[2,1,3], Dunia Jawdat[1,3]

[1]King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [2]King Abdullah Specialized Children Hospital, Riyadh, Saudi Arabia, [3]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, [4]King Saud University, Riyadh, Saudi Arabia

Background: Minimal manipulation of obtained bone marrow as a source of stem cells is required for RBC reduction in case of major ABO incompatibility or preparation for cryopreservation. The Stem Cell Laboratory has deployed two main approaches during the past decade. All patients who had product manipulation were included. The methodologies for RBC reduction, cryopreservation, storage, and viability testing were in accordance with FACT-JACIE standards.

Methods: All patients less than 14 years old who underwent allogenic bone marrow transplantation and product manipulation for RBC reduction were evaluated. Demographics, disease type, conditioning regimens, donor type, stem cell dose pre- and post-processing, cell viability, time to neutrophil engraftment, time to platelet engraftment, and outcome were among the data obtained and analyzed. In this study, we compared the RBC reduction using Sepax cell processing for Ficoll density gradient protocol and the Optia cell separator for bone marrow processing (BMP) protocol.

Results: Over 10 years, 70 patients received allogeneic RBC-reduced stem cell products. The transplant characteristics and outcomes of patients are displayed in the table. One patient in each group did not effectively undergo engraftment. We compared cell dosage and percentages of differential cell recovery per procedure, time to neutrophil and platelet engraftment, and outcome. Refer to the table.

Conclusions: All RBC reduction procedures demonstrated optimal time to neutrophil and platelet engraftment. Implementing Optia manipulation has resulted in improved cell recovery with reduced processing time and less effort.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P672

CLINICAL OUTCOMES AFTER TRANSPLANTATION OF CRYOPRESERVED OR FRESH PERIPHERAL BLOOD HEMATOPOIETIC CELLS: A SINGLE CENTRE REPORT

Jean-François Tourigny[1], Jean-Sébastien Delisle[2,1], Martin Giroux[2], Nadia Bambace[1,2], Léa Bernard[1,2], Sandra Cohen[1,2], Thomas Kiss[1,2], Sylvie Lachance[1,2], Denis-Claude Roy[1,2], Guy Sauvageau[1,2], Olivier Veilleux[1,2], Jean Roy[1,2], Imran Ahmad[1,2]

[1]Département de Médecine, Faculté de Médecine, Université de Montréal, Montréal, Canada, [2]Institut Universitaire d'Hématologie-Oncologie & de Thérapie cellulaire, Hôpital Maisonneuve-Rosemont, Montréal, Canada

Background: During the SARS-CoV-2 pandemic, timely administration of allogeneic hematopoietic cells (alloHC) became jeopardized by travel restrictions and the possibility of infection among donors and recipients. Several scientific bodies recommended graft cryopreservation prior to pretransplant conditioning. While safety is well established for the cryopreservation of autologous transplantation, the literature on cell viability, engraftment and rates of graft-versus-host disease (GVHD) is inconsistent for cryopreservation in the allogeneic setting. Our aim was to identify the impact of cryopreservation of alloHC on clinical outcomes when compared to fresh products. We hypothesized that

hematopoietic cell transplantation (HCT) from cryopreserved alloHC was associated with delayed engraftment.

Methods: We conducted a retrospective study of subjects transplanted at our centre between April 1, 2018, and December 31, 2021. Bone marrow and umbilical cord grafts, as well as second or third HCT, were excluded. Our primary endpoint was time to neutrophil engraftment with cryopreserved alloHC as compared with fresh alloHC. Secondary outcomes included platelet engraftment, achievement of full donor chimerism blood counts at 100 and 180 days, rates of poor graft function, graft failure, secondary cellular interventions for poor graft function or graft failure, GVHD, relapse and non-relapse mortality. Statistical analyses included multivariable models. Adjusting variables varied based on the analyzed outcome. Collected variables included: graft transit and storage time, temperature breach, processing other than cryopreservation, CD34+ and total cell content, viability, conditioning regimen and GVHD prophylaxis, patient & donor age and sex mismatch, ABO mismatch, donor type (matched sibling, haploidentical, matched unrelated), comorbidity score, performance status, patient CMV status and disease relapse risk.

Results: A total of 202 patients were included in our analysis, of which 67 received a fresh graft and 135 received a cryopreserved graft. HCT types were: 112 matched related or unrelated ATG-based myeloablative or reduced-intensity regimens, 35 post-transplant cyclophosphamide-based haploidentical, and 34 related or unrelated donor nonmyeloablative HCT. No significant difference was found in time to neutrophil engraftment (median 18.7 vs 17.1 days, $p = 0.070$). No other outcomes were significantly different between groups, except median CD4+ count at 180, significantly lower among patients who had received cryopreserved stem cells (median 138 vs 290, $p = 0.028$), even after adjustment for potential confounders.

Conclusions: Cryopreservation does not seem to have a significant effect on engraftment and other clinical outcomes. Small sample size may have precluded the detection of differences in some outcomes. Cryopreservation seems to independently impair CD4+ reconstitution,. Effect on risk of opportunistic infection among transplant recipients remains unknown. Further, prospective studies are needed, but cryopreservation can probably be used safely if required.

Disclosure: Nothing to disclose.

2 - Stem Cell Mobilization, Collection and Engineering

P673

FLOW CYTOMETRIC CHARACTERIZATION OF HSC SUBPOPULATIONS IN AUTOLOGOUS PBSC PREPARATIONS AFTER CRYOPRESERVATION

Anabel Heuer[1], Stefanie Uhlig[1,2], Svetlana Hetjens[3], Britta Pflästerer[1], Anke Diehlmann[1], Harald Klüter[1], Karen Bieback[1,2], Patrick Wuchter[1]

[1]Institute of Transfusion Medicine and Immunology, Mannheim, Germany, [2]FlowCore, Mannheim, Germany, [3]Medizinische Statistik, Biomathematik und Informationsverarbeitung Mannheim, Mannheim, Germany

Background: Autologous stem cell transplantation has become a routine procedure with only a marginal number of non-engraftment cases, but the time to hematopoietic recovery may vary considerably from patient to patient. While CD34 represents for more than 30 years the decisive marker to enumerate hematopoietic stem cell (HSC) products, we hypothesize that the cellular composition of autologous HSC grafts with respect to defined CD34 subpopulations may have an impact on hematopoietic reconstitution.

Methods: The two-color ISHAGE protocol represents the current gold standard but encompasses only the amount of viable $CD45^+/CD34^+$ cells per body weight (bw) of the recipient. We adapted a multi-color flow cytometric marker panel for advanced characterization of CD34 subpopulations (Worel N et al., *Transfusion. 2017 Sep;57(9):2206-2215*) in autologous PBSC products ($n = 49$, from $n = 31$ patients with multiple myeloma) which had been cryostored within a wide range of 2-15 years. Antibodies were measured with a BD FACSCanto including CD34, CD38, CD133, CD45, CD45RA, CD10 and viability stain 7AAD. Functional data in terms of differentiation capacity was assessed by colony forming assay (CFA). In addition, we correlated our findings with clinical engraftment data including reconstitution of leucocytes ($\geq 1x10^3$/ul), neutrophilic granulocytes ($\geq 0{,}5x10^3$/ul) and platelets (≥ 20 and $\geq 50x10^3$/ul) in days after TPL.

Results: We modified the above-mentioned protocol to analyze samples of PBSC products after cryopreservation and thawing regarding different processing conditions as well as different viability dyes. We demonstrated that an identification of autologous HSC subpopulations by flow cytometry after cryopreservation is feasible. Regarding the distribution of HSC subpopulations, we observed a remarkably different pattern as compared to data from the above mentioned literature of fresh autologous material. Our samples indicated a shift from very immature multipotent progenitors (MPPs) into more mature progenitor cells, like lympho-myeloid progenitors (LMPPs) and erythroid-myeloid progenitors (EMPs). Furthermore, we observed that a high ratio of LMPPs, which represent an immature stage of differentiation, correlated significantly with early neutrophil and leucocyte engraftment ($p = 0.025$ and $p = 0.0034$). Conversely a high amount of differentiated cells correlates with late engraftment of neutrophilic granulocytes ($p = 0.0235$). Our findings are in line with the revised model of early hematopoiesis (first described by Goergens et al., *Cell Rep. 2013 May 30;3(5):1539-52*), demonstrating that the progenitor cells are following the specific pathways of differentiation (Dmytrus et al., *Bone Marrow Transplant, 2016;51(8):1093-100*).

Conclusions: We established an advanced flow cytometric panel to assess the differentiation capacity of cryostored autologous PBSC grafts and correlated it with clinical hematopoietic reconstitution data. This approach might offer a faster and more objective way to identify hematopoietic stem and progenitor subpopulations than CFA. This assay may be used to predict engraftment in critical situations prior to transplantation or as an addition to standard CD34 enumeration in patients with unknown cause for late engraftment.

Disclosure: All authors confirm that there are no potential conflicts of interest to disclose.

2 - Stem Cell Mobilization, Collection and Engineering

P674

FACTORS INFLUENCING PBSC MOBILIZATION IN ADULT ALLOGENEIC DONORS

Silvia Monsalvo[1], Jorge Verdejo[1], Angela Salas[1], Guiomar Bautista[1], Ana Belen Bocanegra[1], Carlos De Miguel[1], Isabel Salcedo[1], Carlos Vilches[1], Rafael Fores[1], Jose Luis Bueno[1], Rafael F Duarte[1]

Hospital Universitario Puerta de Hierro, Madrid, Spain

Background: Mobilized peripheral blood stem cells (PBSC) are the commonest source for autologous and allogeneic HSCT in adult patients. Factors influencing autologous mobilization in patients have been thoroughly studied. However, although less prone to mobilization failure overall, factors influencing SC mobilization in allogeneic donors are less clear. Here, we analyze our experience in mobilization of adult allogeneic donors and aim to identify factors that may associate with poor PBSC mobilization in this setting.

Methods: We included all consecutive related and unrelated allogeneic donors mobilized in our center in the past decade. Donors were mobilized with G-CSF at 5mg/kg/12h. Apheresis procedures were performed with Spectra, Optia and Amicus. We defined a poor-mobilization as a peripheral blood count on day +5 of <20 CD34+ cells/μL. Statistical analysis was performed using SPSS with Mann-Whitney test, Chi-squared test, univariate and multivariate logistic regressions.

Results: We performed 282 PBSC apheresis in 243 consecutive donors between 2012 and 2022, including 38 donors who had a second apheresis (15.6%) and one with a third day of apheresis. Sixty-three (25.9%) were unrelated donors. Six out of 282 procedures (2.1%) required a central line access. Apheresis were performed in Amicus (173, 61%), Optia (95, 33.7%), Spectra (7, 2.5%), and started on +5 day of G-CSF mobilization in all cases. Donor characteristics and mobilization data are described in table 1. The rates of mobilization failure were very low. All collected a minimum of >2 CD34 $\times 10^6$/kg of recipient body weight. Overall, median peripheral blood CD34+ count on day +5 was 81.2 cells/μL (range, 11.3-299.8). Nine donors (3.7%) were classified as poor mobilizers (< 20 CD34+ cells/μL). Of these, three (33.3%) required 2 days of apheresis, and one (11.1%) 3 days. Two were rescued with plerixafor. Eight out 9 poor mobilizers (88.9%) were women ($p = 0.003$), with a rate of poor mobilization much higher than in men (8.2% vs 0.7%; $P < 0.001$). Donors who mobilized poorly had lower total blood volume (TBV; $p = 0.045$) and were found across all ages (Figure 1), although those older than 55 had a higher risk of being poor mobilizers in the univariate analysis (OR 1.94; IC95% 0.38-9.8). We performed a logistic regression analysis with being a poor mobilizer as dependent variable, and exploring donor sex (male or female), age (below or over 55 years) and TBV (below or over 5000 mL) as independent variables. Sex was the only significant independent factor predicting poor mobilization, with an OR = 13 (CI95% 1.6-106.0). Age and TBV were not related to poor mobilization in the multivariate analysis.

Figure 1: Donor's CD34+ count at day +5 by donor age. The dotted line defines the limit to be considered a poor-mobilizer.

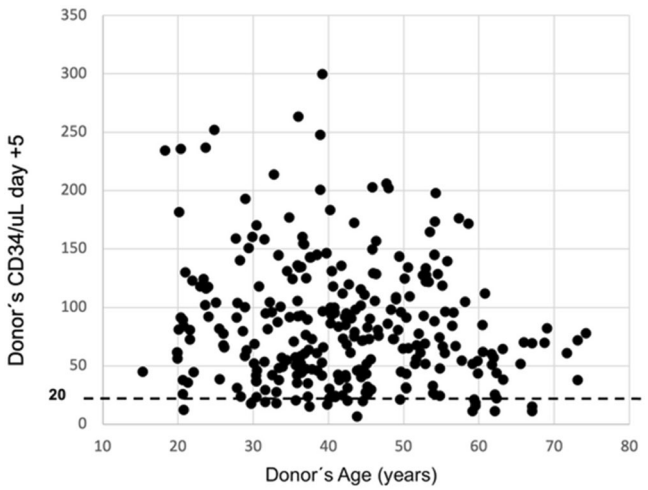


Table 1: Features in poor and good mobilizer donors.

	Total (n = 243)	Poor-Mobilizers (n = 9)	Good-Mobilizers (n = 235)	p
Age (years) median (range)	40 (15-74)	37 (29-67)	41 (15-74)	NS
TBV (mL) median (range)	4759 (2883-6508)	3494 (2883-5021)	4805 (3097-6508)	0.045
Sex (Female); number (%)	97 (39.9)	8 (88.9)	89 (38)	0.003
At day 1 of collection				
· **Hemoglobin** (g/dL) median (range)	14.4 (10.4-17.6)	13.4(12.1-16.2)	14.4 (10.4-17.6)	NS
· **Platelets** ($\times 10^9$/L) median (range)	220 (110-434)	226 (173-285)	219.5 (110-434)	NS
· **Leukocytes** ($\times 10^9$/L) median (range)	47 (5.9-83.1)	36.9 (5.9-49.6)	47.7 (21.9-83.1)	0.045
· **CD34+** (cells/μL) median (range)	81.2 (11.3-299.8)	17.8 (11.3-19.8)	83.0 (21.3-299.8)	0.007
Apheresis Procedures				
· **Days** (number) median (range)	1 (1-3)	2(1-3)	1(1-2)	0.006
· **TBV processed*** median (range)	2.5 (0.32-4.9)	3.3 (0.5-4.8)	2.5 (0.3-4.9)	0.055
CD34+ collected ($\times 10^6$/kg) median (range)	6.06 (2.35-20.28)	4.39 (3.01-7.14)	6.11(2.35-20.28)	0.014

Conclusions: Our understanding of PBSC mobilization in allogeneic donors is less clear than that of patients for autologous HSCT. Our data suggest that although mobilization failure is rare overall in allogeneic donors, women have a significantly higher independent risk of being poor mobilizers, and may potentially benefit from a more proactive monitoring and analysis to identify cases at risk.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P675

CHANGES TO MOBILISATION AND CRYOPRESERVATION DURING COVID-19: RESULTS FROM A SINGLE CENTRE

Wendy Merrison[1], Sarah Ward[1], Joanne Berridge[1], Shazia Aref[1], Kikaiweji Liley[1], Rik Lewin[1], Sarah Wharin[1], Katherine Hodgson[1], Anna Tsoulkani[1], Alexander Martin[1]

[1]University Hospitals of Leicester, Leicester, United Kingdom

Background: The emergence of Covid-19 due to fast spreading of SARS-CoV-2 created major challenges for HPC transplant programmes globally. Expert guidance from EBMT recommended adaptations from the normal guidance for autologous and allogeneic patients, depending on disease risk[1].

Autologous patients in the main were switched to GCSF-only priming for their stem cell harvests, in order to reduce the immunosuppression associated with chemotherapy priming[2]. Cells from matched unrelated allogeneic donors were cryopreserved, to ensure that cells were available prior to embarking on recipient conditioning.

Methods: An audit was carried out on all patients from Leicester and Northampton, who had cells collected between January 2016 and December 2022 for both autologous and allogeneic transplants. Data was compared for the periods 2016 to

Years	Allogeneic transplants	Age Median (yrs) range	Number cryopreserved	Neutrophil engraftment Median days	Platelet engraftment Median days	Autologous transplants	Age Median (yrs) range	Collections 1	2	3	Neutrophil engraftment Median days	Platelet engraftment Median days
2016–2019	112	54.9 (17.7–71.9)	2 (1.8%)	13.8	20	230	54.9 (19.3–75.1)	144	76**	9	11***	19***
2020–2022	59	53.9 (20.4–74.2)	32 *(54%)	13.9	27	163	59.9 (19.7–74.9)	65	83$	44$ $	11.2	21

*one patient died prior to infusion of cells

**5 attended twice to collect sufficient for 2 transplants
***Data from 2018-2019, as cryopreservation techniques changed at this point.
$ 16 attended twice to collect sufficient for 2 transplants
$$ 2 attended 3 times to collect sufficient for 2 transplants

2019 and 2020 to 2022. 564 patients were identified (351 male and 213 female). The following data for allogeneic patients was collected: number of CD34 cells/kg collected; number of bags collected and cryopreserved. In addition for autologous patients; the number of days harvested; number of days for infusions; mobilisation of patients with the addition of Plerixafor usage (patients were eligible for augmentation with Plerixafor, if their peripheral blood CD34 levels were between 4 -15 x 10^6 cells/l at the predicted time of collection). The primary endpoint was successful mobilisation; secondary endpoint was neutrophil and platelet engraftment (days to neutrophil engraftment >.0.5 x 10^9/l; days to platelets > 50 x 10^9/l).

Results: Data collected in table below:

For allogeneic transplants there has been no significant change to neutrophil and platelet engraftment, despite cryopreservation of cells. However, since cryopreserved cells mean more volumes being returned, this has impacted on staffing for infusions, cryostorage capacity, as well as additional consumables being used.

For autologous patients, almost 40% of infusions have taken place over two days since the pandemic, whereas prior to 2020 just 11% of transplants were infused over 2 days. Plerixafor usage was not statistically different between groups. However, the dose of CD34 being received was significantly different. The mean CD34 amount for the 2016 group ($m = 5.067$, $SD = 2.938$) was significantly larger than the mean for the post Covid group ($m = 3.475$, $SD = 1.965$) $p < 0.001$. Neutrophil engraftment times are still similar (median 11 days) despite the change to the apheresis procedure. This has had an impact for infusions with an increase in bags being cryopreserved for transplants.

