EBMT

ABSTRACTS COLLECTION

The 48th Annual Meeting of the European Society for Blood and Marrow Transplantation: Physicians - Oral Sessions (O009-O155)

Bone Marrow Transplantation (2022) 57:16–99; https://doi.org/10.1038/s41409-022-01815-2

19–23 March 2022 ● Virtual 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.

Acute leukaemia

O009

Prediction of non-relapse mortality in patients with AML and all receiving alloSCT in first CR with post-transplantation cyclophosphamide-based GVHD prophylaxis

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Background: GVHD prophylaxis with post-transplantation cyclophosphamide (PTCY) has been established to reduce severe GVHD, and thereby potentially reducing NRM after alloSCT. Current NRM risk scores have not been developed and validated in PTCY-based GVHD-prophylaxis. Therefore, we set out to (1) evaluate the predictive capacity of existing NRM risk scores for alloSCT with PTCY-based GVHD-prophylaxis; and (2) develop and validate a novel PTCY-specific NRM risk model.

Methods: We identified 1861 adults with AML or ALL in first CR in the EBMT registry who received alloSCT with PTCY-based GVHD-prophylaxis. NRM was estimated using competing risk analysis, with relapse considered as a competing event. The predictive capacity of the HCT-CI, EBMT-score, and integrated EBMT score for 2-year NRM was estimated using the areas under the ROC curves (AUC). The PTCY-risk score was developed using multivariable Fine and Gray regression, selecting covariates with a subdistribution hazard ratio (SHR) of ≥1.2 in the training-set (70% of full data) and the subscore for each covariate rounded to the nearest integer. The performance of the PTCY-risk score was assessed in both the training and test (30% of full data) sets.

Results: The majority (76.4%) of patients received alloSCT for AML, with a median age at transplant of 51 years (range: 18–79). The most frequent comorbidities were pulmonary disease (moderate: 12.2%; severe: 7.0%), infection (7.0%), and prior solid tumor (6.3%). Matched related, matched unrelated, and mismatched unrelated/haploidentical donors were used in 13.7%, 29.8%, and 56.6% of transplants, respectively.

The overall 2-year NRM in the full cohort was estimated at 18.4 ± 1.0%. Using the risk groups of the existing HCT-CI, EBMT-score, and integrated EBMT risk score, we observed moderate to poor discrimination of 2-year NRM (AUC of 56.1%, 51.7%, and 59.2%).

Next, we developed and validated a novel risk model, which included 11 covariates which were associated with NRM. Variables were assigned points based on their rounded SHR, allowing for stratification into low-, intermediate-, and high-risk groups. These risk groups were associated with a 2-year NRM of 11 ± 2%, 19 ± 2%, and 36 ± 3% (training-set), and 11 ± 2%, 17 ± 3%, and 31 ± 5% (test-set). The AUCs were 64% and 63% in the training and test-set, respectively.

Conclusions: PTCY-based GVHD prophylaxis is associated with a NRM of 18%, but current NRM risk scores were associated with limited discriminative ability. We developed a novel risk score for NRM prediction in patients with AML or ALL in CR1 receiving PTCY that better predicted 2-year NRM compared with existing models, and which might be better applicable to the specific toxicities of high-dose cyclophosphamide.

Disclosure: Nothing to declare

O011

Impact of IDH1 and IDH2 mutational subgroups in acute myeloid leukemia patients after allogeneic hematopoietic cell transplantation

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Background: The role of allogeneic hematopoietic cell transplantation (alloHCT) in patients with acute myeloid leukemia (AML) with mutated *IDH1/2* has not been defined. Therefore, we analyzed a large data set of 3234 AML patients in first complete remission (CR1) and 1687 patients with relapsed or refractory disease (r/r AML) undergoing alloHCT or conventional chemo-consolidation and investigated outcome in respect to *IDH1/2* mutational subgroups.

Methods: Genomic DNA of patients enrolled within the SAL AML registry (NCT03188874), AML96 (NCT00180115), AML2003 (NCT00180102), AMLCG1999 (NCT00266136), AML60+ (NCT00180167), AMLCG2008 (NCT01382147), and SORAML (NCT00893373) was extracted from bone marrow aspirates or peripheral blood samples at diagnosis. All patients received intensive induction chemotherapy. Samples were screened for *IDH* mutations by denaturing high performance liquid chromatography. Positive screens were further analyzed by Sanger sequencing, ultradeep next generation sequencing (NGS) or myeloid panel NGS. Statistical as-treated analyses were performed using R (Version 4.0.3) and standard statistical methods (Kruskal-Wallis test, χ^2 test, log rank test, Cox regression). AlloHCT was analyzed as a time-dependent covariate. CR and survival rates (overall survival, OS; relapse-free survival, RFS) were evaluated.

Results: From 3234 patients achieving CR1, 7.8% harbored *IDH1 mutations* (variant proportion: 36% R132C and 47% R132H) and 10.9% were positive for *IDH2* (variant proportion: 77% R140Q and 19% R172K). In both cohorts (CR1 and salvage) *IDH* mutated patients demonstrated significantly higher age ($p < 0.001$ and $p = 0.004$), higher count of peripheral and bone marrow blasts (both $p < 0.001$), a lower rate of complex karyotype ($p < 0.001$), were less likely categorized as adverse risk according to ELN2017 ($p = 0.001$ and $p < 0.001$) and showed a higher rate of concomitant *NPM1* mutations ($p < 0.001$). A total of 852 patients underwent alloHCT in CR1. Variants *IDH1* R132C and *IDH2* R172K showed a significant benefit from alloHCT in CR1 for OS ($p = 0.017$ and $p = 0.049$) and RFS (HR = 0.42, $p = 0.048$ and $p = 0.009$) compared with patients receiving chemotherapy only. AlloHCT in *IDH2* R140Q mutated AML resulted in longer RFS (HR = 0.4, $p = 0.002$).

IDH mutational landscape was similar in the salvage cohort comprising 1687 r/r AML patients: 8% were characterized by *IDH1* (50% R132C and 36% R132H), 10.4% harbored *IDH2* mutations (70% R140Q and 28% R172K). 643 patients underwent alloHCT as part of salvage therapy. All patients (*IDH1* R132C, R132H and *IDH2* R140Q, R172K) benefited from salvage alloHCT, while this effect was pronounced in *IDH1* R132H with a 5-year OS of 55% with alloHCT as compared to 0% with salvage chemotherapy only; HR = 0.09, $p = 0.003$.

Conclusions: Here we report significant beneficial impact of alloHCT on survival of AML with different *IDH* mutational subclasses, both for patients in first complete remission and r/r AML in need for salvage treatment, respectively. Poor prognosis was effectively mitigated by alloHCT regarding the respective disease stage. Therefore, some *IDH1/2* mutational subclasses could be potentially implemented in standard AML risk stratification and therapeutic decision making.