Conclusions: Neutrophil and platelet engraftment times do not appear to be significantly different as a result of the changes in apheresis and in cryopreservation for allogeneic or autologous transplants, but there has been an impact due to other factors such as increased costs and supply chain issues for consumables, and storage for increased number of bags. In addition, processing times in the lab, and times for infusions have increased. The recovery of a more normal clinical service resuming since the end of lockdowns, has led to an increase in patient referrals, with consumable availability and cell storage continuing to be problematic.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P676

THE OUTCOME OF CRYOPRESERVED PRODUCTS COMPARED TO FRESH PRODUCTS IN PEDIATRIC ALLOGENIC STEM CELL TRANSPLANTATION DURING COVID-19 PANDEMIC: SINGLE CENTER STUDY

Rodaina Abujoub[1], Noha Alneedy[1], Walid Almashaqbeh[2], Shahbaz Memon[1], Abdulrahman Alsultan[3], Mohammed Essa[1,4,2]

[1]King Abdullah Specialist Children Hospital, Riyadh, Saudi Arabia, [2]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, [3]King Saud University, Riyadh, Saudi Arabia, [4]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Background: Protective measures as per EBMT guidelines were implemented during COVID-19 pandemic including the use of cryopreserved products if bone marrow is the stem cell source and postponing elective indications during the peak of the outbreak. There is a concern about losing a percentage of the total nucleated cells during cryopreservation procedure which may impact on engraftment.

Methods: All patients less than 14 years of age who underwent Allogenic HSCT in 2020-2021 were reviewed including who received cryopreserved products during early 2020. The data collected included demographics, disease, conditioning regimens Donor type, stem cell dose, time to neutrophil engraftment, time to platelet engraftment and outcome. The volume of bone marrow collected were adjusted if permitted to collect a higher cell dose during this period. RBC depletion techniques, cryopreservation, storage and viability testing were according to hospital policy and FACT/JACIE requirements.

Results: A total of 17 patients who underwent HSCT received cryopreserved products over a 5-month period during the peak of COVID-19 pandemic. All patients received cryopreserved products except patients with severe aplastic anemia or patients who had more than one family matched donors. In addition, all elective cases were cancelled. 115 patients received fresh products during the following two years after restrictions removal. Patient, transplant characteristics and outcome are shown in the Table. All patients engrafted successfully except one in each group. Cell dose, time to neutrophil and platelets engraftment and all outcome measures were comparable. 2 patients died in the cryopreserved group due to infections. 3 patients died in the control group due to infections or relapse.

Patient and Transplant Characteristics	Cryopreserved Product group N = 17 Median (range) or N (%)	Fresh product group (Control) : N = 115 Median (range) or N (%)
Age (years)	4.8 (0.3-14.3)	6.7(0.3-14)
Gender (F/M)	9/8	46/69
Donor type:		
MRD	8	95
MUD/MMUD	7	6
MMD	2	14
Diagnosis:		
Neoplastic	5	23
Hemoglobinopathy	4	53
Primary immunodeficiency	5	18
HLH	2	7

Patient and Transplant Characteristics	Cryopreserved Product group N = 17 Median (range) or N (%)	Fresh product group (Control) : N = 115 Median (range) or N (%)
Bone marrow failure syndrome	1	7
Aplastic anemia	0	7
Conditioning regimen:		
Myeloablative (MAC)	13	92
Reduced Intensity (RIC)	4	23
Infused nucleated cell dose (X 108/kg)	3.7(1.8-13.05)	4.9 (1.0-16.3)
Infused CD34 cell dose (X 106/kg)	11.5(2.2 -33)	8.4 (1.8-25.6)
Time to Neutrophil engraftment (days)	20(15-28)	21 (12-64)
Time to Platelet engraftment (days)	32(17-66)	30 (13-150) **2 patients with PID who received RIC had delayed engraftments**
Successful engraftment	16 (0.94)	114 (0.99)
Chimerism (donor cells > 90%)	16 (0.94)	106(0.92)
aGVHD (Grade II or above)	4 (0.23)	14 (0.12)
cGVHD	3 (0.17)	2 (0.02)
Outcome:		
Alive	15 (0.88)	112 (0.97)
Relapse/Graft failure	0	3 (0.3)
Follow up (days)	746 (17-887)	473 (65-1052)

Conclusions: The use of cryopreserved products in HSCT during pandemics is safe and comparable to fresh products during regular days however this may increase stem cell laboratory personnel workload. Cryopreserved products is an alternative to fresh products if indicated.

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to Declare from authors.

2 - Stem Cell Mobilization, Collection and Engineering

P677

HAPLOIDENTICAL TRANSPLANT FROM PBSC WITH POST TRANSPLANTATION CYCLOPHOSPHAMIDE AND CONTROLLED NUMBER OF T LYMPHOCYTES

Stefano Rossi[1], Elena Soncini[1], Giulia Baresi[1], Marta Comini[2], Marianna Maffeis[1], Federica Bolda[2], Alessandra Beghin[2], Arnalda Lanfranchi[2], Fulvio Porta[1]

[1]Pediatric Hematology and Oncology Unit and Pediatric Bone Marrow Transplant Center - ASST Spedali Civili of Brescia, Brescia, Italy, [2]Stem Cell Laboratory, Section of Hematology and Blood Coagulation, Clinical Chemistry Laboratory, ASST Spedali Civili of Brescia, Brescia, Italy

Background: The use of post-transplant cyclophosphamide is now well established in transplants with donor bone marrow cells haploidentical with excellent results. The use of PBSC in this setting is limited by the risk of a major incidence and severity of GVHD compared to the use of bone marrow cells. In the last period, new data are emerging describing the use of post-transplant cyclophosphamide in combination with or without traditional immunosuppression also in MFD and MUD donor transplants with promising data, such as reduced risk of GVHD and fewer viral reactivations. We already reported the use of a technique comprising CD34 + positive selection and later addback of a controlled number of T lymphocytes (30x10^ 6 / kg / recipient) in the MUD setting, documenting rapid engraftment, rapid immunological reconstitution and low incidence of acute GVHD and chronic.

Methods: In the past 2 years we carried out at our Center 6 transplant procedures using the peripheral stem cells as a source of haploidentical donor stem cells and performing product manipulation with CD34+ selection and CD3+ addback with controlled number and subsequent post-transplant Cyclophosphamide. We included patients with both malignant and non-malignant diseases.

Results: The neutrophil engraftment was on average at day +19, that of platelets at day + 30. There was no documented presence of significant acute GVHD or chronic GVHD. Last chimerism assessment documented a full donor chimerism for all the patients analyzed.

Only one case of invasive infection (Adenovirus pneumonia) resolved after targeted therapy. We observed a case of CMV viral reactivation without clinical signs of infection and negativization after antiviral therapy.

Conclusions: We believe this is a safe technique in haploidentical donor transplantation that can guarantee rapid engraftment for the greater number of CD34 + (> 10 x 10 ^ 6 / kg) and a net decrease in the incidence and severity of GVHD, presenting the advantage of the high number of CD34 + obtainable through PBSC and a reduced number of lymphocytes T of the donor with the lowest risk of GVHD. Certainly, more experience is needed to consolidate it.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P678

STEM-CELL MOBILIZATION WITH CYCLOPHOSPHAMIDE 4 G/M^2 ALLOWS COLLECTION OF HIGH NUMBERS OF CD34+ CELLS AFTER DARA-VTD INDUCTION FOR MULTIPLE MYELOMA

Tommaso Perini[1], Virginia Girlando[1], Valeria Ferla[1], Alessia Orsini[1], Francesca Farina[1], Sarah Marktel[1], Fabio Ciceri[1], Magda Marcatti[1]

[1]IRCCS Ospedale San Raffaele, Milan, Italy

Background: Autologous stem cell transplantation (ASCT) is the standard of care for eligible patients with newly diagnosed multiple myeloma (NDMM). Recently, the CASSIOPEIA trial established Daratumumab-VTD as the standard induction therapy for NDMM. As per protocol, patients underwent stem-cell mobilization with cyclophosphamide (3 g/m^2) and granulocyte colony-stimulating factor (G-CSF). However, a lower number of collected CD34+ cells and a higher use of plerixafor were reported in the Dara-VTD vs VTD regimen ($6{\cdot}3 \times 10^6$ per kg versus $8{\cdot}9 \times 10^6$ per kg). Collecting less CD34+ cells might have consequences on the possibility to perform a second ASCT or a stem cell boost in cases of prolonged cytopenia after ASCT or CAR-T cell therapies in subsequent lines. We here report our experience on stem cell mobilization with cyclophosphamide 4 g/m^2 and G-CSF after Dara-VTD induction.

Methods: We collected our single-center, real life data on stem cell collection in 17 consecutive NDMM treated with Dara-VTD after its approval (January 2022), followed by mobilization with cyclophosphamide 4 g/m^2 and G-CSF. Plerixafor was used as per institutional practice. Patients were enrolled in the study upon written informed consent for transplant procedures and use of medical records for research and were treated according to institutional standard of care.

Results: We analyzed 17 consecutive patients treated with 4 cycles of Dara-VTD. Standard institutional stem cell mobilization with cyclophosphamide 4 g/m^2 and G-CSF was administered in outpatient regimen. Successful mobilization with this approach was reached in 15/17 patients (88%). Median number of CD34+ cells collected was 11,37 × 10^6 per kg (IQR 9,21 × 10^6 to 12,42 × 10^6), with the lowest collection procedure yielding a total of 4,92 × 10^6 CD34+ per kg. As per institutional protocol, stimulation with G-CSF was started 5 days after CTX and continued until collection and mean total G-CSF administered per patient was 63,8 mcg/kg (SD +/− 20,1). Median time from CTX to first day of apheresis was 12 days, with the majority of patients (10/15) needing 2 days of apheresis to complete cell collection. Plerixafor was needed in 5 patients who failed to achieve a CD34+ count higher than 20 cells/uL on the day of planned apheresis. Of the 2 patients failing the first round of stem cell collection, one was later mobilized with a chemo-free regimen of GCSF and plerixafor, the other did not respond to chemo-free mobilization and required a bone marrow harvest. 3/17 patients (18%) had G3 febrile neutropenia requiring hospitalization, that promptly resolved after antibiotic treatment and leukocyte recovery. No other adverse event related to the mobilization procedure was observed.

Conclusions: Overall, our data show that in NDMM patients treated with Dara-VTD a mobilization regimen based on CTX 4 g/m^2 allows the collection of high numbers of CD34+ cells and can be safely administered in the outpatient setting. We suggest that mobilization with CTX 4 g/m^2 is a valuable approach to achieve an optimal CD34+ collection after Dara-containing quadruplets, able to guarantee more than 1 ASCT and possible stem cell boosts in cases of prolonged cytopenia in subsequent therapies.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P679

STEM CELL MOBILIZATION WITH ETOPOSIDE AND G-CSF IN PATIENTS WITH RELAPSED/REFRACTORY CLASSIC HODGKIN LYMPHOMA

Galina Petrova[1], Ilia Monin[1], Nataliya Nikiforova[1], Inga Zavodnova[1], Ekaterina Orlova[1], Larisa Maltseva[1], Aleksandra Efirkina[1], Natalia Zaguzina[1], Viktoriya Grishina[1], Ivan Kondakov[2], Demuri Mkheidze[1], Alexandra Palladina[1], Valeria Shpirko[1], Olaga Baranova[1], Iuliia Kliuchagina[1], Maria Kichigina[1], Aidemir Ibragimov[1], Alina Antipova[1], Daria Tupitsyna[1], Evgeniya Paramonova[1], Anastasiya Semenova[1], Gayane Tumian[1], Dzhelil Osmanov[1]

[1]Federal State Budgetary Institution «National Medical Research Center of Oncology named after N.N. Blokhin» of the Ministry of Health of Russia, Moscow, Russian Federation, [2]Krasnoyarsk State Medical University named after Professor V. F. Voyno-Yasenetsky, Krasnoyarsk, Russian Federation

Background: Hematopoietic stem cell collection with etoposide is reported to be highly effective in patients with multiple myeloma. Since the optimal mobilization strategy prior to autologous stem cell transplantation (ASCT) for patients with relapsed/refractory classic Hodgkin lymphoma (r/r cHL) has not been determined yet, here we present a single center experience of chemo-mobilization with intermediate-dose etoposide and granulocyte colony-stimulating factor (G-CSF) in patients with r/r cHL in the era of new drugs.

Methods: Effectiveness of stem cell collection with etoposide and G-CSF in patients with r/r cHL between September 2019 and November 2022 was subjected to retrospective analysis. Mobilization schedule was as follows: etoposide at a dose of 375 mg/m^2 in days 1 and 2 and filgrastim at a dose of 10 μg/kg/day once daily starting on day 4 and continued to the last day of stem cell apheresis.

Results: During the indicated time frame 88 patients with r/r cHL (relapsed, n = 46; refractory, n = 42) underwent 90 aforementioned mobilization cycles. Patients' median age was 33 (range 19-60). In 84 cases (93%) stem cell collection was performed for the first time, while in 6 cases (7%) etoposide was used as a second stem cell harvest regimen due to a previous failure following "steady-state" mobilization with G-CSF (n = 2), chemo-mobilization with etoposide (n = 2), gemcitabine (n = 1) or DHAP (n = 1). In 69% cases (n = 62/90) check-point inhibitors (nivolumab or pembrolizumab) were prescribed prior admission to stem cell collection unit (median courses 5, range 1-24). Just less than a half of patients (42/90; 47%) were treated with brentuximab vedotin (BV) before stem cells harvest (median courses 5, range 1-16). In 27% cases (n = 24/90) patients were consistently administered both nivolumab and BV. The median time from diagnosis to chemo-mobilization was 32 months (range 8,4–197). Intermediate-dose etoposide and G-CSF administration resulted in successful collection (> 2 × 10^6 CD34+ cells/kg) in 91 % of cases (n = 82/90) within a median 2 (1-4) apheresis days. Median total CD34+ cells/kg collected was 5,145 × 10^6 (0,116-18,7). Stem cells were harvested between days 11 and 15, with a median on the 12th day. Seventy-nine percent of patients (n = 71/90; 79%) were defined as good mobilizers as their yield was >2 × 10^6 CD34+ cells/kg in ≤2 days of apheresis. Subsequent ASCT was performed to 81% patients (n = 71/88). Hematopoietic recovery after ASCT was achieved at the expected time in all cases. Stem cell yield was affected significantly neither by patients' age nor by diagnosis-to-mobilization time interval. Prior exposure to targeted therapy with BV and/or immunotherapy with check-point inhibitors and its duration did not impair stem cell collection either (p > 0,05).

Conclusions: Chemo-mobilization with intermediate-dose etoposide and G-CSF results in effective stem cell collection in majority of heavily pretreated r/r cHL patients in the era of novel agents.

Clinical Trial Registry: not applicable.

Disclosure: nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P680

THE ASSESSMENT OF VIABILITY AND POST-THAW CELL RECOVERY OF CRYOPRESERVED PERIPHERAL BLOOD STEM CELLS AND LEUKOCYTES SUBPOPULATION USING THE ANNEXIN V STAINING METHOD

Vladimira Rimac[1], Ines Bojanić[1], Sanja Dabelić[2], Koraljka Gojčeta[1], Branka Golubić Ćepulić[1]

[1]University Hospital Centre Zagreb, Zagreb, Croatia, [2]University of Zagreb, Zagreb, Croatia

Background: Due to the expansion of cell therapy using autologous and allogenic cells, the influence of various factors that could affect cell viability and recovery after processing needs to be examined to ensure the quality of cell therapy products. The standard flow cytometry method for viability testing using 7-aminoactinomycin D (7-AAD) determines cells in necrosis and late apoptosis. In our prospective study, we compared 7-AAD/annexin V method which detects early apoptotic cells with the standard 7-AAD method in the assessment of viability and recovery of hematopoietic stem cells (HSC) and leukocyte subpopulations. The factors besides cryopreservation that could adversely affect post-thaw recovery were also assessed.

Methods: Thirty autologous and 30 allogeneic peripheral blood stem cell products cryopreserved in University Hospital Centre Zagreb were included in the study. In fresh and thawed cryopreserved samples, the viable cell counts of HSC, T and B lymphocytes, NK cells, and monocytes were determined using single platform methods with 7-AAD and 7-AAD/annexin V on flow cytometer BD FACS Canto II (BD Biosciences, San Jose, California).

Results: In fresh autologous samples for all analysed cell populations the medians of viability were ≥99.5% using the 7-AAD and ≥99.4% using the 7-AAD/annexin V method, while in thawed samples were ≥ 94.2% and ≥92.5% respectively. In allogeneic products, the medians of viability in fresh samples were ≥99.3% with 7-AAD and ≥98.6% with 7-AAD/annexin V method, while in thawed samples were ≥93.9% and ≥92.1%, respectively. The viability tested using 7AAD/Annexin V method was statistically significantly lower than the 7-AAD method for all cell populations in fresh and thawed samples in both autologous and allogeneic products.

In autologous samples, statistically significantly lower recovery rates were detected using 7-AAD/annexin V method for CD34+ ($P < 0.001$), CD19+ ($P = 0.037$), CD14+ ($P < 0.001$) and CD16 + 56+ cells ($P = 0.002$), while in allogeneic samples that method-dependent effect was detected only for CD34+ ($P = 0.002$) and CD16 + 56+ cells ($P = 0.001$). The assessment of factors that could affect post-thaw recovery showed in autologous samples weak correlation between platelets and CD3+ recovery using the 7-AAD method ($P = 0.042$, $r2 = -0.374$), and between platelets and CD3 + CD4+ recovery with 7-AAD/annexin V method ($P = 0.043$, $r2 = -0.372$). Also, weak correlation between storage time and CD3 + CD8+ recoveries using 7-AAD ($P = 0.028$, $r2 = -0.401$) and 7-AAD/annexin V method ($P = 0.028$, $r2 = -0.401$) was observed. A good correlation was observed in allogeneic samples between granulocytes (%) and T cell recoveries (CD3+ cells: $P < 0.001$, $r2 = -0.660$ for 7-AAD method, $P < 0.001$, $r2 = -0.670$ for 7-AAD/annexin V method; CD3 + CD8+ cells: $P < 0.001$, $r2 = -0.594$ for 7-AAD method, $P < 0.001$, $r2 = -0.608$ for 7-AAD/annexin V method; CD3 + CD4+ cells: $P < 0.001$, $r2 = -0.637$ for 7-AAD method, $P < 0.001$, $r2 = -0.637$ for 7-AAD/annexin V method).

Conclusions: Cell viability determined using the 7-AAD/annexin V method was statistically significantly lower in all samples compared to 7-AAD method, but the differences were not clinically significant. Since there was the difference in post-thaw recovery between leukocyte subpopulations, each transplantation centre should evaluate how cryopreservation and other factors affect the viability and recovery of the cell population of interest in their settings.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P681

THE USE OF PRE-CD34 RESULTS AS A PREDICTOR OF END-CD34 RESULTS

Yona Skosana[1], Tanya Glatt[1,2], Thabo Gcayiya[1], Riana Cockeran[3]

[1]South African National Blood Service, Boksburg, South Africa, [2]University of Johannesburg, Johannesburg, South Africa, [3]South African National Blood Service, Roodeport, South Africa

Background: Prior to commencing a Haematopoietic Stem Cell Harvest of apheresis donors, a peripheral blood pre- CD34 count is performed to assess if the donor is adequately mobilized for collection. A pre-CD34 count of 10 cells/µl is expected to result in an end-harvest yield of approximately 1 $X10^6$ cells/kg. However, the pre-CD34 count is not the only predictor of the end harvest yield, other factors that contribute to the achieved yield include the collection efficiency of the apheresis device, the volume of blood processed, and recipient weight. In this study, we investigated if the pre-CD34 count is a reliable predictor of the end-CD34 count of apheresis collections performed by the Specialised Therapeutic Services (STS) of the South African National Blood Service (SANBS).

Methods: Stem cell harvests performed between 1 January 2022 and 31 October 2022 by STS in all 21 clinical facilities serviced across South Africa were included. The pre-CD34 counts, end-CD34 counts, and collection efficiencies (CE) for each apheresis collection were analysed. All collections were performed using the Spectra Optia, Terumo BCT. All allogeneic, autologous, adult, and paediatric apheresis collections during this period were included.

The optimal CE was set at ≥ 35%. For collections in which the pre-CD34 did not correlate well with end harvest yield and/ or collections with CE < 35%, bedside procedure notes were reviewed to assess any documented procedure-related occurrences.

Statistical analysis of the correlation coefficiency between the pre-CD34 and the end-CD34 harvest yield using Excel, for all included collections was performed.

Results: During the 10-month period, 268 apheresis collections were performed – 15 allogeneic and 253 autologous. Optimal collection efficiency was achieved in 87% of the collection. The correlation coefficient between pre-CD34 and end-CD34 harvest yield was 0.92.

Collections in which the pre-CD34 did not correlate well with end harvest yield and/ or collections with CE < 35%, the following occurrences were noted: vascular access problems, machine malfunction, and procedure aborted early.

Vascular access problems were commonly seen in paediatric patients, in patients with positional lines or with underlying conditions which predispose them to have a hyper-viscous state. Power interruptions increased machine-related problems. Procedures were aborted early due to donor discomfort (Anticoagulant Citrate Dextrose Solution ACD-A side effects) or on request of the clinician if the target yield is already reached.

Conclusions: This study shows a very good correlation between pre-CD34 count and end CD34 harvest yield, indicating that the pre-CD34 is a good indicator of end CD34 harvest yield. However, these results cannot be used in isolation, as factors that negatively contribute to the end harvest yield were mainly vascular access problems and machine malfunction, and to a lesser extent procedures that were aborted early.

In conclusion, the collection efficiencies of haematopoietic stem cells by SANBS Specialised Therapeutic Services are very good, and there is a strong correlation between pre-CD34 and end-CD34 harvest yield.

Disclosure: No conflict of interest to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P682

TAILORED MOBILIZATION IN AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT

Olga Santos[1], Soraia Campaniço[1], Isabel Branco[1], Dialina Brilhante[1]

[1]Instituto Português de Oncologia de Lisboa Francisco Gentil, EPE, Lisbon, Portugal

Background: Autologous hematopoietic stem cell transplant (aHSCT) is a well-established treatment option for patients with relapsed/refractory lymphoma, multiple myeloma and some childhood solid tumours.

Successful engraftment correlates with the number of CD34+ cells infused and so prevention of mobilization failure should be a priority given that failure rates with conventional strategies are as high as 40%.

We aim to analyse this percentage at our Institute as well as the salvage strategies.

Methods: We retrospectively analysed the data from all patients who underwent PBSC mobilization, from December 2019 to November 2022.

Mobilization strategies:

(1) G-CSF-alone;
(2) disease-specific chemotherapy-based mobilization (QTd) in lymphoma and other malignancies;
(3) specific chemo-mobilization (QTm) in MM patients with < 55 years.

We use filgrastim biosimilars and use them in higher doses (≥ 10 µg/Kg/day).

Salvage strategies:

(1) plerixafor (PLX) on demand during the first mobilization attempt;
(2) pre-emptive plerixafor use in remobilization.

Plerixafor is used according to Summary of Product Characteristics.

The definition of poor mobiliser used is the one proposed by the "Gruppo Italiano Trapianto di Midollo Osseo" but performing 2 leukapheresis (LKP) per mobilization maximum.

CD34+ cells are counted by flow cytometry using BD FACSCalibur™ and BD™ Stem Cell Enumeration Kit.

Leukapheresis is performed using the CMNC protocol of the Spectra Optia® system processing up until 4 total blood volume (TBV) in each.

We aim to harvest CD34 + ≥ 2x10^6/Kg/aHSCT.

Results: In the study period, a total of 105 patients underwent PBSC mobilization, 49 were female and 56 were male. The median age ± SD was 47 ± 15 years (range 2-68). There were 34 patients diagnosed with Multiple Myeloma (MM), 45 with non-Hodgkin Lymphoma (NHL), 16 with Hodgkin Lymphoma (HL) and 10 with other malignancies.

Among the 105 mobilized patients, 20 patients (4 MM, 11 LNH, 3 LH, 1 pineoblastoma and 1 neuroblastoma) had peripheral blood (PB) CD34 + < 20/µL (19,0% poor mobilizers).

Among the 20 poor mobilizers, 9 yielded ≥ 2×10^6 CD34 + /Kg as a result of leukapheresis efficiency: 5 after 1 leukapheresis and 4 after 2 leukapheresis. Other 7 poor mobilizers yielded ≥ 2×10^6 CD34 + /Kg after plerixafor on demand: 3 after plerixafor + 1 leukapheresis and 4 after plerixafor + 2 leukapheresis. Other 2 didn't yielded ≥ 2×10^6 CD34 + /Kg: 1 was proposed to allotransplantation after mobilization with plerixafor on demand failed and 1 refused remobilization with pre-emptive plerixafor. Other 2 patients had their mobilization cancelled: 1 due to disease progression, 1 refused remobilization.

And thus only 4 patients didn't yield ≥ 2×10^6 CD34 + /Kg (3,8%).

Conclusions: At our Institute the rate of poor mobilizers given the peripheral blood CD34+ cell count is 19,0% which is relatively low compared with the literature.

Choosing the appropriate mobilization regimen based on patient characteristics, optimizing the mobilization protocol for each patient (customizing the dose and duration of mobilizing agents), adopting as fit for purpose CD34+ cell count assessments and optimising the leukapheresis protocol, results in a "tailored mobilization" thus improving mobilization outcomes.

This customizing has allowed us to harvest the amount of PBSC necessary to proceed to aHSCT in 96,2% of the cases.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P683

THE IMPACT OF COVID-19 PANDEMIC ON HPC DONATION AND DONOR UNAVAILABILITY: SINGLE CENTER ANALYSIS

MM	**n**	**Median age ± SD (range)**	**PB CD34 + < 20/µL**	**Mobilization canceled**	**1 LKP**	**2 LKP**	**PLX + 1 LKP**	**PLX + 2 LKP**	**Yield <2x10^6 /Kg**
G-CSF	27	60 ± 4 (47-68)	4	0	2	1	1	0	0
G-CSF + Qm	7	46 ± 7 (29-57)	0	0	0	0	0	0	0
NHL	n	Median age ± SD (range)	PB CD34 + < 20/µL	Mobilization canceled	1 LKP	2 LKP	PLX + 1 LKP	PLX + 2 LKP	Yield <2x10^6 /Kg
G-CSF	5	60 ± 6 (48-67)	2	0	0	0	2	0	0
G-CSF + QTd	40	51 ± 10 (15-67)	9	1	1	3	0	2	2
HL	n	Median age ± SD (range)	PB CD34 + < 20/µL	Mobilization canceled	1 LKP	2 LKP	PLX + 1 LKP	PLX + 2 LKP	Yield <2x10^6 /Kg
G-CSF	1	29	1	0	1	0	0	0	0
G-CSF + QTd	14	35 ± 13 (15-61)	1	0	0	0	0	1	0
G-CSF + QTm	1	39	1	0	0	0	0	1	0
Other malignancies	n	Median age ± SD (range)	PB CD34 + < 20/µL	Mobilization canceled	1 LKP	2 LKP	PLX + 1 LKP	PLX + 2 LKP	Yield <2x10^6 /Kg
G-CSF	3	8 ± 8 (2-21)	1	0	1	0	0	0	0
G-CSF + QTd	7	7 ± 5 (2-17)	1	1	0	0	0	0	0

Grzegorz Hensler[1], Tigran Torosian[1], Alicja Wozniak[1], Katarzyna Szymanska[1], Iwona Tomanek[1]

[1]Fundacja DKMS, Warsaw, Poland

Background: The COVID-19 pandemic had a huge impact on the health care system especially at the beginning, in 2020, forcing the centers involved in the collection and transplantation of HSC to react quickly to the changing recommendations and restrictions such as border closing, air traffic suspension, quarantine, donor testing.

In the wake of the COVID-19 pandemic all donor centers created precaution policies to protect both donors from the risk of acquiring SARS-CoV-2 during collection related activities, and recipients, to prevent viral transmission with the transplant.

DKMS regularly updated Confirmatory Typing (CT) and Workup (WU) procedures to protect donors against excessive exposure and infection with SARS-CoV-2. Donors with risk factors of severe COVID-19 (e.g. obesity, hypertension, asthma), as well as health care workers (doctors, nurses, paramedics) were excluded from the procedure due to the higher risk of infection and the potential shortage of medical staff in the face of a pandemic. Donors were tested for SARS-CoV-2 at PE and/or collection days.

Objectives: To analyze the impact of COVID-19 pandemic on donor availability at WU stage in 2020. To verify the risk of SARS-CoV-2 transmission via HPC product and the risk of harm to donor if positive at collection.

Methods: In 2020 DKMS Poland received 1,673 WU requests (10% less than in 2019). 1233 collections were performed. 205 procedures were canceled by transplant centers. 235 WU procedures were closed for donor-related reasons. Those related to the COVID-19 pandemic were analyzed, dividing and coding them as follows:

- Medical reasons, including COVID-19 diagnosis at the WU and co-occurrence of medical risk factors of severe COVID-19.
- Non-medical reasons, including donors withdrawing due to fear related to the pandemic.

Results: Out of the 1468 WU requests 236 donors were unavailable (16%). 90 procedures were closed for non-medical reasons (unable to contact, not interested, abroad, private reasons and COVID-19 related fear). Medical issues were the reason of deferral of 146 donors.

Among 236 unavailable donors 63 cases were COVID-19 related. Most of these were personal reasons: fear of pandemic (36) or health care workers blocked at the early stage of WU (3). 24 donors were blocked for COVID-19 related medical reasons such as quarantine (8), COVID-19 diagnosis (13), respiratory infections without conformation (2), risk factors of severe COVID-19 (1).

In spite of the precautions there were 3 donors that tested positive for SARS-CoV-2 on collection day. In 2 cases TC accepted the product, donors underwent collections without any adverse reactions and the cells were infused. No viral transmission was reported after transplantation. In 1 case TC chose an alternative donor.

Conclusions:

- In 2020 COVID-19 was a substantial reason of donor unavailability: 27% of the total number of unavailable donors.
- The COVID-19 related donor unavailability was mainly due to personal reasons: 62% of COVID-19 related cases.
- We had 3 SARS CoV-2 positive donors on collection day. Two of those donors underwent apheresis with no adverse reactions and no viral transmission evidence to recipient.

Disclosure: nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P684

CRYOPRESERVATION OF ALLOGENEIC HAEMATOPOIETIC STEM CELLS – THE SOUTH AFRICAN COVID-19 EXPERIENCE

Tanya Nadia Glatt[1,2], Hlulani Mahosi[2], Riana Cockeran[2]

[1]University of Johannesburg, Johannesburg, South Africa, [2]Sanbs, Johannesburg, South Africa

Background: Prior to the advent of Covid-19, cryopreservation of Haematopoeitic Stem Cells was used in autologous or cord blood Haematopoeitic Stem Cell Transplants (HSCT), while allogeneic HSCT were infused as fresh products and not cryopreserved. During the Covid-19 pandemic, due to concerns of the possibility of donor infections, recipient infections and travel / transport restrictions, international HSCT societies and registries recommended that all allogeneic HSCT grafts be cryopreserved. Since then, data has shown poorer outcomes of cryopreserved grafts in comparison to fresh grafts. This study looks at the engraftment outcomes of allogeneic HSCT that were cryopreserved at SANBS during the Covid-19 pandemic.

Methods: All allogeneic HSC grafts that were cryopreserved at SANBS from January 2020 until December 2021 were included. Neutrophil and platelet engraftment for each patient was assessed. The engraftment outcomes were compared to the 2019 engraftment outcomes at SANBS.

HSCT engraftment was defined as: Day 1 of Neutrophil count of >0.5 x109/l for three consecutive days and Day 1 of platelet count of > 20 x109/l for three consecutive days without platelet transfusions in the past 7 days.

Successful engraftment was defined as engraftment at/before day 28 post-transplant.

Delayed/non-engraftment was defined as engraftment after day 28 post-transplant

Results: During this 24 month period, 14 patients fulfilled inclusion criteria. Two patients demised prior to day 28 (14.3%), onepatient had delayed neutrophil engraftment (7.1%) and fourpatients had delayed platelet engraftment (28.6%).

In comparison, the 2019 engraftment outcomes were as follows: of the 92 HSC reinfusions performed, 3.3% of patients demised prior to day 28; no patients had delayed neutrophil engraftment and 2.2% of patients had delayed platelet engraftment.

Conclusions: Although this study is a small sample size, it concurs with international data in showing poorer neutrophil and platelet engraftment outcomes of cryopreserved allogeneic HSC grafts in comparison to pre-Covid-19 engraftment. Whenever logistically feasible fresh allogeneic HSCTs are recommended over cryopreserved grafts.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P685

IMMUNOPHENOTYPIC CHARACTERIZATION AND CLINICAL CORRELATION OF A MANIPULATION TECHNIQUE BASED ON CD34+ STEM CELL SELECTION WITH CD3 + T CELL ADD-BACK

Stefano Rossi[1], Giulia Baresi[1], Elena Soncini[1], Marta Comini[2], Marianna Maffeis[1], Federica Bolda[2], Alessandra Beghin[2], Arnalda Lanfranchi[2], Fulvio Porta[1]

[1]Pediatric Hematology and Oncology Unit and Pediatric Bone Marrow Transplant Center - ASST Spedali Civili of Brescia, Brescia, Italy, [2]Stem Cell Laboratory, Section of Hematology and Blood Coagulation, Clinical Chemistry Laboratory, ASST Spedali Civili of Brescia, Brescia, Italy

Background: Less than 25% of children requiring hematopoietic stem cell transplantation (HSCT) have an HLA-identical sibling. For them, a matched unrelated donor (MUD) or mismatched related donor represent (MMRD)valid alternatives, even if associated to a greater risk of graft failure, delayed engraftment and immune reconstitution, and increased risk of graft-versus-host disease (GvHD). A CD34+ positive selection can mitigate HLA compatibility issues, but the resulting CD3 + T cell depletion hampers engraftment and facilitates infections. To mitigate those problems, we apply a technique comprising CD34 + positive selection and later addback of a controlled number of T lymphocytes (30x10^ 6 / kg / recipient) derived from MUD or MMRD PBSCs, documenting rapid engraftment, rapid immunological reconstitution, and low incidence of acute and chronic GVHD. The phenotype of the CD3+ lymphocytes infused and of the CD20+ and CD56 + 16+ lymphocytes comprised in the negative fraction can be variable and little is known about the impact of these differences on clinical outcomes. Our aim was to characterized the immune phenotype of the lymphoid population infused in association to CD34+ stem cell in a small cohort of HSCT performed with this manipulation.

Methods: We performed an analysis of Lymphocyte subset from negative fraction after CD34+ positive selection and T cell addback in 6 patients (3 MUD and 3 Haploindetical donor).

Results: The products presented slight differences in the distributions of the lymphocytes subsets. All the products showed a positive CD4 + /CD8+ ratio except for one haploidentical product, that showed a higher proportion of CD8+ cells. In particular CD4+ and CD8+ ranged between 9.02x10^6/Kg to 23.33x10^6/Kg recipient (mean value 16.18x10^6/Kg recipient) and 6.16x10^6/Kg recipient to 13.82/Kg recipient (mean value 10.00x10^6/Kg recipient), respectively. The proportion of T αβ and T γδ cells ranged between 86.5% and 97.3% (mean 94.8%) and between 2.4% and 12.7% (mean 4.7%). On the other hand the proportion of CD4 + CD45RA+ range d between 41.2% and 64.9% (mean 53.42%) while that of CD4 + CD45RO+ ranged between 35.1% and 58.8% (mean 46.58%). At last, CD20+ cells ranged between 2.22x10^6/Kg recipient and 14.8x10^6/Kg recipient (mean 7.99 x10^6/Kg recipient) while CD56 + CD16+ ranged between 1.40 x10^6/Kg recipient and 5.19x10^6/Kg recipient (mean 3.48x10^6/Kg recipient).

Conclusions: We already described the feasibility and results of a transplant technique based on CD34+ positive selection and T cells addback. Nevertheless we observed slight differences in T, B and NK cells distribution in different products, while a clear correlation with clinical outcomes is still missing. Further analysis of a greater number of HSCT products is needed to clarify the clinical impact of the differences observed.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P686

NEW METHOD FOR BONE MARROW COLLECTION AND FILTRATION: APPROVED, COST-EFFICIENT AND COMPATIBLE WITH CURRENT EU-MDR

Emanuel Berger[1], Martina Brandl[1], Ulrich Hahn[1], Ludmila Sytik[1], Jana Hoppe[1], Nina Schupp[1], Jeannie Noerholm[1], Tanja Beck[1], Lorena Morale[1], Lisa Baur[1], Renate Hintermeier-Knabe[1], Sabine Naydek[1], Franziska Menne[1], Hans Knabe[1]

[1]Stiftung Aktion Knochenmarkspende Bayern, Bayerische Stammzellbank gGmbH, Gauting, Germany

Background: With the implementation of the revised Medical Devices Regulation (MDR) in the European Union, the availability of commercial bone marrow collection systems on the European market has been greatly reduced. Therefore, an alternative bone marrow collection and filtration method has been setup and validated that only consist of components that are certified according to the current MDR.