Disclosure: Nothing to declare.

O012

Evaluation in trends in outcome over 2 decades of patients with secondary AML undergoing allo-HCT from sibling and unrelated donors: an ALWP EBMT analysis

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Background: Outcome of hematopoietic stem cell transplantation (HSCT) from matched sibling (MSD) and unrelated donors (UD) in patients (pts) with de novo acute myelogeous leukemia (AML) has improved over time. However, data assessing trends in outcome of transplantation in pts with secondary AML (sAML) are rather limited.

Methods: We evaluated results of HSCT from MSD or 9–10/10 UD in adult pts (>18 years) with sAML in first CR comparing outcomes of two cohorts according to the year of transplant (2000–2010 and 2011–2020). Multivariate analysis (MVA) adjusting for differences between the groups and including factors known to affect outcome was performed using Cox's proportional-hazards regression model for outcomes.

Results: A total of 4224 pts were included, 1337 were transplanted in 2000–2010 and 2887 in 2011–2020. In all, 326 (33%) and 620 (28%) of the pts had therapy related AML (tAML). Median F/U was 9.7 (95% CI: 9.2–10) and 3.6 (95% CI: 3.3–3.9) years, respectively ($p = 0.0001$). Median age was 54 (18–74) and 59 (18–78) years ($p > 0.0001$), and 51% and 53% were male. Cytogenetic risk categories in pts with available information were intermediate-risk (25.7% and 38.9%) and adverse-risk (10.9% vs 18%), respectively. Donors were siblings in 65% vs 37%,10/10 UD in 27% vs 50%, and 9/10 UD in 8% vs 13% of the transplants in both periods ($p < 0.0001$). Graft source was peripheral blood in 86% and 93% of the pts, respectively. A total of 65% and 67% of pts and 51% and 53% of donors were CMV seropositive, respectively. A total of 74% and 72% of pts were with KPS >90. Conditioning was myeloablative in 46% and 38%; TBI was used in 30% and 15% of the HSCTs, respectively. The most frequent anti-graft-versus-host disease (GVHD) prophylaxis was cyclosporine A (CSA) methotrexate in 45% and 38%, or CSA with and mycophenolate mofetil (MMF) in 24% and 29%, respectively. Anti-thymocyte globulin (ATG) was administered in 38% and 57% of the transplants. Day 60 incidence of neutrophil and platelet engraftment was 97.8% and 98% and 94.7% and 94.5%, respectively. Day 100 incidence of acute GVHD grades II-IV and III-IV were 17% vs 22% ($p < 0.001$) and 6% vs 7% ($p = 0.18$), while 2-year total and extensive chronic GVHD were 41% vs 36% ($p < 0.003$) and 19% vs 16% ($p < 0.005$), respectively. Two-year non -relapse mortality (NRM) was lower in pts transplanted in the 2011–2020 vs those transplanted in 2000–2010, 18% vs 21% HR 0.8 (0.67–0.97; $p = 0.02$). Two-year relapse incidence (RI) was similar between the two groups 32% vs 31%; HR 1.05 (0.9–1.22, $p = 0.55$). Likewise, leukemia-free survival (LFS), overall survival (OS) and GVHD-free, relapse-free survival (GRFS) were comparable as well; 50%, 57% and 39% for the 2011–2020 period vs 49%, HR 0.95 (0.84–1.06; $p = 0.36$), 54%, HR 0.93 (0.82–1.05; $p = 0.22$) and 37%, HR 0.97 (0.87–1.07; $p = 0.53$) for the 2000–2010 period, respectively.

Conclusions: Incidence of aGVHD and NRM in HSCT for sAML has been significantly reduced in the last two decades, rescuing half of the pts with this defined subgroup of high risk AML. Hopefully, with the recently approved novel agents including CPX-351 results may further improved.

Disclosure: Nothing to declare

O013

Allogeneic transplantation for AML aged ≥70 years. A study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

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Background: Accessibility to allogeneic hematopoietic cell transplantation (HCT) programs for older patients is growing constantly, due to the availability of alternative donors.

Methods: We report on the clinical outcomes of a group of adults aged ≥70 years, with acute myeloid leukemia (AML) in first complete remission (CR1), who received a first allogeneic HCT, from HLA-matched sibling donors (MSD), 10/10 HLA-matched unrelated donors (MUD), 9/10 HLA-mismatched unrelated donors (mMUD) or haploidentical donors (haplo). All patients underwent transplantation between 2000 and 2019 and their data were reported to the ALWP of the EBMT.

Results: A total of 701 patients with a median age of 71 (range 70–80) years were included in the analysis. Median follow-up was 2.9 years. Donors were MSD ($n = 114$), 10/10 MUD ($n = 407$), 9/10 mMUD ($n = 85$) and haplo ($n = 95$). Sixty-six percent of patients were male. Cytogenetics was classified as: intermediate-risk in 51%, adverse-risk in 14%, favourable risk in 8% and not available in 34% of patients. Karnofsky performance status (KPS) was <90% in 193 patients. A total of 102 patients received a myeloablative regimen (MAC). Patients transplanted from MUD more frequently received female donors ($p < 0.01$). Recipients of MSD more frequently received marrow grafts ($p < 0.01$) and total body irradiation (TBI)-based conditioning regimens. The overall 2-year rates of overall survival (OS) were 48.1% (95% CI 44.1–52.1), progression-free survival (PFS) 45.3% (95% CI 41.3–49.2), relapse incidence (RI) 25.2% (95% CI 21.9–28.7), non-relapse mortality (NRM) 29.5% (95% CI 26–33.1) and graft-versus-host disease (GVHD)-free, relapse-free survival (GRFS), 33.4% (95% CI 29.5–37.3). Global incidence of grade III-IV acute GVHD at day 100 was 7.6% (95% CI 5.8–9.8), while 2-year extensive chronic GVHD incidence was 18.2% (95% CI 15.1–21.5). OS was 33.7% (95% CI 23.3–44.4) for mMUD, 39% (95% CI 29.1–48.8) for MSD, 52.5% (95% CI 47.1–57.5) for MUD and 54.1% (95% CI 41.6–65) for haplo (Fig. 1). In a multivariate model, inferior OS was observed in patients with KPS <90% (HR 0.75, 95% CI 0.58–0.97), adverse-risk cytogenetics (HR 1.47, 95% CI 1.05–2.04) and female donor to male recipient (HR 1.64, 95% CI 1.21–2.22). PFS was 33.2% (95% CI 22.9–43.8) for mMUD, 36.7% (95% CI 27.2–46.2) for MSD, 48.51% (95% CI 42.8–53.2) for MUD and 55.8% (95% CI 43.5–66.4) for haplo (Fig. 2). Patients transplanted from haplo and MUD presented the lowest rates of RI (HR 0.46, 95% CI 0.25–0.8, $p = 0.02$ and HR 0.44, 95% CI

0.28–0.69, $p = 0.001$, respectively); this translated into prolonged PFS for haplo (HR 0.62, 95% CI 0.39–0.99, $p = 0.04$). Patients transplanted from mMUD exhibited the highest NRM rates (HR 2.33, 95% CI 1.26–4.31, $p = 0.007$). OS (Fig. 1) and PFS (Fig. 2) for patients transplanted from HLA-matched siblings (yellow), 10/10 HLA-matched UD (light blue), 9/10 UD (green) and haploidentical donors (black).