Methods: During collection, bone marrow is aspirated repeatedly from the donor's iliac crest using 20mL syringes. The syringes are emptied repeatedly into 1000mL collection bags (Fresenius Kabi) in which anticoagulants have been added using a three-way stopcock that connects the syringe to the bags' tubes via a Luer-Lock system. After collection is completed, the bags are transferred from the operating room to the laboratory. A Drip SWAN® Transfusion device (Codan) containing a 200µm pore size filter is connected to the tubing of each collection bag using a sterile connection device. Filtered bone marrow is collected in a 2000mL transfer bag (Fresenius Kabi) that has been connected downstream of the filter by sterile docking. Subsequently, the filtered bone marrow is split up into equal portions using a tube switch and up to three 600mL CompoFlex® transfer bags (Fresenius Kabi) and is ready for transport to the transplant centre.

Results: In a pre-trial this method was validated by comparing it to the commercially available bone marrow collection and filtration kit purchased from Fresenius Kabi. Both methods revealed a high filtration rate with a low occurrence of small aggregates in the bone marrow filtrate. No bacterial contamination occurred due to filtration indicating a high safety of the filtration methods. Furthermore, the content of $CD34^+/CD45^+$ stem cells and their viability was analysed and their proliferative capacity was assessed by evaluating the number of colony forming units (CFUs) after filtration. Considering the biological variability of the bone marrow itself, both filtration methods revealed equal results on a high quality level. Based on this pre-trial, twelve additional bone marrow collections were evaluated to see whether they meet the quality specifications. Except for single outliers, all specifications were met by the new method. In addition, a high viability of $CD45^+$ leukocytes after >72h storage at 4°C was obtained and the feedback from the clinicians regarding the overall success rate of the transplantations was consistently positive. Consequently, responsible German authorities have approved the application of this method for bone marrow collection and filtration. Moreover, due to the use of bulk components, the expenses for consumables can be reduced by a factor of five to six.

Conclusions: The newly setup method to collect and filtrate bone marrow from healthy donors combines commercially available, low-prize and MDR-certified bulk components without the need for a cleanroom. The validation process has proven that this method delivers high-quality bone marrow filtrates that are consistently comparable to the ones obtained by using the filtration system from Fresenius Kabi. This helps to maintain the care of children with haematopoietic disorders, for which bone marrow still is the superior stem cell source.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P687

STEM CELL MOBILIZATION WITH PLERIXAFOR IN PATIENTS WITH MYELOMA AND LYMPHOMA – A SINGLE-CENTER RETROSPECTIVE ANALYSIS

Vladan Vucinic[1], André Drechsler[1,2], Yvonne Remane[2], Enrica Bach[1], Mandy Brueckner[1], Janine Kirchberg[1], Madlen Jentzsch[1], Florian Ramdohr[1], Simone Heyn[1], Song-Yau Wang[1], Sebastian Schwind[1], Marco Herling[1], Klaus Metzeler[1], Georg-Nikolaus Franke[1], Wolfram Pönisch[1], Dietger Niederwieser[1], Maximilian Merz[1], Uwe Platzbecker[1]

[1]University Leipzig Medical Center, Celltherapy and Hemostaseology, Leipzig, Germany, [2]University Leipzig Medical Center, Pharmacy, Leipzig, Germany

Background: About 5-30% of patients with lymphoma and myeloma that are intended to undergo high-dose therapy with autologous stem cell transplantation (ASCT) experience frustraneous efforts of mobilization by granulocyte-colony stimulating factor (G-CSF) ± chemotherapy. Plerixafor is an antagonist of the CXC-motif-chemokine-receptor 4 (CXCR4) and is licensed in combination with G-CSF for stem cell mobilization in patients with lymphoma and myeloma intended to undergo high-dose therapy with ASCT. We performed a retrospective analysis of stem cell collections after mobilization with plerixafor (+ G-CSF) in our institution within the past 10 years.

Methods: From January 2010 through December 2019, 94 stem cell collections of 80 patients (36 (45%) female, 44 (55%) male) with a median age of 62 years (range 32-76) were performed after application of plerixafor. The hematological diagnosis was multiple myeloma in 43 (54%) patients and lymphoma in 37 (46%). Mobilization with chemotherapy and G-CSF (chemo-mobilization) preceded 72 collections (77%), while 22 (23%) were performed as steady-state mobilizations (no prior chemotherapy). Collections were initiated at peripheral blood (pB) $CD34^+$ concentrations of ≥ 10/µl, with target yields ≥ 2 x 10^6 $CD34^+$ cells/kg body weight.

Results: Administration of plerixafor led to a median 3-fold increase of $CD34^+$ cells in pB from 9.6/µl (range 2.1-36.0) to 29.6/µl (range 9.0-136.3). No difference in median $CD34^+$ concentrations in patients with lymphoma vs myeloma were noted (30.5/µl (range 10.0-85.1) vs 28.1/µl (range 9.0-136.3), respectively ($p = 0.988$)). Furthermore, no differences in median $CD34^+$ concentrations after steady-state vs chemo-mobilization were detected (median 30.8/µl (range 9.0-95.1) vs 28.4/µl (range 10.0-136.3) after plerixafor ($p = 0.964$).

The median yield of collections was $3.8x10^6$ $CD34^+$ cells/kg body weight (range 0.6-30.3). These did not differ between patients with lymphoma vs those with multiple myeloma $3.9x10^6$ (range 0.8-13.1) vs $3.7x10^6$ (range 0.6-30.3) $CD34^+$ cells/kg body weight, respectively ($p = 0.964$)). We also noticed no differences in yields after steady-state vs chemo-mobilizations; median $3.2x10^6$ (range 0.7-10.5) vs $3.8x10^6$ (range 0.6-30.3) $CD34^+$ cells/kg body weight, respectively ($p = 0.437$).

Cell viability in the collections after cryopreservation was at median 83.4% (range 58-98) without differences regarding the diagnosis ($p = 0.095$) or modality of collection ($p = 0.416$). 71 of collected patients eventually underwent high-dose therapy with ASCT. At median $4x10^6$ $CD34^+$ cells/kg body weight (range 1.7-13.1) were infused. Leukocyte regeneration (absolute neutrophile counts ≥ 500/µl) occurred after a median of 11 days (range 9-15). Platelet recovery (≥ 20000/µl) occurred after a median of 14 days (range 10-75).

Conclusions: We conclude that the use of plerixafor in adult patients with multiple myeloma and lymphoma is an effective strategy for stem cell mobilization. Application of plerixafor in addition to G-CSF can enable access to high dose therapy even for poor mobilizers. Further studies are necessary to define factors that predict poor mobilization.

Disclosure: Vladan Vucinic receives honoraria from Sanofi.

2 - Stem Cell Mobilization, Collection and Engineering

P688

HIGH DOSE PLERIXAFOR AND LARGE VOLUME LEUKAPHERESIS – IS IT THE ANSWER FOR AUTOLOGOUS STEM CELL TRANSPLANTS IN ABSOLUTE POOR MOBILIZERS?

Amit Jain[1], Ratna Sharma[1], Rajesh Patil[1], Nidhi Mehta[1], Pranoti Kini[1], Ashutosh Walawalkar[1], Srishti Srivastava[1], Mamta Manglani[1]

[1]MCGM - Comprehensive Thalassemia Care, Pediatric Hematology-Oncology & BMT Centre Borivali, Mumbai, India

Background: Peripheral blood stem cell (PBSC) collection is a challenge in patients undergoing autologous stem cell transplant (ASCT), if their absolute peripheral blood (PB) CD34 count is <5 cells/ul after 7 doses of G-CSF at Day 4 considered as an absolute poor mobilizer. They have a high chance of requiring multiple apheresis procedures and are at risk of mobilization failure. Hence, additional strategies like the use of high-dose plerixafor and large-volume leukapheresis (LVL) have been implemented to overcome this problem.

The aim was to study the efficacy of high-dose plerixafor with LVL to achieve a stem cell dose of >3*10^6 in patients undergoing ASCT with day 4 Peripheral blood CD34 count of <5 cells/ul.

Methods: Retrospective analysis of all pediatric patients who underwent ASCT from July 2018 to November 2022 with a day 4 PB CD34 + ≤ 5 cells/ul after receiving 7 doses of GCSF (5 mcg/kg/dose). These children were administered high-dose Plerixafor (0.48 mg/kg, maximum 24 mg) followed by LVL (4TBV). The outcome measure was CD34 + ≥ 3.0 x 10^6cells/kg.

Results: Of a total of 99 patients who underwent ASCT, 16 (M:F ::1.66:1) were absolute poor mobilizers and included in the analysis (14 - Neuroblastoma, 2-Hodgkin Lymphoma). The mean age was 6.5 years (1 to 15 years), mean body weight was 18 kg (9.9 - 41.6 kg). The optimal stem cell dose was achieved in 11/16 (73.3%) in single apheresis while 4/16 (25%) required the second apheresis. Only one patient failed to mobilize with this approach. The mean stem cell dose was $6.4*10^6$/kg (3.4 to $12.8*10^6$/kg). No significant adverse events were observed related to plerixafor and LVL.

Conclusions: High-dose plerixafor with GCSF and LVL is a safe and effective strategy in achieving an optimal stem cell dose in pediatric patients with absolute peripheral CD 34 < 5 cells/ul. Prospective randomized controlled trials are needed to establish this strategy as the standard of care.

Disclosure: None.

2 - Stem Cell Mobilization, Collection and Engineering

P689

SUCCESSFUL COLLECTION OF PERIPHERAL HEMATOPOIETIC STEM CELLS 4 HOURS AFTER PLERIXAFOR ADMINISTRATION IN POOR MOBILIZER HEALTHY DONORS

Aurora Vassanelli[1], Maurizio Cantini[1], Denise Pavone[1], Annarosa Gandini[1], Annachiara Giuffrida[1], Sabrina Genesini[1], Giorgio Gandini[1]

[1]Collection Center - Verona, Italy

Background: At the Collection Center in Verona, Italy, between 2017 and November 2022, 13 HPC donors was poor mobilizer (4% of healthy donors, both family and non-family).

Methods: Of these healthy donors, 9 were female, with a mean weight of 59 kg, and 4 were male, with a mean weight of 82 kg; mobilization was performed with G-CSF at the standard dose of 10 mcg/Kg. At day 5' (5D) in these donors the CD34 circulating were on average 29/mmc (range 16-53): in all 13 cases, Plerixafor was administered at a dose of 0.24 mg/kg sc with the informed consent of the donor, and the collection was started 4 hours after the administration of Plerixafor.

In 8/13 donors the collection on day 5D was made (despite the low CD34 value) collecting an average of 79 x 10e6 CD34 (range 41-116 x 10e6 CD34) ; the mobilization with G-CSF was continued at the same dose also for the following day and the day after (6D) these 8 donors received Plerixafor at a dose of 0.24 mg/kg sc, mobilizing circulating CD34 91/mmc and obtaining an average of 405 x 10e6 CD34 on collection bag.

Results: In the next 5 donors due to poor mobilization, Plerixafor was administered as early as day 5D. In these 5 donors excellent mobilization was achieved (circulating CD34 4 hours after receiving 0,24 mcg/Kg Plerixafor: average 105/mmc), collecting 520 x 10e6 CD34 (range 363-641 x 10e6) with a single apheresis, without administering additional doses of G-CSF to the donor, without changing the donor's schedule, and without affecting the travel plans or transplant schedule. Plerixafor was well tolerated by the donor in all cases and no side effects or adverse reactions occurred.

Conclusions: In our experience, in poor mobilizer donors after standard-dose mobilization with G-CSF (10 mcg/kg), the administration of Plerixafor, at a dose of 0.24 mg/kg sc is feasible without significant side effects and successful, starting the donation on the 5D, the day scheduled for the first HPC collection, 4 hours after administration, without need of further administration of G-CSF and without interfering with the organizational aspects of donation, transport and transplantation.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P690

ERYTHROCYTE REDUCTION OF BONE MARROW GRAFTS VIA 1×*G* SEDIMENTATION WITH GELAFUNDIN: A TECHNICAL NOTE

Krasimira Aleksandrova[1], Christiane Dehn[1], Ariane Franke[1], Diana Ladas[1], Jana Leise[1], Stephan Klöß[1], Christoph Priesner[1], Lubomir Arseniev[1], Ulrike Köhl[1], Maya Yordanova[2]

[1]Hannover Medical School, Hannnover, Germany, [2]University Hospital Queen Johanna-ISUL, Sofia, Bulgaria

Background: Erythrocyte reduction of bone marrow (BM) grafts is applied in major ABO-incompatible allogeneic transplantations or for cryopreservation of autologous BM. The BM harvest is usually carried out in bad mobilisers or where indicated, especially for paediatric patients.

Methods: For the studied time period between 2012 and 2020 allogeneic bone marrow harvested from 68 donors (62 for the German and 6 for the Bulgarian site) was subjected to an overhead 1×*g* sedimentation in a ratio of 2:1 with Gelafundin 4% (Gelatinepolysuccinate, BBraun, Germany) for 60-90 min. at room temperature. The erythrocyte sediment was let out and the remaining cell suspension was washed via centrifugation to remove the sedimentation agent and adjust final volume. The major specifications were: <1 ml/kg incompatible erythrocytes (RBC) or <15% haematocrit for cryopreservation.

Results: Median values and ranges are presented. All numbers are referred to viable cells. In Germany the harvested BM had a volume of 1116ml (207-1874ml), >4 $\times 10^8$ nucleated cell(NC)/kg (1.4-16.9$\times 10^8$/kg) with 7.9ml incompatible erythrocytes/kg (3.5-38.0ml/kg). The procedure resulted in a BM graft volume reduction of 85% (52-95%). The RBC were reduced by 95% (85-98%) to 0.5 ml/kg of the recipients (0.15-2.25ml/kg). The NC recovery was 72% (53-98%), resulting in 3.1 $\times 10^8$NC/kg (0.8-11.8 $\times 10^8$NC). The same values for $CD34^{pos}$ cells were 77% (43-100%) and 2.8 $\times 10^6$/kg (0.3-11.1 $\times 10^6$/kg). However, a higher loss rate was observed for the $CD3^{pos}$ cells: recovery 44% (7-98%). The Bulgarian site showed similar results: incoming BM-volume 861ml (192-1540ml) with a final volume of 176ml (115-600ml). The RBC were reduced by 93% (63-97%) resulting in 0.5 ml/kg (0.26-1.41 ml/kg). 89% (67-100%) of the NC were recovered, resulting in 3.2 $\times 10^8$NC/kg (1.75-4.98$\times 10^8$NC/kg) for transplantation. For the $CD34^{pos}$ yield was 73% (63-100%) with 2.1 $\times 10^6$/kg (0.7-3.5 $\times 10^6$/kg) in the grafts.

Conclusions: There is a major trend for automatisation and standardisation of the cellular medicinal product manufacturing. The described manual process is subjected to standardisation also and is performed in an EU-GMP-compliant manner. The lower costs and similar working time allow its use by sites with no direct access to cell separators or processors for this relatively infrequent demand. Although personal skills play a significant role in the processing, the specifications defined in advance are regularly met. Overall erythrocyte reduction of more than 90% was achieved. Furthermore, an acceptable technology transfer was carried out as shown by the results of the Bulgarian group. No notifications of adverse effects were received in the studied period.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P691

PLERIXAFOR FOR AUTOLOGOUS STEM-CELL MOBILIZATION AND COLLECTION IN A PORTUGUESE CENTRE

Rita Pombal[1], Sara Lopes[2], Ana Salselas[2], Susana Roncon[2]

[1]Centro Hospitalar Vila Nova de Gaia/Espinho, EPE, Vila Nova de Gaia, Portugal, [2]Instituto Português de Oncologia do Porto FG,EPE, Porto, Portugal

Background: Mobilization failure is an important issue in stem cell transplantations (SCT), as these patients cannot be proposed to SCT. In our centre, plerixafor is used with granulocyte colony-stimulating factor (G-CSF) as a risk-adapted approach or in a second attempt to mobilize. We usually perform mobilization without chemotherapy (G-CSF administration starts 4 days before leukapheresis, which is carried out on day 5). The main purpose of this study was to evaluate the efficacy of plerixafor in our patients requiring autologous SCT.

Methods: Observational retrospective study of the patients under plerixafor for autologous stem-cell mobilization between January 2017 and June 2022. Bivariate analysis was performed with Wilcoxon, Mann-Whitney and Independent T tests.

Results: During 5 years and a half, 595 patients underwent autologous apheresis collection; 6% (n = 36) received G-CSF in combination with plerixafor as a remobilization attempt (n = 32) or in a risk-adapted approach (n = 4). Thirty-two were adults: 63%

(n = 20) female, with a median age of 58 years (IQR 19); 4 patients were pediatric: 75% (n = 3) female, with a median age of 11 years (IQR 13). Hematologic malignancies prevailed: 58% (n = 21) Non-Hodgkin's Lymphoma (86% on III/IV stages), 22% (n = 8) Hodgkin's Lymphoma (25% on III/IV stages) and 14% (n = 5) Multiple Myeloma (20% on ISS3 stage); only 6% (n = 2) were Germ Cell Tumors (100% on IV stage). The median number of previous chemotherapy regimens was 2 (IQR 1; Min 1; Max 5). We found a total of 42 plerixafor mobilization attempts, of which 38 proceeded to collection, with a total of 64 leukaphereses [median of 2 sessions per patient (IQR 1; Min 1; Max 5), 4 blood volumes (IQR 2.5; Min 1.8; Max 7) and 238 minutes (SD 97; Min 98; Max 402) per apheresis, 91% with central venous catheter, without major adverse events]. Four patients didn't proceed to collection due to very low peripheral blood (PB) CD34+ cells count. We analyzed the 64 leukaphereses, comparing good versus bad mobilizers and found some relevant differences (Table 1). Among patients in a remobilization attempt (n = 32), there was a statistically significant difference between the PB CD34+ cells median number before (3 CD34 + /µL (IQR 4)) and after (9 CD34 + /µL (IQR 18)) plerixafor ($p < 0.001$) and the median number of CD34+ cells/kg collected before (0,38 x10^6 (IQR 0,53)) and after (2,39 x10^6 (IQR 2,38)) plerixafor ($p < 0.001$). Therefore 78% (n = 25) reached the minimum necessary CD34+ cell yield for transplantation and, at the end of the study, 86% (n = 24) had undergone autologous SCT, with a 12-month survival rate of 67%. The 4 adult patients under the plerixafor risk-adapted approach had hematologic malignancies: 3 reached the minimum CD34+ cell yield in the first mobilization attempt and underwent SCT; the one that failed was treated with CAR T-cell therapy.

Table 1. Leukapheresis features on good and bad mobilizers with plerixafor.

Good Mobilizers	Bad Mobilizers	*p* Value
Timing between plerixafor administration and leukapheresis beginning (hours and minutes)		
Mean 11h50m (SD 1h20m; Min 10h30; Max 14h30)	Mean 11h60m (SD 1h40m; Min 9h; Max 13h40)	0,770
Peripheral blood CD34+ cells/µL		
Median 9 (IQR 15; Min 0; Max 197)	Median 1 (IQR 1,75; Min 0; Max 6)	<0,001
Number of blood volumes processed		
Median 5 (IQR 2,6; Min 1,8; Max 7)	Mean 3 (SD 0,6; Min 2,2; Max 4)	0,003
Time of leukapheresis (minutes)		
Mean 238 (SD 97; Min 98; Max 402)	Mean 170 (SD 53; Min 104; Max 268)	0,001
Collection yield (CD34+ cells x10^6/Kg)		
Median 1,29 (IQR 1,81; Min 0,11; Max 12,19)	Mean 0,2 (SD 0,14; Min 0,05; Max 0,48)	<0,001

Conclusions: In our patients, with previous G-CSF mobilization failure (n = 32;5%), we found that plerixafor was well-tolerated and effective in improving autologous stem cell mobilization and collection. Probably leukapheresis shouldn't be considered in the bad plerixafor mobilizers. Additionally, more studies should be conducted to explore the optimal attitude for plerixafor risk-adapted approach and for pediatric patients.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P692

STEM CELL APHERESIS: PREDICTION OF THE STEM CELL YIELD USING PRE-APHERESIS CD34$^+$ CELL COUNT - COMPARISON BETWEEN THE ALLOGENEIC AND AUTOLOGOUS SETTING

Johannes Gaertner[1], Kerstin Schaefer-Eckart[1], Knut Wendelin[1], Sabine Dressler[1], Francoise Kerache[1], Stefan Knop[1]

[1]Klinikum Nuernberg, Paracelsus Medical University, Nuernberg, Germany

Background: In the allogeneic setting, we could show, that the prediction of the stem cell yield based on the pre-aphesis peripheral CD34+ cell count is accurate and reliable (EBMT 2022, P554). This is essential for planning and executing of the PBSC leukapheresis procedure.

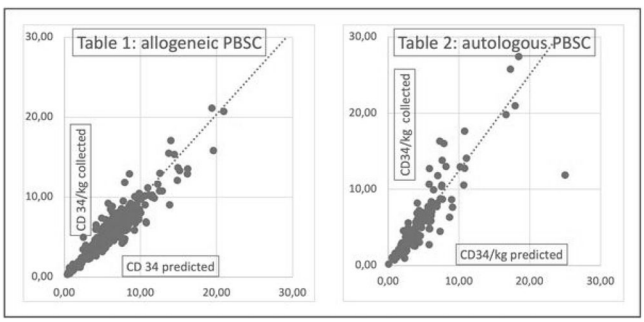
We investigated whether this is also true for the autologous stem cell collection and compared these results with allogeneic setting.

Methods: In 2021 and 2022 we performed 462 allogeneic apheresis and 138 autologous stem cell apheresis, using the spectra optia system (Terumo BCT). For GCSF stimulation lenograstim was used in the allogenic setting and filgrastim for the autologous collections.

The calculation of the final CD34$^+$ count (CD34+ per kg bodyweight recipient) in the product was based on the CD34+ cell count in peripheral blood before apheresis with the following method: Predicted CD34$^+$x10^6/kg = (benchmark collection efficacy x processed blood volume x peripheral CD34$^+$ count per µl) / (patient's weight x metric conversion factor).

We retrospectively investigated the correlation between the initially predicted and the finally collected CD34 + /kg for the allogeneic and autologous setting. Also, the ratio between predicted and collected stem cell yield (prediction coefficient) was analyzed.

Results: We investigated 462 allogeneic and 138 autologous apheresis procedures during the years 2021-2022. The median CD34+ count in the donor blood pre-apheresis was 67/ul in the allogeneic and 49,5/ul in the autologous setting. The rate of second day aphereses for the allogeneic respectively autologous collection was 6,28% / 29,9%. Additionally, in the autologous setting the supplementary application of plerixafor was necessary in 21,7% of the cases. For the allogeneic aphereses, the median value of the prediction coefficient of was 1.08, translating into only slight underestimation of the finally collected stem cell count. The Spearman's correlation coefficient (r) between calculated and actual collected CD34/kg was 0.96 ($p < 0.01$) (Table 1). In the autologous setting the median prediction coefficient was 1,21, representing a slightly higher underestimation rate (Table 2). The Spearman's correlation coefficient (r) was 0,95 ($p < 0,01$).



Conclusions: In the autologous setting, the method of calculating the stem cell yield based on the pre apheresis CD34+ count in the peripheral blood is also highly predictive for the number of CD34$^+$ cells actual collected, as has been shown for allogeneic aphereses.

For the autologous setting, despite a higher rate of low mobilizers, different mobilizing procedures (e.g. mobilizing by chemotherapy, steady state mobilizing, use of Plerixafor) and heavily pretreated patients, the accuracy of our calculation method is still very high.

This makes planning and adjusting of the apheresis procedure very reliable. For the autologous stem cell apheresis this is at least as important as in the allogeneic setting, because of a higher risk for low mobilizers, needing a second day apheresis and an often higher stem cell yield, e.g. for multiple myelomas or germ cell tumors.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P693

INTER-LABORATORY METHOD VALIDATION OF CD34+ FLOW-CYTOMETRY ASSAY: THE EXPERIENCE OF TURIN METROPOLITAN TRANSPLANT CENTRE

Deborah Rustichelli[1], Sara Castiglia[1], Loretta Gammaitoni[2], Alessandra Polo[2], Massimo Geuna[3], Marisa Pautasso[4], Ivana Ferrero[1]

[1]Regina Margherita Childrens' Hospital, Turin, Italy, [2]Candiolo Cancer Institute IRCCS, Candiolo (Turin), Italy, [3]AO Mauriziano Hospital, Turin, Italy, [4]AOU San Luigi Hospital, Orbassano (Turin), Italy

Background: According to Joint Accreditation Committee of ISCT and EBMT (JACIE) standards, relevant and standardized assay for quantifying hematopoietic stem cell (HSC) population needs to be established and periodically validated to keep the entire process under control.

The Turin Metropolitan Transplant Centre (CIC 305) was established in 2012 to optimize the management of clinical and laboratory resources necessary for maintaining the performance of critical activities related to HSC transplantation. In the CTMT there are 4 flow-cytometry laboratories assessing quality control on HSCs, with different instruments and operators. Therefore, the CD34+ enumeration assay should be validated on a regular basis. Here, we describe the validation plan with relevance to the risk analysis to test the inter-laboratory reproducibility of the method.

Methods: All the steps from transport of samples to the final report were carefully examined adopting a failure mode and effect analysis (FMEA) method.

Stabilized blood (BD TM Stem Cell Control cod. 340991, Becton Dickinson) samples were stained with Stem-Kit reagent (cod. IM3630, Beckman Coulter) according to manufacturer's instructions and acquired using the Beckman Coulter FC500 at Regina Margherita Children's' Hospital (CIC 305-1), Beckman Coulter Navios at Candiolo Cancer Institute FPO-IRCCS (CIC 305-2), BD Biosciences FACSLyric™ at A.O.U. San Luigi Orbassano (305-3), and Beckman Coulter Navios EX at Mauriziano Hospital (CIC 305-4).

The ISHAGE guidelines were followed for estimating % and absolute number of CD34+ cells in single-platform method.

The test was repeated on LOW (lot BC0622L: CD34 + /ul =11,3 [5.9-16.7], % CD34 + = 0,187 % [0.099-0.275] and HIGH (lot BC0622H CD34 + /ul =29,4 [19.5-39.3], % CD34 + = 0,472 % [0.314-0.630] samples, in two consecutive days for two weeks.

For each sample repeatability limit (r), reproducibility error, uncertainty of reproducibility error and coefficient of variation (CV) was reported.

Results: The repeated measurements (in percentage and absolute value) from each single laboratory (or for each single instrument) have a variability, expressed as reproducibility error (r), systematically lower than the repeatability limit for that single parameter (low: 0.0421 for CD34 + %, 2.312 for CD34 + /ul; high: 0.103, for CD34 + %, 3.625 for CD34 + /ul).

The corrected reproducibility error is always lower than the repeatability limit r (low: 0.0427 for CD34 + %, 2.255 for CD34 + /ul; high: 0.085, for CD34 + %, 3.165 for CD34 + /ul) except for the percentage value of the "low" count where it is just higher (0.0427 with r = 0.0421). The analysis of inter-laboratory variance (low: 0.0001588 for CD34 + %, 0.334302958 for CD34 + /ul; high: 0.001129 for CD34 + %, 0.602479375 for CD34 + /ul) is within the maximum acceptable variance value (low: 0.0009 for CD34 + %, 2.512225for CD34 + /ul; high0.0036 for CD34 + %, 4.950625for CD34 + /ul). In addition, the CV of all measurements for each parameter analyzed is less than 8%, indicating low measurement variability among laboratories. The table 1 summarize the results.

Table 1. Summary of results

	LOW		HIGH	
	CD34+ %	CD34/ul	CD34+ %	CD34/ul
Sample Range	0.099-0.275	5.9-16.7	0.314-0.630	19.5-39.3
Mean	0.195	12.269	0.4705	29.651
SD	0.015043796	0.825762168	0.036631163	1.294615976
CV	7.714767033	6.73047655	7.785581941	4.366179813
Repeatability limit (r)	0.042122628	2.31213407	0.102567256	3.624924734
Reproducibility error	0.06	3.17	0.12	4.45
Uncertainty of reproducibility error	0.017320508	0.915100177	0.034641016	1.284604349
Corrected reproducibility error	0.042679492	2.254899823	0.085358984	3.165395651
Inter-laboratory variance	0.000158792	0.334302958	0.001128958	0.602479375
Maximum acceptable variance	0.0009000	2.5122250	0.0036000	4.9506250

Conclusions: Evaluating the overall data we can assume that the four laboratories are perfectly aligned and the results are reproducible. The standardization of the method in use among the different laboratories of the CTMT allows optimizing the processes, and guarantees the continuity of the services even in situations of emergencies and disasters.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P694

PRECLINICAL EVALUATION OF DIFFERENT SOLUTIONS FOR WASHING OUT DMSO FROM PERIPHERAL BLOOD STEM CELL GRAFTS AFTER THAWING

Iwona Mitrus[1], Marcin Wilkiewicz[1], Wojciech Fidyk[1], Agata Hadryś[1], Agnieszka Ciomber[1], Andrzej Smagur[1], Paulina Borzdziłowska[1], Agata Chwieduk[1], Magdalena Głowala-Kosińska[1], Sebastian Giebel[1]

[1]Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland

Background: Peripheral blood stem cells are cryopreserved in dimethyl sulfoxide (DMSO) – a cryoprotective agent that prevents

the damaging effects of intracellular ice formation. Infused with the thawed cells, the DMSO can cause adverse reactions. In some patients these reactions are life-threatening; to prevent that, the DMSO must be removed from the graft after thawing.

The main aim of the study was to compare 4 different solutions used for DMSO washing out on the recovery of cells.

Methods: A total number of 16 cryobags (100 ml, 5% DMSO each) from 4 allogeneic donors were used for the evaluation of 4 different washing solutions. The cells were intended for disposal due to the death of recipients.

To compare solutions, the bags from one donor were thawed in 37°C and immediately resuspended in 100 ml of one of the following solutions:

1. 0,9% NaCl with 2.5% HSA (human serum albumin);
2. 0,9% NaCl with 2.5% HSA and 10 ml of ACD-A;
3. 0,9% NaCl with 2.5% HSA and 10U/ml of heparin;
4. 0,9% NaCl with 2.5% HSA and 10U/ml of heparin + 10 ml of ACD-A;

Next, the bags were centrifuged (15 min., 1000×G), the supernatant was removed and the cells were resuspended in the same solution. Each final product was tested for total nucleated cell recovery, cell viability, and CD34+ enumeration.

Results: Cell clumping was observed in all bags. The mean of nucleated cells recovery was similar in all solutions (respectively: solution 1: mean +/- SD: 60.4% +/-7.0%; solution 2: 70.1% +/- 10.6%; solution 3: 60.2% +/- 8.1%; solution 4: 67.9% +/- 7.9%;). The recovery of CD34+ cells was as follow: 94.7% +/- 12.5%; 109.4% +/- 7.3%; 107.4% +/- 16.7%; 108.6% +/- 18.8%.

No significant difference was found between compared solutions.

Conclusions: The washing of graft is a labor-intensive procedure and may cause cell clumping or contamination of the product. For this reason, most of the transplant centers avoid carrying out this procedure. If necessary, the DMSO may be removed by manual washing. Despite the loss of nucleus cells, the loss of CD34 cells is limited.

Clinical Trial Registry: The washing of graft is a labor-intensive procedure and may cause cell clumping or contamination of the product. For this reason, most of the transplant centers avoid carrying out this procedure. If necessary, the DMSO may be removed by manual washing. Despite the loss of nucleus cells, the loss of CD34 cells is limited.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P695

STEM CELLS COLLECTION IN MULTIPLE MYELOMA PATIENTS:COMPARISON BETWEEN PATIENTS RANDOMISED TO DARA PROTOCOLS VERSUS OTHER TREATMENTS AND CANDIDATE TO STEM CELL COLLECTION FROM PERIPHERAL BLOOD

Cristina Tassi[1], Emanuela Sergio[2], Serena Rocchi[1], Ernesto Rago[1], Giuseppe Scarcelli[1], Giovanni Portelli[1], Anna Gasparini[1], Cristiano Boccafogli[1], Elisa Iannotti[1], Patrizia Rapacchiani[1], Vanda Randi[3]

[1]IRCCS University of Bologna, bologna, Italy, [2]IRCCS University of Bologna, Bologna, Italy, [3]AUSL Bologna, Ospedale Maggiore, Bologna, Italy

Background: Daratumumab (DARA) has been included in the first line treatment of newly diagnosed or high risk patients affected by Multiple Myeloma (MM). Several laboratory and clinical adverse events due to DARA administration are noteworthy. Recently, the DARA pre-treatment seems to prevent bone marrow stem cells from migrating in the peripheral blood after mobilising protocols. Therefore, the rate of poor mobilisers has become significantly high, the collections of CD34+ cells difficult, and the target severely impaired. The aim of this report is to present the preliminary results obtained in MM patients in the Cell Collection Unit of the IRCCS Sant'Orsola Policlinic Blood Bank.

Methods: From January 2021 to December 2022, 91 MM patients in various status of disease underwent to stem cell collection after EDX 2/3g/mE2 plus G-CSF mobilizing treatments. 28/91 (31%) patients had previously received four or more DARA courses in a 4-6 month period, with a mean interval of 1.5 months to the mobilising therapy. The required CD34+ cell target dose ranged from 3 to 9x 10E6/kg of Body Weight, with >15/uL as the circulating CD34+ trigger value to start the collection. In poor mobilizers, one dose of Plerixafor was administered seven hours before collection start. The procedures were carried out by means of the Spectra Optia equipment, treating 2 to 3 total blood each time; procedures were replicated for a maximum of three consecutive days.

Results: Main data are presented in the Table. Pre collection CD34/uL are significantly lower in the DARA group and in patients who did not reach the required CD34+ target dose. Plerixafor was added to GCSF in patients expected as poor mobiliser. 156 collection were carried out: 1.8 was the mean collection index. By comparing DARA vs notDARA groups (column 7), 3 collections are more frequent in the DARA group, 25% vs 11%, and more than 15 litres were processed per patient in the 22% of the subjects. The minimum dose of 3x10E6/kg BW was unobtainable in 15 patients, being the 33% of them in the DARA group (column 3). In 3 no mobilisers, a second mobilising attempt done by G-CFS alone, led to collect a minimum of 3x10E6/kg cells. Whenever the initial target dose was impossible to be obtained, the target was reconsidered and lowered. No adverse events procedure-related were registered.

Conclusions: In conclusion, stem cell collection from peripheral blood is feasible in the majority of DARA pre-treated MM patients, but in case of a required high target of CD34+ cells, the probability of a collection failure may be significant. Collection courses in DARA pre-treated patients seem to be particularly challenging. To overcome collecting difficulties stemming from DARA treatment, some countermeasures should be applied both in the clinical settings (e.g. by re-designing the mobilising treatment and timing) and in the technical management of the

PATIENTS	PTS/COLLECTIONS	PTS NOT TARGET*	CD34 TARGET R**	p.05	CD34 TARGET NR***	TBV processed/PTS	COLL/PTS, %pts with >2Coll
DARA	28/52	5/28 18%	61 (11–257)	0.004	38 (16–78)	20.6 (8.7–35) L	1.9 mean, 3Coll:25% 7/28
NOT DARA	63/104	10/63 16%	84 (21–234)	0.002	28 (14–42)	18.4 (7–35) L	1.7 mean, 3Coll 11% 7/63
OVERALL	91/156	15/91 16%	72 (11–257)	0.004	33 (14–78)	19.5 (7–35) L	1.8 mean

Legend: *PTS* patients, *TBV* total blood volume, *COLL* collection performed,*Patients target not reached, **CD34pre in target reached, ***CD34pre in not reached targ.

collection (e.g. by processing higher volumes of blood and by improving the collection efficiency).

Clinical Trial Registry: No clinical trials

Disclosure: No conflict of interest.

2 - Stem Cell Mobilization, Collection and Engineering

P696

DOES INFUSION TIME REALLY AFFECT IN THE CELL VIABILITY IN THE AUTOLOGOUS STEM CELL TRANSPLANT?

María Casado Sánchez[1], Laura Posada Alcon[1], Juan José Mateos Mazón[1], Amaia Uresandi Iruin[1], Rosa María Mazariego Santolin[1], Julia Arrieta Aguilar[1], Sara Hormaza de Jauregui[1], Laura Aranguren Del Castillo[1], Ana Lobo Olmedo[1], Gorka Pinedo Martín[1], Paula María Zoco Gallardo[1], Ariadna Garcia Ascacibar[1], Angela Lozano Ochoa[1], Itxaso Plazaola Matilla[1], Maria Elena Amutio Diez[1], Juan Carlos Garcia Ruiz[1]

[1]Hospital Universitario Cruces, Barakaldo, Spain

Background: In routine clinical practice, cryopreserved hematopoietic progenitor cells (HPCs) are thawed and infused as quickly as possible to reduce the exposure time to DMSO, which on thawing releases heat and can damage HPCs, decreasing cell viability. The recommended infusion rate is between 5 and 20ml/min, with a total infusion time of about 20 minutes. On occasion this is not achieveable due to adverse effects related to DMSO. We therefore intend to test whether the total infusion time really affects cell viability in autologous transplantation and, secondarily, determine whether the duration of cryopreservation at -80°C influences cell viability.