Fig.1

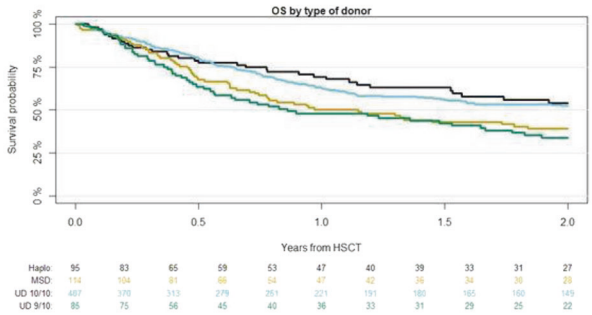
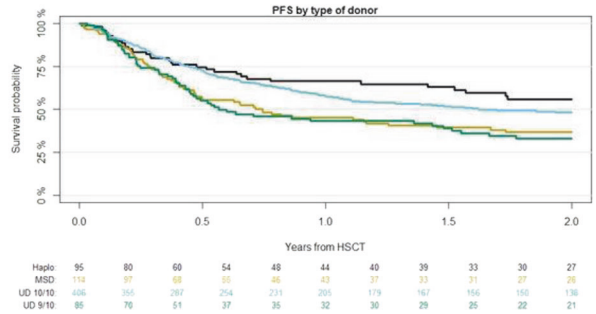


Fig.2



Conclusions: HCT in >70 years in selected CR1 AML patients is feasible, with acceptable NRM and survial rates. Further studies are warranted to study the impact of HCT donor.

Disclosure: There are no conflicts of interest to declare.

O014

CD34+ dose effects on clinical outcomes after fludarabine-busulfan conditioning regimen for acute myeloid leukemia using peripheral blood stem cells—study from the ALWP of EBMT

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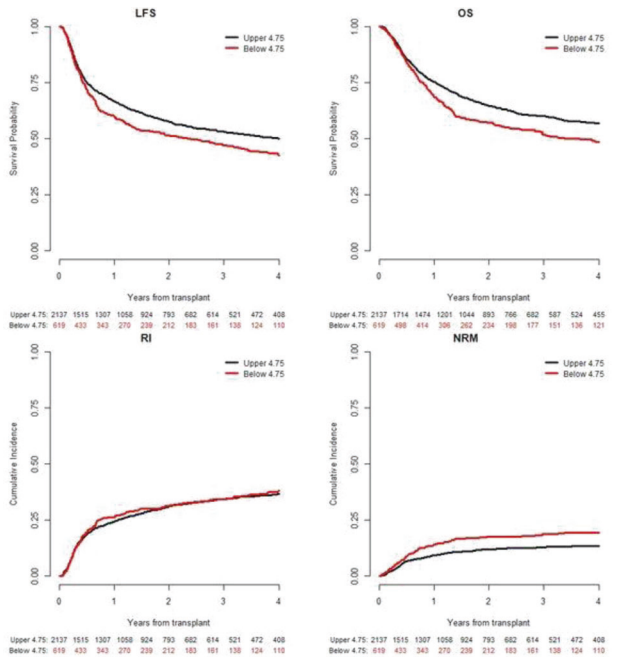
Background: Previous studies have reported inconsistent results regarding the possible impact of CD34+ cell dose on clinical outcomes after allogeneic hematopoietic stem cell transplantation (allo-HCT). These disparities may be partly explained by disease heterogeneity, disease status at transplant, donor type, and conditioning regimens.

Methods: We conducted a retrospective analysis on 2756 patients with acute myeloid leukemia (AML) in first and second complete remission (CR), who received their first allo-HCT with peripheral blood stem cells (PBSC) after a fludarabine and busulfan conditioning regimen. They received a T-cell replete allo-HCT from a matched sibling donor (MSD), a 10/10 matched unrelated donor (UD), or a 9/10 UD, between 2010 and 2020. The graft-versus-host disease (GVHD) prophylaxis was cyclosporine A (CSA) alone, CSA+Mycophenolate mofetil (MMF) or CSA +Methotrexate (MTX).

Results: Median age of the population was 58 years (range 18–80 years). Eighty-two percent of patients were in CR1. A total of 1069 (39%) received an MSD, 1426 (52%) a 10/10 UD, and 261 (9%) a 9/10 UD. The median CD34+/kg dose infused was 6.1×10^6 cells/kg. GVHD prophylaxis was antithymocyte globulin (ATG) in 89% of patients. The optimal CD34+ cells/kg threshold (estimated by the Hothon-Lausen method) on the non-relapse mortality (NRM), was 4.75×10^6. A total of 2137 (77.5%) received $>4.75 \times 10^6$ CD34+/kg, and 619 (22.5%) received less than or equal to this threshold. In multivariate analysis, recipients of $<4.75 \times 10^6$/kg CD34+ cells experienced higher NRM (hazard ratio [HR] 1.57; 95% CI 1.24–2; $p < 0.001$), a shorter leukemia-free survival (LFS) (HR 1.24; 95% CI 1.09–1.43; $p = 0.002$), overall survival (OS) (HR 1.29; 95% CI 1.11–1.49; $p < 0.001$) and GVHD-free, relapse-free survival (GRFS) (HR 1.17; 95% CI 1.03–1.32; $p = 0.02$), compared to the group receiving the higher cell doses. Moreover, kinetics of engraftment was positively affected by the higher CD34+ cell dose ($p = 0.002$). No significant associations were noticed between CD34+ cell dose and either relapse or incidence of acute or chronic GVHD. Considering donor type, 10/10 UD had a significantly higher NRM (HR 1.85; 95% CI 1.41–2.44; $p < 0.001$) and a lower RI (HR 0.77; 95% CI 0.67–0.91; $p = 0.002$) compared to MSD. OS, LFS and GRFS were similar between these two groups. Patients who received a 9/10 UD experienced higher NRM and lower OS and GRFS in comparison to patients with a MSD.



Conclusions: These results strongly suggest that, in AML patients in CR at time of transplantation using PBSC after fludarabine-busulfan based conditioning, infusion of more than 4.75×10^6 CD34+ cells/kg in T-cell replete allo-HCT from MSD, or 10/10 or 9/10 UD is beneficial for NRM, LFS and OS.

Disclosure: Nothing to declare

O015

Segregation of high-resolution B haplotypes points towards protective donor KIR genotypes after unrelated hematopoietic stem cell transplantation for patients with AML or MDS

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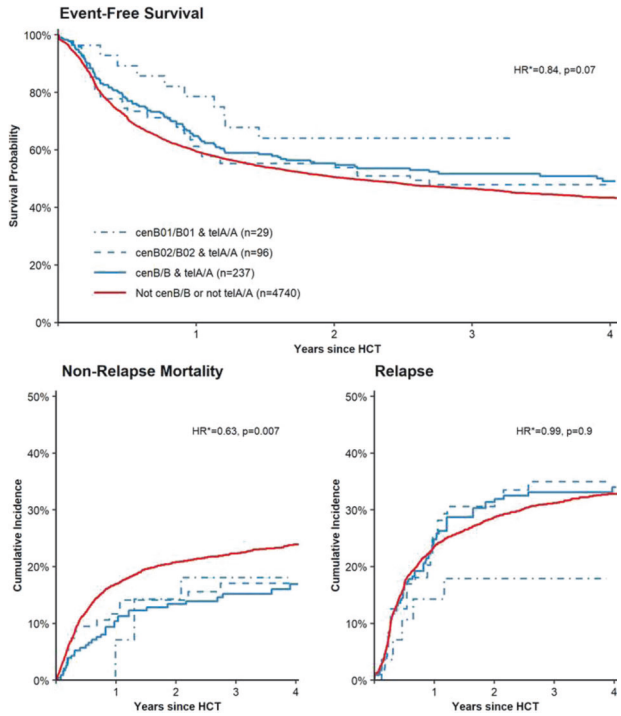
Background: Optimizing natural killer (NK) cell alloreactivity could further improve outcome after allogeneic hematopoietic cell transplantation (alloHCT). Different models have been proposed aiming at maximizing NK cell activation through activating KIR-ligand interactions or minimizing repressive signals through inhibitory KIR-ligand interactions. Alternative models aimed at predicting outcome after alloHCT according to KIR-haplotype motifs. Based on high-resolution KIR genotyping, B haplotypes can be segregated into different subsets which are more homogeneous than those identified by commonly used low resolution KIR genotyping, and allow identification of homo- or heterozygous pairs of KIR haplotypes (i.e., diplotypes). With this study, we aimed to validate proposed models and explore refined classification approaches.

Methods: Donor samples were retrieved from the Collaborative Biobank (Dresden, Germany). Medical characteristics and patient outcome data were extracted from the EBMT and CIBMTR. High resolution amplicon-based next generation sequencing of all KIR genes was performed on all donor samples. KIR haplotypes were constructed based on absence/presence of KIR genes. The impact of classifiers on time-to-event outcomes was tested in multivariable Cox regression models stratified for the registry cohort and adjusted for established risk factors. Endpoints were event-free survival (EFS), relapse or progression and non-relapse mortality (NRM).

Results: Data from 5019 patients were analyzed. The median age at alloHCT was 57 years (18–81 years). Indications for alloHCT were AML (81.2%), sAML/tAML (6.3%) or MDS (12.5%). Disease risk was low for 3.4%, intermediate for 69%, high for 26.1% and very high for 1.6% of patients. Donors were 10/10 HLA-matched (78.6%), 9/10 matched (20.1%) or ≤8/10 matched (1.3%). Reduced-intensity conditioning regimens were most common (50.6%) and peripheral blood stem cells were the predominant graft source (89.8%). ATG was administered to 51.3% of patients. Median follow-up was 3.8 years. We could not validate several previously reported models (see Table).

Model	Event-free survival		Relapse incidence		Non-relapse mortality	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
KIR3DL1-Bw4 weak/non-inhibiting vs strong inhibiting (Boudreau, *JCO* 2017)	1.09 (0.99–1.20)	0.07	1.09 (0.96–1.23)	0.2	1.09 (0.95–1.26)	0.2
Activating *KIR2DS1* vs *KIR2DS1* negative (Venstrom, *NEJM* 2012)	1.00 (0.92–1.09)	0.97	1.02 (0.91–1.14)	0.7	0.98 (0.86–1.11)	0.8
KIR2DL1 absence in C1/C1 donors (Schetelig, *NK Immunity* 2019)	1.01 (0.90–1.13)	0.9	1.04 (0.89–1.20)	0.6	0.98 (0.82–1.17)	0.8
B-content *B/x* vs *A/A* (Cooley, *J Immunol* 2014)	0.98 (0.90–1.07)	0.7	1.04 (0.93–1.16)	0.5	0.92 (0.81–1.04)	0.2
B-content neutral vs best (Cooley, *J Immunol* 2014)	1.10 (0.96–1.26)	0.2	1.14 (0.95–1.37)	0.2	1.06 (0.86–1.30)	0.6
iKIR score (cutoff = 2) (Boelen, *Sci Immunol* 2018)	1.03 (0.95–1.11)	0.5	1.07 (0.97–1.19)	0.2	0.96 (0.85–1.08)	0.5
cenB/B-telA/A vs other	0.84 (0.69–1.01)	0.07	0.99(0.78–1.25)	0.9	0.63(0.45–0.88)	0.01

However, the donor *cenB/B-telA/A* diplotype prevalent in 4.8% of all donors was associated with a reduced risk of NRM (HR 0.63, $p = 0.01$) and a trend to better EFS (HR 0.84, $p = 0.07$). Further analysis of the respective contribution of B subtypes, showed that only the rare *cenB01/B01-telA/A* diplotype was associated with a reduced risk of relapse (HR 0.41, $p = 0.05$) while all subtypes contributed to a reduced risk of NRM (see Figure).



Conclusions: This study suggests that outcomes after alloHCT may better associate with donor KIR diplotypes rather than individual genotypes. Homozygosity for the *cenB/B-telA/A* diplotype was associated with a trend to better EFS and a reduced risk of NRM. Only the *cenB01/B01-telA/A* diplotype showed a reduced risk of relapse or progression while all B subtypes contributed to a reduced risk of NRM.

Disclosure: Nothing to disclose.