Methods: We chose 6 cryopreserved units from patients who would not require them. 3 units had been at -80° for less than 6 months (bags 1,2 and 3) and the other 3 units had been at -80° for more than 1 year (bags 4,5 and 6).

We thawed each unit by immersing it in water at 37º. We then extracted 3 samples of each unit at 0, 30 and 60 minutes of thawing, and performed viability studies using the triptan blue exclusión method and hematimetry.

Results: The results obtained are shown in the attached table. Although with such a small sample we cannot establish statistical significance, we observe how cell viability decreases in each of the 6 units when we measure 30 minutes after thawing, from a decrease of 1% in bag number 2 to a decrease of 38.8% in bag number 4. This decrease is much more remarkable when the elapsed time is 60 minutes. In this case, the range varies from a decrease of 16.67% to 55.5%. The number of leukocytes per microliter is also reduced.

We additionally observe that the 3 units that had spent the longest time at -80° had a lower viability at minute 0 than the 3 most recent units. In addition, there were difficulties in performing hematimetry in the older bags due to the formation of cellular aggregates, despite the fact that the proportion of anticoagulant used was the usual one established in the bibliography.

Conclusions: The results obtained in our study coincide with the published literature in that the infusion time could influence the viability of hematopoietic progenitor cells. This fact supports the recommendations to perform the infusion in less than 30 minutes to minimize the damage of DMSO on the thawed cells although after this time there is still a sufficient amount of live cells.

In addition, our results show that cell viability also depends on the time the HPCs spend frozen at -80°C, hence the importance of freezing samples in liquid nitrogen within 6 months of apheresis.

Disclosure: Nothing to declare.

	CRYOPRESERVATION DATE	Patient's disease	MINUTE 0		MINUTE 30	MINUTE 60	
			VIABILITY	LEUKOCYTES/ µL	VIABILITY	VIABILITY	LEUKOCYTES/ µL
< 6 months	26/01/2022 (1)	Richter syndrome	98%	251.160	89%	75%	189.060
	27/01/2022 (2)	Richter syndrome	96%	256.430	95%	80%	166.830
	1/12/2021 (3)	Richter syndrome	98%	52.940	90%	79%	49.380
> 6 months	22/11/2018 (4)	Multiple Myeloma	75%	185.990	65%	60%	32.590
	9/08/2017 (5)	Acute myeloid leukemia	95%	106.580	70%	55%	90.190
	7/11/2018 (6)	Diffuse large B cell lymphoma	90%	251.310	55%	40%	202.670

2 - Stem Cell Mobilization, Collection and Engineering

P697

GENERIC/BIOSIMILAR G-CSF ARE EFFECTIVE FOR PERIPHERAL BLOOD STEM CELL MOBILIZATION AND NON-CRYOPRESERVED AUTOLOGOUS TRANSPLANTATION IN MULTIPLE MYELOMA. A SINGLE CENTER EXPERIENCE IN ORAN (ALGERIA)

Nabil Yafour[1], Mohamed Brahimi[1], Soufi Osmani[1], Kamila Amani[1], Belkacem Mansour[1], Leila Charef[1], Samira Bouchama[1], Badra Enta Soltane[1], Farah Bouamama[1], Faiza Serradj[1], Mohamed Chekkal[2], Rachid Bouhass[1], Abdessamad Arabi[1], Mohamed Amine Bekadja[1]

[1]Université d'Oran 1, Ahmed-Ben-Bella, Établissement Hospitalier et Universitaire 1(er) Novembre 1954, Faculté de Médecine, Service d'Hématologie et de Thérapie Cellulaire, Oran, Algeria, [2]Université d'Oran 1, Ahmed-Ben-Bella, Établissement Hospitalier et Universitaire 1(er) Novembre 1954, Faculté de Médecine, Service d'Hémobiologie et de Transfusion Sanguine, Oran, Algeria

Background: In autologous stem cell transplantation (ASCT), G-CSF can be used alone to mobilize CD34+ stem cells, or after a chemotherapeutic mobilization regimen. The objective of this study was to assess whether biosimilar/generic G-CSF have the same efficacy as the reference product G-CSF when used in the mobilization of non-cryopreserved storage peripheral blood stem cells (PBSCs) in patients (pts) undergoing ASCT for MM.

Methods: From May 2009 to 2019, 287 pts with MM pts were included. Mobilization was performed using G-CSF alone (10 µg/

kg/day for 5 -6 days). 140 pts (group 1, G1) were received originator G-CSF (Neupogen®, or Granocyte®) and 147 pts (group 2, G2) received generic/biosimilar (Zarzio® 23pts, immunef (copy) 124 pts). Leukapheresis was perform using a standard cell separator (Comthec Optia ® and fresenius ®). The grafts were kept in a conventional blood bank refrigerator at +4°C until reinfusion on day 0. The evaluation is based on the performance of harvested CD34+ cell count after leukapheresis. Mobilization failure was defined as a CD34+ cell count/kg < 2×10^6/kg.

Results: There was no difference between the characteristics of the pts of G1 and G2 in terms of age 59 years (33-77 years) vs 52 years (29-67 years) ($p = 0.54$), sex-ratio male/female 0.6 vs 0.58, and treatment with lenalidomide before ASCT; 12 pts (9%) vs 10 pts (7%) ($p = 0.62$) respectively. The apheresis results are comparable in the originator G-CSF (G1) and generic/biosimilar G-CSF (G2): number of apheresis 2 (1-3) vs 2 (1-3), median number of CD 34+ cells/kg collected 2.85 x 10^6 (1.22 -13.62) vs 3.17 x 10^6 (1.32-12) ($p = 0.23$) and failure to mobilize 15 pts (11%) vs 16 pts (11%) ($p = 0, 96$).

Conclusions: Biosimilar/Generic G-CSF are as effective as originator G-CSF in mobilizing PBSCs in pts undergoing no cryopreserved storage ASCT for MM.

Disclosure: Nothing to disclose.

2 - Stem Cell Mobilization, Collection and Engineering

P698

CYTARABINE FOR MOBILIZATION OF HEMATOPOIETIC STEM CELLS IN A REFERENCE HOSPITAL IN THE NORTHEAST OF BRAZIL: A RETROSPECTIVE COHORT ANALYSIS

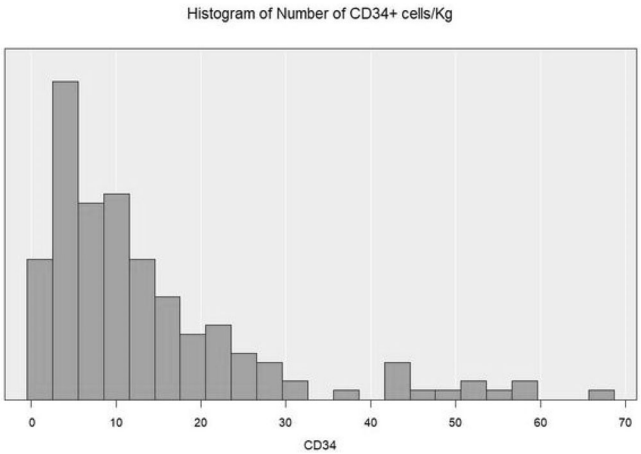
Luís Fábio Botelho[1], Kaio Jose Andrade[1], Rodolfo Calixto[2]

[1]Federal University of Paraiba, Joao Pessoa, Brazil, [2]Real Português Hospital, Recife, Brazil

Background: Autologous hematopoietic stem cell transplantation (auto-HSCT) is largely used in treating patients with hematological malignancies. As these cells circulate in small amounts in the periphery, using regimens that promote their mobilization is essential. Cytarabine has emerged as an alternative to Cyclophosphamide in this scenario with some studies suggesting it has been a safer drug.

Methods: In this study, we retrospectively analyzed the efficiency and safety of mobilization based on intermediate-dose cytarabine (1.6 g/m^2) + filgrastrin (10 mcg/kg/day) in patients treated by the Public Health System at the Hematology and Bone Marrow Transplantation Service of the Real Português de Beneficência Hospital, in Recife – Brazil between 2014 and 2016. Peripheral CD34+ cell counts were not performed, due to the unavailability of a flow cytometer in the service. Leukoapheresis was therefore performed when the total white blood cell count reached 5000 cells/mm^3. The procedure was carried out by processing 4-6 blood volumes, using a COBE® Spectra machine, with the aim of collecting 2.0x106 CD34+ cells/Kg. The dosage of collected CD34+ cells was performed in a central laboratory. Mobilization failure was considered when the collection was less than 0.7 x 106 cel CD34 + /Kg already in the first apheresis or when less than 2.0x106 cel CD34 + /Kg after two apheresis.

Results: A total of 157 patients were included. The sample included patients with the diagnosis of Multiple Myeloma (58.6%), Lymphomas (29.9%), and other malignancies (11.5%). The median age was 51 years (34-60) with 74 patients being male (47.1%). The target yield of 2.0 x 106 CD34+ cells/Kg was achieved by 148 patients (94.3%), in most cases (84.1%) in single apheresis, and the median number of CD34+ cells collected was 9.5 x 106 cells/ Kg. No patient mobilized experienced febrile neutropenia, however, 79 patients (50.3%) required platelet transfusion, and 1 patient (0.63%) required red cell transfusion. The median days of neutrophil recovery were 11 days. The median number of CD34+ cells/Kg was higher in patients the required only one apheresis procedure (10.8 x 106 cells/kg vs. 3.6 x 106 cells/kg, $p < 0.05$). Age, gender, or diagnosis was not associated with higher CD34+ cells number.



Conclusions: In view of these results, we suggest that the use of intermediate-dose cytarabine + filgrastim is safe and effective as a mobilization protocol, being extremely useful in centers where the costs of transplantation can be challenging or lack a local laboratory to measure the peripheral CD3$+ cell count.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

P699

CHEMOMOBILIZATION WITH ETOPOSIDE IN A CHILD WITH HIGH-RISK NEUROBLASTOMA WHO FAILED STEM CELL HARVEST WITH PLERIXAFOR

Young Bae Choi[1], Eun Sang Yi[2], Na Hee Lee[3]

[1]Ajou University Hospital, Ajou University School of Medicine, Suwon, Korea, Republic of, [2]Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea, Republic of, [3]Cha Bundang Medical Center, Cha University, Sungnam, Korea, Republic of

Background: High-dose chemotherapy with autologous hematopoietic stem cell transplantation improves treatment outcomes in patients with high-risk neuroblastoma. However, in heavily prior-treated patients, poor marrow function can be a problem for stem cell harvest. We describe a case of effective chemomobilization with etoposide in a child with high-risk neuroblastoma.

Methods: A 11-year-old girl with high-risk neuroblastoma, who treated prior 8 cycles of intensive chemotherapy and failed to mobilize stem cells with 2 cycles of plerixafor, underwent chemomobilzation with an etoposide (375 mg/m^2 on days +1 and +2) and granulocyte-colony stimulating factor (G-CSF; 10 μg/kg once daily from day +8 through the final day of collection).

Results: The patient underwent peripheral blood stem cells for 5 days (days +15 through +19) and collected 5×10^6 CD34$^+$ cells/kg and 19.4×10^8 total nucleated cells/kg in leukapheresis. Adverse effects of the regimen included grade 1 chemotherapy-

induced nausea and vomiting, supportive transfusion (1 time of red blood cells and 4 times of platelets), and bone pain managed with acetaminophen.

Conclusions: We have shown a case of chemomobilization with etoposide in a child with high-risk neuroblastoma. Etoposide and G-CSF appears to be a safe and effective mobilization regimen for heavily pretreated patients undergoing autologous stem cell transplantation.

Disclosure: There is no conflict of interest.

2 - Stem Cell Mobilization, Collection and Engineering

P700

HIGH EFFICIENCY CD34$^+$ APHERESIS COLLECTION IN A MULTIPLE SCLEROSIS PATIENT: A CASE REPORT

Yandy Marx Castillo-Aleman[1,2], Ruqqia Mir[1,2], Nameer Abdul Raheem Al-Saadawi[1,2], Yendry Ventura-Carmenate[1,2], Fatema M. Al-Kaabi[1,2], Inas El-Najjar[1,2], May Ann Martinez[1], Pierre Christophe Krystkowiak[1,2], Dina El-Mouzain[1,2], Hiba Abdelrahman Mohamad Abdelrahman[2], Ottorino Del Foco[1,2], Carlos Agustin Villegas-Valverde[1], Maysoon Mohamed Abdulrahman Al-Karam[2], Antonio Alfonso Bencomo-Hernandez[1]

[1]Abu Dhabi Stem Cells Center, Abu Dhabi, United Arab Emirates, [2]Yas Clinic Khalifa City Hospital, Abu Dhabi, United Arab Emirates

Background: Autologous non-myeloablative hematopoietic stem cell transplantation (HSCT) can reverse neurologic disability in patients with relapsing-remitting multiple sclerosis (RRMS). Indeed, autologous HSCT is considered the standard of care for highly active RRMS patients who failed disease-modifying therapies and a clinical option for progressive multiple sclerosis (MS) with active inflammatory components and aggressive MS. Unlike stem cell transplants for classical indications, there are limited publications regarding CD34$^+$ cell harvesting in MS patients undergoing autologous HSCT. We report the first case of an MS patient undergoing this kind of treatment in the United Arab Emirates with the apheresis performed at Abu Dhabi Stem Cells Center (ADSCC).

Methods: Peripheral blood stem cells were mobilized with intravenous cyclophosphamide at 2.0 g/m^2 once, followed five days later by G-CSF at 5 µg/Kg/day for five days. The apheresis procedure was performed on the Amicus Blue™ Separator System running software v6.0 (Fresenius Kabi, Germany) through central venous access. A 12:1 whole blood (WB) to ACD-A anticoagulant ratio was used, 1.25 mg/Kg/min citrate infusion rate, maximum WB draw rate of 50 mL/min, and 12 total cycles. The mononuclear cells (MNC) offset was set at 1.5 mL, red blood cells (RBC) offset to 6.8 mL, cycle volume 900 mL and plasma storage fluid of 50 mL. Apheresis was initiated when the CD34$^+$ count reached 20 cells/µL in peripheral blood, with a collection goal of 2.0 – 5.0 × 10^6 CD34$^+$ cells/Kg.

Results: A 24-year-old female patient with aggressive MS was found eligible for autologous HSCT and signed the required informed consent forms. A central venous catheter was placed into the right femoral vein the evening before apheresis (two-lumen inserted, AGB Blue FlexTip ARROWg+ard 12Fr × 20 cm).

Before starting apheresis, the draw line showed sluggish backflow (thrombolytic therapy was applied without changes noted), while the return line was entirely functional. Therefore, a peripheral line was inserted for returning blood and using the return line of the catheter for collection to avoid recirculation and diminished collection efficiency. Thus, CD34$^+$ cells were collected with high efficiency, as shown in **Table 1**, without remarkable adverse events.

Table 1. Peripheral blood/collection cell counts and procedural parameters

Parameters	PB (Pre-apheresis)	PB (Post-apheresis)	Collection
Hemoglobin (g/dL)	13.1	10.4	0.6
Red blood cells (10^{12}/L)	4.5	4.2	0.4
WBC (10^9/L)	13.1	19.9	171.5
Platelets (10^9/L)	139	126	613
Neutrophils (10^9/L)	9.8	16.2	46.6
Lymphocytes (10^9/L)	1.2	1.4	52.8
Monocytes (10^9/L)	2.0	2.3	71.7
CD34$^+$ cells (/µL)	113	NA	4,670
Procedural parameters			
Procedure duration (min)	274		
Whole blood processed (mL)	9,179		
AC to donor (mL)	704		
Product volume (mL)	182		
CD34$^+$ CE_2 (%)	88.8		
MNC CE_1 (%)	77.5		
CD34$^+$ FE (ratio)	41.3		
MNC FE (ratio)	38.9		

AC anticoagulant (ACD-A; acid citrate dextrose solution, solution A); *CE_1* collection efficiency 1; *CE_2* collection efficiency 2; *FE* fold enrichment; *MNC* mononuclear cells; *NA* not available; *PB* peripheral blood; *WBC* white blood cells

The apheresis machine calculated the patient's total blood volume as 3,371 mL, verified via Nadler's equation. Only one apheresis procedure was required, with a final dose of 17.7 × 10^6 CD34$^+$ cells/Kg, similar to that reported for RRMS patients using other apheresis systems, such as Fenwal CS3000 (Baxter, USA) or Spectra (Cobe, USA).

Conclusions: Avoiding the reversal of catheter lines and adding peripheral access for returning blood components resulted in an adequate collection, whereas the Amicus Blue™ Separator System was safe and highly effective in collecting mononuclear and CD34$^+$ cells in our MS patient.

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to declare.

9 - Stem Cell Source

P701

UNRELATED BONE MARROW VERSUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION IN HEMATOLOGICAL MALIGNANCIES

Hiromi Hayashi[1], Makoto Iwasaki[1], Hideki Nakasone[2], Reo Tanoshima[3], Noriko Doki[4], Takashi Tanaka[5], Yukiyasu Ozawa[6], Shinichi Kako [2], Shin-ichiro Fujiwara [7], Yuta Katayama[8], Masashi Sawa[9], Takashi Ashida[10], Ken-ichi Matsuoka[11], Naoyuki Uchida[12], Moeko Hino[13], Yoshinobu Kanda[2,7], Takahiro Fukuda[5], Yoshiko Atsuta[14], Junya Kanda[1]

[1]Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2]Jichi Medical University Saitama Medical Center, Saitama, Japan, [3]Yokohama City University Hospital, Yokohama, Japan, [4]Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan, [5]National Cancer Center Hospital, Tokyo, Japan, [6]Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Nagoya, Japan, [7]Jichi Medical University, Shimotsuke, Japan, [8]Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima, Japan, [9]Anjo Kosei Hospital, Anjo, Japan, [10]Kindai University Hospital, Osakasayama, Japan, [11]Okayama University Hospital, Okayama, Japan, [12]Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital, Tokyo, Japan, [13]School of Medicine, Chiba University, Chiba, Japan, [14]Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan

Background: While past reports indicate generally similar outcomes of bone marrow (BM) transplantation compared to peripheral blood stem cell (PBSC) transplantation, some controversial issues remain due to limited evidence for unrelated transplantation. Herein, we analyzed whether there are circumstances in which the collection method is more appropriate to improve transplantation outcomes.