O016

A transcriptomic-based rational approach for considering VISTA as a new molecular target in acute myeloid leukemia

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Background: Immunotherapy-based regimens are now integrated in clinical practice for a wide range of cancers. However, responses to immunotherapy are inconsistent across the neoplastic spectrum. To this end, deep characterization of intratumor immune architecture is essential for identifying subsets of patients who can benefit from checkpoint inhibitors and other immunomodulatory treatments. V-domain Ig suppressor of T-cell activation (VISTA) has recently been recognized as a key negative immune regulator of anti-tumor immune response and is gaining growing interest as a potential pharmacological target. This molecule can work either as a receptor or as a ligand, is highly expressed in hematopoietic stem cells and myeloid compartment and has been found upmodulated in acute myeloid leukemia (AML). However, despite those characteristics, and its compelling role as a mediator of immune escape in cancer, VISTA-associated immune features are relatively unexplored in myeloid malignancies.

Methods: Herein, we conducted a multiomic study, investigating the transcriptomic and genetic signatures associated with VISTA expression in a large publicly available dataset of patients with AML with the purpose of potentially inspiring selective molecular targeted therapies in defined subsets of patients.

Results: VISTA was found upregulated in 285 samples from AML patients at diagnosis compared to 33 specimens from healthy controls (HC) highlighting its dysregulation at disease onset. When exploring distinct AML subtypes, we observed a pattern reflecting the expression reported in normal myelopoiesis stages, with higher expression levels in myelomonocytic and monocytic subsets and lower levels in promyelocytic leukemia. Accordingly, genomic aberrations associated with higher VISTA expression were more commonly *NPM1* mutations and *MLLT3-KTM2A* gene fusions both enriching M4 and M5 morphologic subgroups respectively. Based on the 75%ile of VISTA mRNA expression in HC, we categorized patients in high ($N = 139$) and low ($N = 146$) expressors and performed a differential analysis between the two groups. High VISTA expressors showed a striking enrichment in genes involved in immune activation with upregulation of antigen presentation and processing pathways, cytokine signaling, toll-like receptor cascade, NK cytotoxicity and response to interferon. To understand the oncogenic potential of diseases associated with strong VISTA activation, we analyzed the correlation between VISTA expression and the mutational burden, through WES analysis, and found that high VISTA expression inversely correlated with the number of somatic hits acquired at diagnosis. This result potentially indicates that VISTA hyperexpression counteracts immunoediting mechanisms that, in an initial phase, sculpt the oncogenic potential of leukemic blasts, selecting clones with lower neoantigenic burden. This phase of immune activation and elimination, is ideally followed by an equilibrium and escape stage, in which regulatory negative mechanisms arise, ultimately facilitating leukemic progression.

Conclusions: Altogether those findings pinpoint the role of VISTA as an early marker of immune activation and potentially a feedback mechanism that ultimately may promote immune escape in AML. Targeting VISTA may be an effective approach for controlling disease recurrence and treatment resistance in molecularly defined subgroups of AML patients. Ongoing experiments will clarify the role of VISTA in mediating AML relapse after allogeneic hematopoietic cell transplantation and evasion from graft versus leukemia effect.

Disclosure: No conflicts of interest to disclose

O018

Increased diagnostic telomere length associates with higher relapse rates in transplanted acute myeloid leukemia patients

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Background: Due to chromosomal instability or replicative immortality both ends of the telomere length (TL) spectrum play a role in predisposition to and progression of cancer, reflecting a sensitive homeostasis. Acute myeloid leukemia (AML) is a heterogeneous clonal disease in which TL dysregulation may be a disease promotor. For most AML patients, allogeneic

hematopoietic stem cell transplantation (HSCT) is the consolidation option with the highest chance of cure. We aimed to specify the impact of TL at diagnosis and in remission prior to HSCT in AML patients.

Methods: Bone marrow mononuclear cells at diagnosis were assessed for TL measurement in 134 AML patients who received a non-myeloablative allogeneic HSCT in complete remission (CR) or CR with incomplete hematologic recovery (CRi) between 2004 and 2021. Of those, 20 matching samples with adequate material in remission prior to HSCT were available. Clinical and molecular data including CD34+/CD38− cell burden at diagnosis and measurable residual disease (MRD) status at HSCT were collected. AML patients were grouped according to the ELN2017 risk classification. For quantification of TL, a digital droplet PCR assay (ddPCR) was developed and validated by cloning and sequencing. For outcome analysis, patients were grouped according to their diagnostic TL into a "long" and "short" TL group using the optimal cut-point package.

Results: At diagnosis, TL was heterogeneous and no significant association with age, other clinical characteristics, or the ELN2017 risk groups were observed, although the ELN2017 adverse group had the longest median telomeres. Regarding molecular genetics, we detected an association between short diagnostic TL and *IDH1* mutations ($p = 0.05$). Longer diagnostic telomeres associated with higher CD34+/CD38− cell burden ($p = 0.03$), but did not impact the MRD status at HSCT. TL in AML patients in remission prior to HSCT was significantly shorter (by a median of 58%; $p < 0.001$) than at diagnosis. With respect to outcome, a higher diagnostic TL associated with a higher cumulative incidence of relapse ($p = 0.05$) following HSCT.

Conclusions: Here we established a sensitive ddPCR assay to quantify mean TL in AML patients, which could be used in future clinical research requiring a high sample throughput. Our data suggest telomere lengthening at time of diagnosis to be a common phenomenon associated with a higher burden of immature CD34+/CD38− cells and a more aggressive disease phenotype, reflected by a higher relapse rate after HSCT. Shorter mean TL in remission could be due to either therapeutic toxicity or depletion of AML blasts with prolonged telomeres. Thus, considering the recent development of telomere-regulating drugs such as Imetelstat, which inhibits telomerase activity and shortens telomeres, it may be feasible to lower relapse rates by incorporating these into treatment regimens of AML patients leading towards HSCT.

Disclosure: The authors declare, that there is no conflict of interest.

O019

Total body irradiation/fludarabine versus busulfan/fludarabine as conditioning in all patients >45 years in 1sr CR – a registry-based study by the ALWP of the EBMT

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Background: Allogeneic hematopoietic cell transplantation (HCT) is the only curative treatment for the majority of patients with acute lymphoblastic leukemia (ALL). For patients aged up to about 45 years, total body irradiation (TBI) ≥12 Gy represents the standard backbone for conditioning, whereas a regimen consisting of Fludarabine + TBI 8 Gy (FluTBI8) is frequently used in patients beyond this age. Fludarabine + either Busulfan 6.4 mg/kg (FluBu6.4) or Busulfan 9.6 mg/kg (FluBu9.6) are popular alternative, irradiation-free regimens. Up to now, no direct comparison has addressed the role of TBI among intermediate/reduced-intensity regimens, both with respect to efficacy and toxicity.

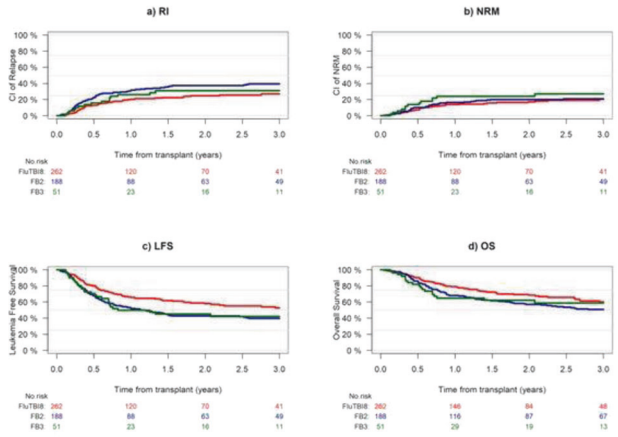
Methods: A retrospective, EBMT registry-based study was performed, including patients aged >45 years transplanted for ALL from matched sibling or matched unrelated donors in first complete remission between 2005 and 2020. Patients had received conditioning with either FluTBI8, FluBu6.4 or FluBu9.6. Outcomes and risk factors were analyzed by univariate and multivariate analysis.

Results: In total, 501 patients could be identified (Ph− B-ALL, $n = 139$; Ph+ B-ALL, $n = 296$; T-ALL, $n = 66$). They had received FluTBI8 ($n = 262$), FluBu6.4 ($n = 188$) or FluBu9.6 ($n = 51$). Patient characteristics were well balanced between the three conditioning subgroups, apart from median age (56, 60, and 55 years, $p < 0.0001$), HCT comorbidity index (HCT-CI ≥3 in 26.2%, 35.0%, and 18.2%, $p = 0.023$), ALL subtype (Ph+ B-ALL 54.2%, 64.4%, and 64,7%, $p = 0.025$) and median year of transplant (2018, 2014, and 2015, $p < 0.0001$). Median follow-up from transplant was 21, 53, and 32 months, respectively.

Time-to-event outcomes are illustrated in Fig. 1. At 2 years, relapse incidence (RI) was 27.2%, 40%, and 30.9% ($p = 0.013$) for patients receiving FluTBI8Gy, FluBu6.4, and FluBu9.6, respectively. Main causes of death were relapse, graft-versus-host disease (GvHD), and infections (51.7%, 20.2%, and 15.7% of all deaths). After conditioning with FluTBI8, FluBu6.4 or FluBu9.6, non-relapse-mortality (NRM) was 23.1%, 20.7%, and 26.8%, respectively ($p = 0.54$). Leukemia-free survival (LFS) was 58%, 42.7%, and 45% ($p = 0.003$), overall survival (OS) was 68.5%, 57%, and 62.2% ($p = 0.06$), and GvHD-free, relapse-free survival (GRFS) was 39.9%, 34.3%, and 40.1%, respectively ($p = 0.29$).

On multivariate analysis, RI was higher after FluBu6.4 (HR [95% CI]: 1.69 [1.08–2.64]), but not after FluBu9.6 (HR: 1.53 [0.04–2.79]) as compared to FluTBI8. LFS was significantly lower for FluBu6.4 (HR: 1.55 [1.09–2.2]) and FluBu9.6 (HR: 1.75 [1.1–2.76]). However, OS was not significantly different among the three subgroups. Risk of NRM, acute GvHD II-IV, and chronic GvHD was not influenced by conditioning. On multivariate analysis, the most important independent risk factors were increasing age (per 10 years), associated with higher NRM and lower OS, LFS, and GRFS; and Ph+ ALL, associated with lower RI and better OS, LFS, and GRFS.

Figure1: Relapse incidence a), non-relapse mortality b), leukemia-free survival c) and overall survival d) according to conditioning (FB2 = FluBu6.4, FB3 = FluBu9.6).



Conclusions: Among intermediate/reduced-intensity conditioning regimens, antileukemic efficacy was stronger after TBI-based conditioning, as shown in the multivariate analysis by a lower RI and longer LFS. However, this did only translate into a non-significant advantage in OS, despite similar NRM rates. FluBu6.4 and FluBu9.6 regimens revealed similar outcomes. Increasing age and Ph+ ALL were the most important factors for overall outcome.

Disclosure: Nothing to declare

O020

Fludarabine versus cyclophospamide in combination with myeloablative TBI as conditioning for patients with AML treated with allo-HCT. A study from the ALWP of the EBMT

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Background: Total body irradiation (TBI) at a dose of 12 Gy combined with cyclophosphamide (Cy) is one of standard myeloablative regimens for patients with acute myeloid leukemia (AML) treated with allogeneic hematopoietic cell transplantation (allo-HCT). Results of a prospective, randomized trial demonstrated that the combination of TBI at reduced dose (8 Gy) with fludarabine (Flu) was associated with survival comparable to CyTBI12Gy [Bornhäuser et al., Lancet Oncol. 2012;13:1035–44]. In clinical practice Flu may also be combined with TBI at a dose of 12Gy to increase regimen efficacy. However, safety and efficacy of FluTBI12Gy have not been evaluated so far. The goal of this study was to retrospectively compare outcomes of CyTBI12Gy with FluTBI12Gy for patients with AML in first or second complete remission (CR) treated with allo-HCT from either matched sibling (MSD) or unrelated donor (URD).

Methods: Overall, 121 and 1463 adult patients receiving FluTBI12Gy and CyTBI12Gy, respectively, between years 2009-2020 met inclusion criteria for this study. Statistical analysis was based on exact matching for the donor type (MSD/URD), disease status at allo-HCT (CR1/CR2), cytogenetic risk group, and stem cell source (bone marrow/peripheral blood). In a final matched-pair analysis, 109 patients treated with FluTBI12Gy were compared to 109 patients given CyTBI12Gy. Median age was 38 years and 40 years, respectively ($p = 0.87$) with 22% of patients being treated in CR2, 76% receiving transplant form URD, and 96% receiving transplant using peripheral blood as a source of stem cells.

Results: The cumulative incidence of relapse at 2 years was 25% in the FluTBI12Gy compared to 28% in the CyTBI12Gy group ($p = 0.44$) while non-relapse mortality (NRM) was 17% vs. 19%, respectively ($p = 0.89$). The rates of leukemia-free survival and overall survival were 65% vs. 54% ($p = 0.28$) and 70% vs. 60.5% ($p = 0.17$). Cumulative incidence of grade 2-4 acute GVHD was significantly lower for FluTBI12Gy than CyTBI12Gy (16% vs. 34%, $p = 0.005$), while the incidences of grade 3–4 acute GVHD did not differ significantly (7% vs. 10%, $p = 0.27$). The incidence of overall and extensive chronic GVHD was 44% vs. 47% ($p = 0.23$) and 19% vs. 21% ($p = 0.28$), respectively. Finally, the probability of GVHD and relapse-free survival was 49% in the FluTBI12Gy group and 41% in the CyTBI12Gy group ($p = 0.17$).