Methods: Allogeneic transplants using BM or PBSC from HLA 8/8 or 7/8 allele-matched donors for hematopoietic malignancies between 2010 and 2020, enrolled in the national registration database in Japan, and aged 0 up to 70-year-old at the time of hematopoietic stem cell transplantation (HSCT), were included. Propensity scores were calculated according to the year of transplantation, age at transplant, diagnosis, disease risk, HCT-CI, performance status, weight, gender mismatch, ABO compatibility, HLA compatibility, conditioning intensity, and use of TBI. The eligible cohort was selected within a 0.1 caliper by 4:1 matching. The primary endpoint was overall survival (OS). Secondary endpoints were neutrophil and platelet engraftment, grade II-IV and III-IV acute GVHD (aGVHD), extensive chronic GVHD (extensive cGVHD), GVHD-free relapse-free survival (GRFS), cGVHD-free relapse-free survival (CRFS) and non-relapse mortality (NRM).

Results: A total of 4243 (BM n = 3388/PB n = 855) patients were selected for analysis cohort in balance (the AUC of the PS score was 0.78) (Table). ATG was more frequently used in the PB cohort (BM10%, n = 360/PB33.1%, n = 283). The median follow-up years of survivors were 2.5 in BM and 2.1 in PB. OS was statistically similar between the two sources (HR 0.27, 95% CI 0.82-1.06). Both neutrophil and platelet engraftments were significantly preferable in the PB cohort (PBSC vs. BM; neutrophil: SHR 1.91, 95% CI 1.74-2.10/platelet: SHR 1.66, 95% CI 1.51-1.82). Acute GVHD did not show a difference between transplant sources for both grades II-IV and III-IV (PBSC vs. BM; II-IV: SHR 1.02, 95% CI 0.90-1.16, III-IV: SHR 0.96, 95% CI 0.76-1.21). The risk of III-IV aGVHD was lower in transplant with ATG use regardless of the stem cell sources (III-IV: SHR 0.72, 95%CI 0.54-0.97). The risk of extensive cGVHD was higher in the PB group (PBSC vs. BM; SHR 1.43, 95%CI 1.20-1.70), and the use of ATG showed lower risk regardless of the sources (SHR 0.65, 95%CI 0.53-0.91). NRM was lower in the PB group (SHR 0.79, 95%CI 0.65-0.96). GRFS and CRFS showed similar outcomes, with no statistically significant difference by source, but the use of ATG was associated with lower risk of GRFS/CRFS (GRFS: HR 0.78, 95% CI 0.69-0.89/CRFS: HR 0.79, 95% CI 0.69-0.89).

Table of Characteristics

	Before Propensity score matching			After matching		
	BM	PB	p-value	BM	PB	p-value
	N = 9,371	N = 924		N = 3,388	N = 855	
Year of HSCT						
2010-2015	5,451 (58.2%)	133 (14.4%)	<0.001	540 (15.9%)	132 (15.4%)	0.72
2016-2020	3,920 (41.8%)	791 (85.6%)		2,848 (84.1%)	723 (84.6%)	
Age at HSCT	52.0 (38.0-60.0)	54.0 (43.0-62.0)	<0.001	54.0 (42.0-62.0)	53.0 (43.0-62.0)	0.62
Male gender	5,625 (60.1%)	604 (65.4%)	0.002	2,153 (63.6%)	546 (63.9%)	0.87
Disease risk						
Standard	5,862 (62.6%)	537 (58.1%)	0.029	2,113 (62.4%)	516 (60.4%)	0.28
High	3,494 (37.3%)	385 (41.7%)		1,275 (37.6%)	339 (39.6%)	
Performance Status						
PS 0-1	8,712 (93.1%)	869 (94.1%)	0.23	3,200 (94.5%)	807 (94.4%)	0.94
PS 2-4	646 (6.9%)	54 (5.9%)		188 (5.5%)	48 (5.6%)	
HLA compatibility						
8/8	5,605 (59.8%)	635 (68.7%)	<0.001	2,211 (65.3%)	575 (67.3%)	0.27
7/8	3,766 (40.2%)	289 (31.3%)		1,177 (34.7%)	280 (32.7%)	
MAC Conditioning	6,163 (65.8%)	611 (66.1%)	0.83	2,232 (65.9%)	564 (66.0%)	0.96

Conclusions: There was no significant difference between BM and PB in OS. Lower NRM, possibly due to better blood cell engraftments, was observed in the PB cohort; however, the risk of extensive cGVHD was higher. The use of ATG is one of the strategies to reduce GVHD risk in unrelated HSCTs.

Disclosure: Hideki Nakasone received honoraria from Otsuka Pharmaceutical, Bristol-Myers Squibb, Pfizer, Novartis, Takeda Pharmaceutical, Celgene, Janssen Pharmaceutical, Eisai, Chugai Pharmaceutical, Sanofi, Meiji Seika Pharma, and Nippon Shinyaku.

Shinichi Kako received honorarium from Sanofi K.K.

Shin-ichiro Fujiwara received honorarium from Sanofi K.K.

Yoshinobu Kanda received honorarium from Sanofi K.K.

Junya Kanda received honorarium from CSL Behring K.K.,DAIICHI SANKYO Co., Ltd.,MSD K.K., Sumitomo Dainippon Pharma Co., Ltd.,Astellas Pharma Inc., Takeda Pharmaceutical Company Limited, AbbVie Inc., CHUGAI PHARMACEUTICAL Co., Ltd., Amgen Pharma Inc., Novartis Pharma K.K., Otsuka Pharmaceutical Co., Ltd., Bristol-Myers Squibb Co, Ono Pharma Inc., Janssen Pharmaceutical K.K., Sanofi K.K., ASAHI KASEI PHARMA CORPORATION, asclepia, Kyowa Kirin Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Nippon Shinyaku Co., Ltd., and NIPPON KAYAKU CO., Ltd.

9 - Stem Cell Source

P702

OPTIMIZED DOUBLE-UNIT CORD BLOOD TRANSPLANTATION MITIGATES TRANSPLANT RELATED MORTALITY RESULTING IN HIGH PROGRESSION-FREE SURVIVAL IN ADULTS WITH HEMATOLOGIC MALIGNANCIES

Ioannis Politikos[1], Sean Devlin[1], Stephanie Chinapen[1], Sean Quach[1], Parastoo Dahi[1], Boglarka Gyurkocza[1], Ann Jakubowski[1], Esperanza Papadopoulos[1], Doris Ponce[1], Roni Tamari[1], Andromachi Scaradavou[1], Juliet Barker[1]

[1]Memorial Sloan Kettering Cancer Center, New York, United States

Background: While intermediate intensity (Cy50/ Flu150/ Thio10/ TBI400cGy) double-unit cord blood transplantation (dCBT) has been associated with high progression-free survival (PFS) in adults with hematologic malignancies (Barker JN et al, *Blood Advances 2020*), we hypothesized that optimized dCBT prioritizing unit quality (banking practices) & CD34+ cell dose over HLA-match in unit selection, along with letermovir prophylaxis in CMV seropositive patients, may further improve early CBT outcomes.

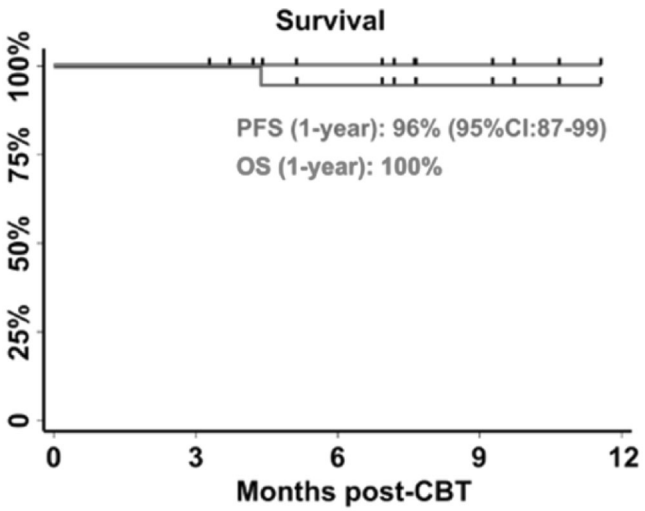
Methods: We analyzed consecutive adult (21-61 years) patients with high-risk hematologic malignancies who underwent first allografts with intermediate intensity dCBT at our center between 3/2018-8/2022. All CMV seropositive patients received letermovir prophylaxis from day +7. During the study period, 2 GVHD prophylaxis strategies were investigated.

Results: Of 72 patients (**Table**), 49 transplanted early in the study period (**Early Group**) received GVHD prophylaxis with cyclosporine-A (CSA), mycophenolate mofetil (MMF) & tocilizumab (8 mg/kg day on day -1), & 23 recent patients (**Recent Group**) received CSA/MMF alone. Most patients were transplanted for acute leukemia & 53% had non-European ancestry. Distribution of diagnoses, CMV serostatus, HCT-CI & graft characteristics were similar between the two groups. However, **Recent Group** patients were younger (median age 37 vs 47 years, $p = 0.04$).

Early Group patients who received tocilizumab had low rates of pre-engraftment syndrome (PES) & grade II-IV aGVHD, but delayed engraftment (median day 25, range 16-40) with one graft failure. One-year TRM was 16% (95%CI: 6-27) & the 1-year relapse was 6% (95%CI: 3-13). With a median follow-up of 41 months (range 17-56), the 1-yr OS was 84% (95%CI: 73-94) & PFS was 78% (95%CI: 66-89). All **Recent Group** patients engrafted with a faster median neutrophil recovery of 20 days (range 11-36, $p = 0.003$) & all engrafted platelets (median 36 days, range 24-92). **Recent Group** patients had a higher incidence of PES (83%, $p < 0.001$) & overall day 100 grade II-IV aGVHD [91% (95%CI: 80-99), $p = 0.03$]. However, the 100-day incidence of grade III-IV aGVHD was low [9% (95%CI: 1-20)] & similar to the **Early Group** patients. Despite the high rates of aGVHD, no **Recent Group** patients had aGVHD-related mortality and no patients developed CMV infection. With a median follow-up of 11 months (range 4-44), the TRM in **Recent Group** pts is 0% to date & the 1-year relapse incidence is 4% (95% CI: 1-13). Consequently, the 1-year OS & PFS are high at 100% & 96% (95%CI: 87-99), respectively (**Figure**).

TABLE

	Early Group (N = 49) *CSA/MMF/ Tocilizumab*	Recent Group (N = 23) *CSA/MMF*	P-value
Demographics			
Median age (range)	**47 years (27-60)**	**37 years (22-61)**	**0.04**
CMV seropositive, N (%)	**31 (63%)**	**14 (61%)**	**NS**
Non-European ancestry, N (%)	**27 (55%)**	**11 (48%)**	**NS**
HCT-CI			**0.42**
0-1	**24 (49%)**	**12 (52%)**	
2	**8 (16%)**	**6 (26%)**	
3 +	**17 (34%)**	**5 (22%)**	
Disease			
AML	**22 (45%)**	**9 (39%)**	
ALL	**12 (24%)**	**5 (22%)**	
MPAL	**3 (6%)**	**2 (9%)**	
MDS	**5 (10%)**	**5 (22%)**	
MPN/CML	**3 (6%)**	**1 (4%)**	
NHL	**4 (8%)**	**1 (4%)**	**0.84**
Median TNC/kg x10^7/ unit (range)	**2.9 (1.5-7.5)**	**2.7 (1.7-5.0)**	**0.46**
Median CD34 + /kg x10^5/unit (range)	**2.4 (1.0-7.7)**	**2.4 (0.9-4.7)**	**0.95**
8-allele HLA-match	**4/8 (3-6/8)**	**5/8 (3-6/8)**	**0.56**
Outcomes			
Neutrophil Engraftment	**94% (87-99)**	**100%**	**0.003**
Median time (range)	**25 days (16-40)**	**20 days (11-36)**	
Graft failure, N	**1**	**-**	
Platelet Engraftment	**94% (87-99)**	**100%**	**0.58**
Median time (range)	**35 days (17-57)**	**36 days (24-92)**	
Pre-Engraftment Syndrome, N (%)	**19 (39%)**	**19 (83%)**	**<0.001**
Median onset (range)	**13 days (7-16)**	**10 days (4-17)**	
Day 100 aGVHD, Grade II-IV	**69% (56-82)**	**91% (80-99)**	**0.03**
Day 100 aGVHD, Grade III-IV	**10% (2-19)**	**9% (1-20)**	**0.83**
Day 100 CMV Infection	**1 (2%)**	**0%**	**NS**
Day 100 TRM	**12% (3-21)**	**0%**	**0.05**
1-year TRM	**16% (6-27)**	**0%**	
1-year Relapse	**6% (3-13)**	**4% (1-13)**	**0.68**
1-year OS	**84% (73-94)**	**100%**	**0.04**
1-year PFS	**78% (66-89)**	**96% (87-99)**	**0.20**



Conclusions: dCBT with tocilizumab-based GVHD prophylaxis is associated with delayed engraftment offsetting the advantage of reduced PES/ aGVHD. Despite high grade II aGVHD rates, unit selection prioritizing quality & CD34+ cell dose, in combination with letermovir CMV prophylaxis, mitigates TRM after CSA/MMF-based intermediate intensity dCBT resulting in high 1-year survival

in young & middle-aged adults. Given the rapid availability of cryopreserved unmanipulated CB grafts & the compromised post-pandemic supply of adult donors, optimized dCBT is a highly attractive curative therapy for such pts with acute leukemia.

Disclosure: I.P. has received research funding from Merck and serves as a member on a Data and Safety Monitoring Board for ExcellThera.

B.G. has received research funding from Actinium Pharmaceuticals and serves on the Data and Safety Monitoring Board for Synthetic Biologics, Inc.

A.S. serves as a consultant at the Scientific Advisory Board of ExCellThera.

J.B. has received consultancy payments from Gamida Cell and the New York Blood Center and a research funding from Merck.

The remaining authors declare no competing financial interests.

9 - Stem Cell Source

P703

SINGLE VS DOUBLE CORD BLOOD TRANSPLANTATION WITH MYELOABLATIVE CONDITIONING: COMPARABLE OUTCOMES IN A SINGLE-INSTITUTION EXPERIENCE

Mizuki Watanabe[1,2,3], Ann Dahlberg[1,4], Laurel A Thur[1], Colleen Delaney[1,4], Filippo Milano[1]

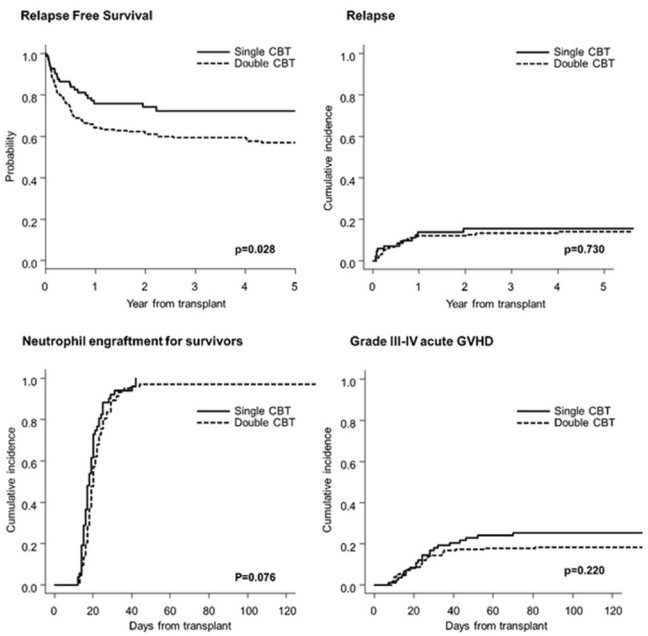
[1]Fred Hutchinson Cancer Center, Seattle, United States, [2]National Cancer Center Hospital of Japan, Tokyo, Japan, [3]Kyoto University Hospital, Kyoto, Japan, [4]University of Washington School of Medicine, Seattle, United States

Background: Double cord blood transplantation (dCBT) has been broadly utilized with the aim of improving engraftment and relapse free survival (RFS). However, there are limited data comparing single (sCBT) versus dCTB. In this study, we retrospectively compared the clinical outcomes of patients receiving either sCBT or dCBT at the Fred Hutchinson Cancer Center.

Methods: Between 2006 and 2022, 291 patients (median age, 36) received a first CBT (sCBT, n = 83; dCBT, n = 208) using myeloablative conditioning regimens. CB donor selection was based on institutional guidelines, with dCBT required when the total nucleated cell (TNC) dose for the best single unit was ≤2.5 x 10e7/kg for a 6/6 or ≤4.0 (± 0.5) x 10e7/kg for a 4-5/6 HLA-matched unit. All patients received cyclosporine and MMF for GVHD prophylaxis. Overall survival (OS) and relapse free survival (RFS) were assessed using the Cox proportional hazard multivariate model, using variables selected manually in the preceding univariate analysis.

Results: Table summarizes the characteristics of the patients by group. Median follow-up for survivors was 4 years (range, 0-15). Majority of patients had acute myeloid leukemia (n = 96) and acute lymphoblastic leukemia (n = 96). Refined diseased risk index (rDRI) were low- intermediate in 199 patients and high-very high in 24 patients. sCBT was more likely to be performed for younger patients ($p < 0.001$) and in more recent years ($p < 0.001$). Surprisingly, median TNC/kg was higher for sCBT ($p < 0.001$), but there was no difference in CD34/kg between the 2 groups ($p = 0.284$). Median time (days) to neutrophil engraftment was shorter in sCBT (18, range 12-42), compared to dCBT (20, range 12-89) ($p = 0.006$). Similarly, median time to platelet engraftment (> 20, 000/μL) was shorter in sCBT (31, range 16-95) than in dCBT (36, range 19-158) ($p = 0.02$). Engraftment rate was 97% for sCBT vs 93% for dCBT. Four-years OS were 73.6% (sCBT) vs 60.9% (dCBT), and 4-year RFS were 72.2% vs 59.4% (Figure). Four-years cumulative incidences (CI) of relapse and non-relapse mortality (NRM) 15.7% vs 13.4% and 12.0% vs 27.2%, for sCBT vs dCBT, respectively. In univariate analysis, sCBT showed superior outcomes compared to dCBT (OS: HR 0.57, $p = 0.022$; RFS: HR 0.59, $p = 0.028$; NRM: HR 0.39, $p = 0.005$). In multivariate analysis, sCBT and dCBT showed comparable results both for OS (vs single, HR 1.29, $p = 0.487$), RFS (HR 1.08 $p = 0.779$) and NRM (HR 1.08 $p = 0.779$. High-very high rDRI (vs. low-intermediate DRI) significantly affected OS (HR 2.43, $p = 0.020$), RFS (HR 1.93, $p = 0.026$) and relapse (HR 2.65, $p = 0.023$). dCBT was associated with lower risk of grade II-IV aGVHD (HR 0.67, $p = 0.046$), while it showed no impact either on the occurrence of grade III-IV aGVHD or cGVHD.