Conclusions: We conclude that for patients with AML treated with allo-HCT in CR1 or CR2 cyclophosphamide may be substituted by fludarabine in a regimen based on TBI at a dose of 12 Gy without negative impact on the efficacy. FluTBI12Gy is associated with reduced risk of grade 2-4 acute GVHD and encouraging LFS and OS rates.

Disclosure: No COI

Aplastic anaemia

O021

Determinants of clonal evolution in aplastic anemia

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Background: Despite therapeutic successes, AA patients exhibit a much higher risk of leukemic evolution than the general population (Fig. 1a). Secondary myeloid neoplasia (sMN) remains the most serious complication with major therapeutic and prognostic implications. Multiple theories have been proposed regarding the origin of leukemic progression, and recent studies have shed light on the multifaceted AA clonal trajectories.

Methods: Here, we took advantage of a multicentric cohort of AA patients ($n = 1008$, M:F ratio 0.99; median age 34 years, median follow-up 8.6 years) to unravel clinical and molecular determinants of malignant progression.

Results: First, we noticed that none of the patients undergoing HSCT upfront ($n = 117$) experienced late clonal complication (sMN or secondary PNH) after a median follow-up time of 8.2 years (IQR, 5.7–10.6). We then studied patients with AA and AA/PNH receiving conventional IST and classical hemolytic PNH. As expected, the 10-year CI of sMN was higher in AA and AA/PNH than in classical

hemolytic PNH (12.8, 13.1 and 3.4%, respectively). In patients with severe disease, older age (>35) at presentation (HR = 1.37 [95% CI 1.2–1.6] $p < 0.001$) and a suboptimal response to IST (HR = 2.60 [95% CI 1.39–4.84] $p = 0.003$) were independently associated with increased risk of sMN whereas the presence of myeloid mutations at onset did not have any impact overall. A similar analysis was conducted for non-severe disease, which identified non-treated cases as the group with the highest risk of sMN (HR = 3.14 [95% CI 0.69–14.26] $p = 0.04$).

After a median time of 4.5 years (1.8–7.7), 94 patients (M:F ratio 1.61; median age 61, 34–69) evolved to a sMN. MDS (76%) was the most frequent diagnosis at evolution, followed by AML (18%) and MDS/MPN (6%).With a median follow-up of 4.7 years, the 5-year OS was 40%, independently influenced by blast >5% (HR = 3.84 [95% CI 1.91–7.71] $p < 0.001$) and older age at primary disease onset (HR = 1.21 [95% CI 1.01–1.44] $p = 0.03$). Looking at cytogenetic and molecular characteristics, patients harboring del7/7q or complex karyotype (CK) had similar mutational burden and survival outcomes to those with normal karyotype (NK), differing instead from cases carrying other cytogenetic alterations. *ASXL1, SETBP1, RUNX1* and *RAS* pathway gene mutations constituted the unique signature of del7/CK carriers, classical leukemogenic drivers such as *DNMT3A, FLT3*, and *NPM1* were typical of NK, whereas cases classified as "others" had puzzling alterations. When comparing our sMN with a cohort of primary MN ($n = 3599$) pair-matched for age, gender, disease type and blast percentage, higher-risk IPSS-R scores (54% vs 37%, $p = 0.03$), *ASXL1* (24% vs 12%, $p = 0.03$) and *RUNX1* (21% vs 8%, $p = 0.03$) mutations were more frequent in sMN.

Cross-sectional studies of clonal dynamics from baseline ($n = 302$) to evolution revealed that immune-privileged *PIGA/HLA* lesions dramatically decreased over time, being swept by clones with classical myeloid hits. Most importantly, a cox-proportional hazard model predicted *PIGA* and *BCOR/L1* mutations carriers to have a lower risk of sMN progression while CHOP-like lesions marked the group with a higher risk.

Conclusions: We propose that AA malignant evolution is the consequence of a relentless autoimmune attack producing a maladaptive response to immunosuppression, characterized by invariant genomic features, clinical phenotypes and outcomes.

Clinical Trial Registry: Not applicable.

Disclosure: MS: BMS: consultancy; Abbvie: consultancy. BJP: Apellis: consultancy, other: educational talks, speakers bureau; Alexion: consultancy, other: educational talks, speakers bureau. MTV: Jazz: consultancy, honoraria, speakers bureau; Celgene/BMS: consultancy, honoraria, research funding, speakers bureau; Abbvie: speakers bureau; Novartis: speakers bureau. RC: Novartis Brasil: honoraria; Alexion Brasil: consultancy; AA&MDS International Foundation: research funding; Agios: membership on an entity's Board of Directors or advisory committees; Instituto Butantan: consultancy; Team Telomere, Inc.: membership on an entity's Board of Directors or advisory committees. R.PdL: Novartis: consultancy, honoraria, research funding; Pfizer: consultancy, honoraria, research funding; Amgen: research funding; Alexion Pharmaceuticals: consultancy, honoraria, research funding; Apellis Pharmaceuticals Inc: consultancy, honoraria; Swedish Orphan Biovitrum AB: consultancy, honoraria. JPM: Novartis: consultancy; Regeneron: consultancy; Bristol Myers Squibb/Celgene: consultancy; Alexion: consultancy.

O022

In-depth diagnostics of pediatric bone marrow failure increases detection rate of underlying causes: a multi-center prospective cohort study

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Background: Pediatric cytopenia caused by bone marrow failure (BMF) often represents a critical condition requiring swift management. Patients are at risk for invasive infections and bleeding complications. Previous studies report low rates of identifiable causes of pediatric BMF, rendering most patients with a descriptive diagnosis such as cytopenia of unknown origin or aplastic anemia (AA). Here we aimed to assess the diagnostic value of a protocolized in-depth evaluation of pediatric BMF.

Methods: We conducted a multi-center prospective cohort study in which a novel diagnostic approach for pediatric patients with suspected BMF was implemented. After exclusion of malignant, transient or reversible causes of BMF, patients entered the full diagnostic evaluation. This included bone marrow biopsy and aspiration analysis, whole exome sequencing (WES) including copy number variation (CNV) analysis on blood samples, single nucleotide polymorphisms (SNP) array analysis on bone marrow samples, Mitomycin-C test, telomere length analysis, PNH clones analysis and explorative flowcytometric analysis of the lymphocytes subpopulations, IgGAM levels and anti-nucleotide antibodies (ANA) screening. Here we report the analysis of the first 50 patients (2017–2021) evaluated by this approach.