		Single CBT		Double CBT		P-value
		n = 83	%	n = 208	%	
Transplant year		2018 (2006 - 2022)		2013 (2006 - 2022)		<0.001
Age at CBT		9 (1 - 60)		38 (6 - 70)		<0.001
Patient sex	Female	39	47.0	101	48.6	0.809
	Male	44	53.0	107	51.4	
Disease type	AA/MDS/CML	10	12.0	40	19.2	0.063
	AML	34	41.0	62	29.8	
	ALL	27	32.5	69	33.2	
	Lymphoma	0	0.0	8	3.8	
	Others	12	14.5	29	13.9	
refined DRI	Low/ Intermediate	60	72.3	139	66.8	0.191
	High/Very high	3	3.6	21	10.1	
TNC / kg		0.52 (0.24-1.17)		0.43 (0.22-1.12)		<0.001
CD34+cell / kg		0.31 (0.05-1.17)		0.27 (0.05-2.20)		0.284
HLA-MM	0-1	52	62.7	52	25.0	<0.001
	2-	30	36.1	152	73.1	



Conclusions: No significant differences in clinical outcomes were observed between sCBT and dCBT. Importantly, nearly all patients engrafted and the incidence of relapse and NRM was low overall, resulting in excellent outcomes for both groups. Our data supports performing sCBT in patients with an adequate cell dose, which may have a significant impact in reducing the cost associated with CBT without compromising outcomes.

Disclosure: Nothing to declare.

9 - Stem Cell Source

P704

DOES THE LENGTH OF TIME IN CRYOPRESERVATION AFFECT THE QUALITY OF CORD BLOOD UNITS (CBUS) OR IMPACT ENGRAFTMENT?

Alex Ross[1], Alexandra Griffiths[1], Guy Parkes[2], Ulrike Paulus[1], Rachel Pawson[1]

[1]NHS Blood and Transplant, Bristol, United Kingdom, [2]NHS Blood and Transplant, London, United Kingdom

Background: The NHS Cord Blood Bank has an inventory of nearly 20,000 CBUs suitable for clinical use collected and stored since 1996. Duration of storage is used as one of the selection criteria by some transplant centres. We assessed our CBU inventory to determine whether length of time in cryopreserved storage was associated with a decrease in quality of the cord blood.

Methods: We analysed cord blood units over time in storage to determine whether there was any significant decrease in quality for parameters that allow cords to be released for transplant: total CD34+ count, viable CD34+ count, and total nucleated cell (TNC) count. Storage time was calculated from date of collection to date of issue, and split into six categories, from 0-2 years to >8 years. Cord quality data were extracted from our Laboratory Information Management System (LIMS), median values were calculated for the differences between pre-freeze and post-thaw measurements, and non-parametric tests were used to determine whether any changes in storage were statistically significant. The CBU dataset consisted of cords provided for transplant as these CBU had both pre and post thaw data available.

Eurocord outcome data (for single-cord transplants only, all levels of HLA match) was used to examine associations of CBU storage time with time to neutrophil engraftment and with one-year overall survival, using Kaplan-Meier plots and log-rank tests.

Results: There were 625 CBUs with complete data on total CD34+ count; these were collected 1996-2019, issued 2007-2022, and had a median storage time of 4.3 years (range: 0.5-17 years). The cohorts with available data on viable CD34+ count and TNC were smaller, at 463 and 334 respectively.

Storage time was strongly associated with change in total CD34+ count ($p = 0.0019$) and in TNC ($p < 0.0001$) but less clearly with change in viable CD34+ count ($p = 0.063$). Specifically comparing CBUs stored for >8 years against all others, all three quality parameters showed slightly larger declines in the older units, which were statistically significant (p-values < 0.0001, <0.0001, 0.0021) (Table 1.0).

Looking at patient outcomes, we found no evidence of a difference in either time to neutrophil engraftment ($N = 402$, $p = 0.53$) or one-year overall survival ($N = 353$, $p = 0.19$) based on cord age (Figure 1.0).

CBU storage time (years)	N	Change in CD34+ count ($\times 10^6$) in storage	
		Median	IQR
0 – 2	111	-0.6	-1.8, 0.2
2 – 3	84	-0.4	-1.8, 0.0
3 – 4	97	-0.5	-2.0, 0.3
4 – 6	142	-0.6	-1.8, 0.3
6 – 8	88	-0.5	-1.4, 0.3
> 8	103	-1.2	-2.3, -0.3

Table 1.0 Median change in total CD34+ count pre-freeze to post-thaw

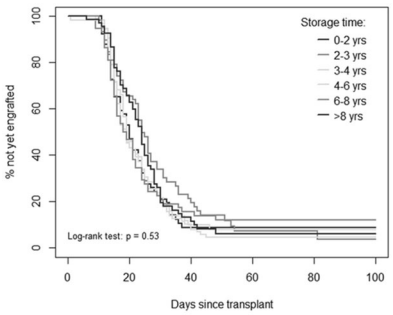


Figure 1.0 Kaplan-Meier plot; time to

Figure 1.0 Kaplan-Meier plot; time to neutrophil engraftment stratified by CBU storage time

Conclusions: Whilst slightly larger declines in quality parameters were found in cords stored for longer than 8 years, we saw no effect on length of time to neutrophil engraftment or one-year survival. Any CBU with sub-optimal TNC or CD34+ doses would have been rejected prior to issue. All CBU released for transplant met both FACT standard and internal QC parameters, regardless of duration in storage. Further work to consider possible effects of changes in testing methodology on the changes in cell counts will be undertaken. The inventory has been constantly temperature monitored over the period of time studied and no warming events have been recorded. This work supports our stability programme which monitors the quality of our CBU inventory annually.

Disclosure: Nothing to declare.

9 - Stem Cell Source

P705

SPLITTING CORDS AND SAVING LIVES: USING THE SAME CORD BLOOD UNIT TO CORRECT SIBLINGS WITH GENETIC DISEASE, THE MANCHESTER EXPERIENCE

Ramya Nataraj[1], Madeleine Powys[1], Denise Bonney[1], Srividhya Senthil[1], Omima Mustafa[1], Claire Donohue[2], Poulton Kay[2], Robert Wynn[1]

[1]Royal Manchester Children's Hospital, Manchester, United Kingdom, [2]Manchester Hospitals NHS Foundation Trust, Manchester, United Kingdom

Background: Umbilical Cord Blood (UCB) is a preferred stem cell source for children with Inherited Metabolic disorders (IMD). The

advantages to using UCB are improved survival and higher donor chimerism. As CB is available off the shelf with details of HLA typing ready to use in comparison to adult donors, the time between decision to transplant and the transplant itself is shorter. The disadvantages of cord blood are cost, lower stem cell dose and delayed engraftment compared to alternate donor transplantation.

We report three sets of HLA identical twins/siblings receiving cells from the same UCB unit, split at thaw into separate doses, after conditioning therapy.

Methods: Retrospective analysis of 3 sets of HLA-Identical twins/Siblings who underwent HCT at the same time for Hurler's Syndrome between 2013 and 2022 using Single CB unit split into two. All patients received pharmacokinetic targeted busulfan and fludarabine conditioning. Anti-Thymocyte Globulin (ATG) was used as serotherapy. All received Steroids and Ciclosporin as GVHD prophylaxis. All received CB infusion as per institutional protocol. The CB unit was thawed and split into two syringes and administered by two dedicated teams to each patient.

Results: Six patients with Hurler's Syndrome were transplanted using 3 cord blood units. We had two pair of identical twins with age at transplant being 4 and 18 months; and a pair of siblings aged 4 months and 24 months. The weight of patients in this cohort ranged from 5.9 kgs – 11.2 kgs. The mean Total Nucleated Cell (TNC) dose was 13.3 x 10^7/kg and CD 34 count was 6.8 x 10^5/kg. 4/6 had mismatched 6/8 CB units and 2 had 8/8 CB HCT. All engrafted with a mean Neutrophil engraftment at 16 days post HCT. We did not see any primary or secondary graft failure. 2/6 had Grade 1 acute skin GVHD which responded to steroids. One of the identical twins had severe Grade 4 Skin GVHD whilst another twin remained GVHD-free. All 6 children remain disease-free, GVHD-free and with full donor chimerism.

Conclusions: Early age at transplant and using the best matched cord blood unit in children with IMD will have the superior outcome. We demonstrate the feasibility of bedside splitting of a single cord to give siblings with the same genetic disease an adequate cell dose from the best matched CB Unit, as well as reducing costs. The GHVD in one identical twin compared to none in the other indicates the complexity of factors beyond tissue type, that might allow development of GVHD.

Disclosure: I have nothing to disclose.

9 - Stem Cell Source

P706

UMBILICAL CORD BLOOD TRANSPLANTATION WITH REDUCED INTENSITY CONDITIONING IN ACUTE MYELOID LEUKEMIA AND HIGH-RISK MYELODYSPLASTIC SYNDROME: A RETROSPECTIVE, SINGLE CENTER EXPERIENCE

Nancy Torres[1], Basil Kaabneh[1], Omar Aljitawi[1]

[1]Wilmot Cancer Institute/University of Rochester, Rochester, United States

Background: Allogeneic hematopoietic stem cell transplantation is a potential curative strategy for patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). Umbilical cord blood is an alternative graft source for patients who are eligible to undergo transplantation but lack HLA-matched donors. Benefits of umbilical cord transplantation (UCBT) include lower incidence of chronic Graft-versus-host disease (GvHD) and lower relapse rates in some studies. Risks include graft failure up to 10% and delayed engraftment. We aimed to retrospectively analyze patients with AML and MDS who underwent UCBT with RIC in our institution.

Methods: In this retrospective study, we collected data from charts of all adult patients with AML and MDS who underwent UCBT and reduced intensity conditioning (RIC) at the Wilmot Cancer Institute, University of Rochester Medical Center between June 2017 and December 2021. We performed descriptive analysis and determined clinically relevant outcomes such as overall survival (OS), leukemia-free survival (LFS), relapse rate, transplant-related mortality (TRM), graft failure (GF), time to engraftment and infectious complications. We also determined the exploratory endpoint of GvHD-free, relapse-free survival (GRFS).

Results: We identified a total of 20 patients, 17 with AML and 3 with MDS who underwent UCBT and RIC in the proposed timeframe. The median age was 58 years (range 29-72 years) and 30% were female. All patients received RIC with fludarabine, cyclophosphamide and total-body irradiation (200-400cGy), 60% of patients also received Thiotepa. Single cord units were used in 35% of patients. To date, half of our cohort patients remains alive. Causes of death included relapsed AML in 5 patients, GvHD and infection in 3 and 2 patients respectively. Acute GvHD was reported in 65% of patients and chronic GvHD in 15%. Almost all patients developed some type of infection during the first 6 months post-transplant. Median time to neutrophil and platelet recovery were 21 days (range 9-34 days) and 33 days (range 27-44 days). One patient had primary graft failure and 2 had secondary GF. The 100-day TRM was 20% and relapse rate to date is 25%. The 100-day OS was 75%; 6-month OS was 70% and 1-year OS was 60%. Median OS was 3.5 years (1287 days). Leukemia-free survival at day 100 was 88.2%; 6-month LFS was 82.4% and 1-year LFS was 76.5%. Median LFS was 2 years. GRFS was 41.2%, median GRFS was 0.5 years (we excluded patients with MDS for LFS and GRFS).

Conclusions: In patients who received UCBT and RIC, outcomes such as 1-year OS and LFS are encouraging. Rates of aGvHD, cGvHD and TRM are similar to published data. Importantly, patients in our cohort had intermediate to high-risk disease and were older. We concluded that UCBT with RIC can be used safely and efficaciously in older patients. Strategies to improve early morbidity and mortality that target homing/engraftment and immune reconstitution post UCBT (such as hyperbaric oxygen therapy) are currently being studied at our institution.

Disclosure: Nothing to declare.

9 - Stem Cell Source

P707

DKMS BMST FOUNDATION INDIA: GIVING INDIAN PATIENTS A SECOND CHANCE AT LIFE

Nitin Agarwal[1], Patrick Paul[1]

[1]DKMS BMST foundation India, Bangalore, India

Background: DKMS BMST foundation India is a stem cell registry, that started working officially in May 2019. As ethnicity plays a major role in identifying a suitable matched unrelated donor (MUD) for HSCT, it is difficult to find an HLA-matched donor in India due to its large patient population and vast ethnic diversity. Our mission is to register as many Indian donors as possible and to provide a second chance at life for as many patients in need of HSCT as possible.

We present here the data about our registered donor and their availability at both confirmatory finding (CT) and workup (WU) levels when requested by transplant centers.

Methods: The data was collected retrospectively from May 2019 to Nov 2022.

Results: As of Nov 2022, DKMS-BMST has registered around 72000 potential stem cell donors. Since inception, DKMS BMST India has received 966 CT requests and 120 work up requests. A total of 72 unrelated donations have been performed till now. Around 35 percent of donors were available at CT while the availability at work up level was higher with 78 percent donors going ahead with their decision to donate. If we don't consider urgent CT+ work up requests (that practically is first time contact to donor and has high chances of unavailable donors), the work up availability rises to 88 percent. (Fig 1) Medical deferral at physical examination led to almost one fifth of these donors being unavailable.

While the availability of Indian donors at CT is low, DKMS-BMST is working hard to increase this number, high WU availability shows that when the donors agreed to donate at CT, they are really committed to the cause and do not back out later. Some of the donors have to travel long distances and stay far away from their hometown for some time, but they are generally happy to do so to give someone a second chance at life. Variables that affect the availability of donors are age group (26 to 40 years donors are more available than younger and older donors) and type of registrations (online registered donors are available more than offline registered donors). Most common reason (and very specific to India) for donors to be unavailable at CT level is pressure from parents and spouse.

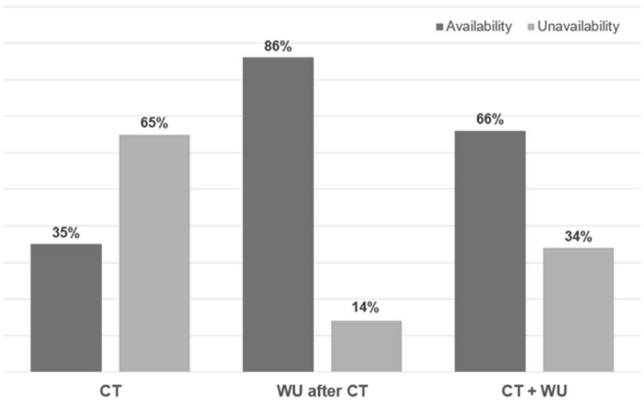


Fig 1.: Availability of Donors at CT and WU level

Conclusions:

1. Donors who agree for the donation at CT level are highly committed and usually donate stem cells.
2. Family plays a major role in donor decisions in India and is one of the reasons for low donor availability.
3. CT/HAC should be requested first and then Work up rather than CT + WU requests, as it filters the uninterested donor early. CT/HAC is not charged by DKMS BMST India.
4. Awareness of the safety procedure of stem cell donation must be increased.

Disclosure: Nothing to declare.

9 - Stem Cell Source

P708

LOW DOSE TOTAL BODY IRRADIATION-BASED ANTI-THYMOCYTE GLOBULIN-FREE CONDITIONING IS HIGHLY SAFE AND EFFECTIVE IN CORD BLOOD TRANSPLANTATION FOR PATIENTS WITH SEVERE APLASTIC ANEMIA

Hee Won Cho[1], Young Rok Do[2], Jungmin Lee[2], Hee Young Ju[1], Ji Won Lee[1], Ki Woong Sung[1], Keon Hee Yoo[1]

[1]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea, Republic of, [2]Keimyung University College of Medicine, Dongsan Medical Center, Daegu, Korea, Republic of

Background: Cord blood transplantation (CBT) has not been recognized as a good alternative for patients with severe aplastic anemia (SAA) who lack a matched related donor because of relatively poor graft performance and high transplant-related mortality. Although adequate cell number remains the most important predictor of successful outcome, recent data suggest that conditioning itself could also affect the outcome of CBT recipients. In this study, we aimed to see the long-term outcome of SAA patients who received CBT and the impact of conditioning regimen on their outcome as well.

Methods: Medical records of 12 patients who received CBT at Samsung Medical Center and Dongsan Medical Center between 2003 and 2018 were reviewed. Double unit transplantation was allowed to procure an acceptable cell dose, but only a CB unit at least 4/6 loci matched to the recipient's HLA was used. Engraftment kinetics, graft-versus-host disease (GVHD), cytomegalovirus (CMV) infection, and survival rates were analyzed. Mann-Whitney U-test was used to compare non-parametric values, Fisher's exact test to compare categorical variables, and the Kaplan-Meier method for the survival estimates.

Results: Patients' median age was 6.6 y (range, 1.9-40). Seven patients received a conditioning regimen including 7.5 mg/kg of anti-thymocyte globulin (ATG) with (n = 2) or without (n = 5) total body irradiation (TBI) (Group A), while the other 5 patients were conditioned with 400 or 500 cGy TBI in combination with chemotherapy without ATG (Group B). The median infused total nucleated cells (TNC) and CD34+ cells were 5.47 x 10^7/kg (range, 2.80-10.97) and 1.79 x 10^5/kg (range, 0.60-5.53), respectively. There were no differences in cell doses between Group A and B. All 12 patients achieved neutrophil engraftment at a median of 19 days (range, 15-25), and 11 patients achieved platelet recovery above 20 x 10^9/L at a median of 41 days (range, 25-121) with one patient in Group A being prematurely dead before platelet recovery. In Group A, 3 out of 7 patients developed grade 3-4 severe acute GVHD and 1 extensive chronic GVHD. However, none developed severe acute or extensive chronic GVHD in Group B. CMV viremia was developed all but one patient with 5 (42%) being confirmed as CMV disease (4 colitis and 1 retinitis). Among children and adolescents less than 18 years old (n = 10), CMV disease occurred exclusively in Group A (n = 3). The projected long-term overall survival rate was 83.3% (median follow-up 6.6 y; range, 2.8-19.4), and all patients in Group B survived with full donor chimerism.

Conclusions: The long-term outcome of CBT recipients was excellent in this study. The small number of our cohort may have limited drawing the conclusion on the superiority of ATG-free regimen. However, low dose TBI-based ATG-free conditioning was safe and effective showing an excellent engraftment and survival rate without severe GVHD. We conclude that CBT remains a reasonable alternative for SAA patients if acceptable cell dose and appropriate conditioning are provided.

Disclosure: Nothing to declare.