Results: In 19 patients (38%) a causative diagnosis was identified. In this group 17 diagnoses were established by genetic analysis, including 13 mutations and 4 (large) chromosomal deletions. The 2 remaining patients had significantly short telomeres and other characteristics compatible with a telomere biology disorder (TBD) while no genetic cause was found. Of the remaining 31 patients (62%) 21 were diagnosed as severe aplastic anemia (SAA) based on peripheral multi-lineage cytopenia alongside a hypoplastic bone marrow and 10 were classified as unexplained cytopenia due to absence of causative findings in any of the diagnostic tests. A total of 28 patients (56%) were treated by hematopoietic stem cell transplantation (HSCT), including 21 patients with SAA, 6 with an inherited bone marrow failure syndrome (IBMFS) and 1 unexplained, transfusion dependent, cytopenia. For the remaining group treatments varied including steroids, androgens and occasional transfusion based on the diagnosis and the clinical condition.

Conclusions: We conclude that a standardized in-depth diagnostic protocol as presented here, can increase the frequency of identifiable causes within the heterogeneous group of pediatric BMF. We underline the importance of full genetic analysis of all patients as genetic causes are not limited to patients with typical (syndromal) clinical characteristics beyond cytopenia. In addition, it is of utmost importance to apply genome wide genetic analysis, since novel genes are frequently discovered in this group. Furthermore, our results illustrate the significance of methods to detect (larger) deletions and concordant functional analysis in addition to extensive genetic analysis. Nevertheless, for most patients the underlying cause of BMF remained elusive. Despite the fact that an autoimmune pathophysiology is often proposed in AA, it is notable that no immunological abnormality has been identified in this group by the here performed analyses. To increase the diagnostic capacity in this patient category, a more detailed characterization, preferably on single cell level, of the individual immune components and the bone marrow microenvironment is crucial.

Disclosure: Nothing to declare

O023

Long-term follow-up of haploidentical transplantation in severe aplastic anaemia: a multicentre prospective study

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Background: Haploidentical stem cell transplantation (haplo-SCT) to treat severe aplastic anaemia (SAA) has achieved great progress in recent decades. However, long-term outcome data are lacking.

Methods: We conducted a prospective multicentre study involving SAA patients who received haplo-SCT as salvage therapy. Long-term outcomes were assessed, mainly focusing on survival and quality of life (QoL). Longitudinal QoL was prospectively evaluated pretransplantion and at 3 and 5 years posttransplantion using the SF-36 scale in adults and the PedsQL 4.0 scale in children.

Results: A total of 287 SAA patients were enrolled, and the median follow-up was 4.56 years (range, 3.01–9.05) among surviving patients. During the long-term follow-up, 268 of 275 evaluable patients (97.5%) achieved sustained full donor chimaerism, and 93.4% had complete haematopoietic recovery. The estimated overall survival and failure-free survival at 9 years were 85.4 ± 2.1% and 84.0 ± 2.2%, respectively, in the whole cohort. Age (≥18 years) and a poorer performance status (ECOGå 1) were identified as risk factors for survival outcomes. For QoL recovery after haplo-SCT, we found that QoL progressively improved from pretransplantion to the 3-year and 5-year time points with statistical significance. The occurrence of chronic graft versus host disease was a risk factor predicting poorer QoL scores in both child and adult cohorts. At the last follow-up, 74.0% of children and 72.9% of adults returned to normal school or work.

Conclusions: Our inspiring long-term outcomes suggest that salvage transplantation with haploidentical donor can be routine practice for SAA patients without HLA matched donors.

Clinical Trial Registry: ChiCTR-ONC-12002107 (www.chictr.org.cn).

Disclosure: Nothing to declare.

Autoimmune diseases

O024

Low dose cyclophosphamide conditioning is safe in systemic sclerosis patients ineligible for standard dose regimens – an interim analysis of the prospective assure trial

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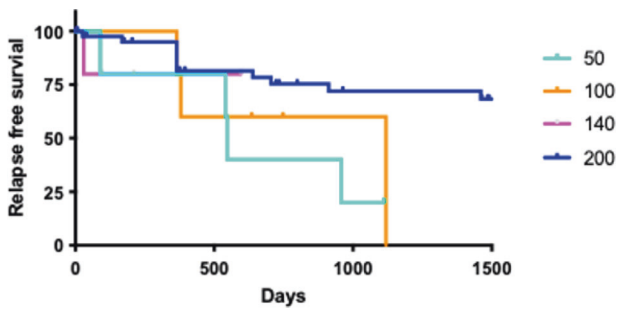
Background: Haematopoietic stem cell transplant (HSCT) is considered to be standard of care in severe systemic sclerosis (SSc). However, cardiac comorbidities often limit eligibility for the procedure due to the risk of transplant related mortality (TRM) possibly due to cyclophosphamide (Cy) induced cardiac toxicity. ASSURE is a prospective clinical trial assessing lower doses of Cy conditioning in those ineligible for HSCT based on modified EBMT criteria (Farge et al., *BMT* 2017).

Methods: All SSc patients referred for HSCT since 2013 underwent a right heart catheter and cardiac MRI along with cardio-respiratory assessment. Patients with no cardiac risk factors were allocated to an ongoing Phase II study of Cy 200 mg/kg with equine ATG 80 mg/kg. Those with cardiac risk factors, age >60 years or DLCO/VA <50% were enrolled in three cohorts of increasing doses of Cy conditioning with the same dose of eATG. Five patients in each cohort received Cy conditioning at doses of 50 mg/kg (Cohort 1), 100 mg/kg (Cohort 2) and 140 mg/kg (Cohort 3). The primary objective was to assess safety of HSCT in this high-risk population as measured by TRM at D100. Stopping rules for TRM, were based on Fleming's procedure and overseen by an independent safety committee. Response rate (RR) was defined as a 25% reduction in skin score and/or a 10% increase in FVC. A concurrent 200 mg/kg standard dose HSCT cohort was used as a comparator.

Results: Fifteen patients (7F:8M), median age 60 years (range 30-67) were enrolled from January 2017 to September 2021. The ASSURE and standard dose conditioning groups were well matched apart from higher age and pulmonary pressures in the ASSURE cohorts. There was no TRM in cohorts 1 and 2 and 1 death due to recurrent aspiration pneumonia in cohort 3 (140 mg)—a TRM of 1/15 (6.7%) compared to 4/44 (9%) in the standard dose cohort. HSCT was well tolerated in the low dose cohorts with a median duration of thrombocytopenia <20 of 0 days (0–3) and 6 days (0–12) of neutropenia <0.5. At a median follow-up of 1245, 635 and 210 days, the response rate was 80%, 100% and 75% in Cohort 1, 2 and 3 respectively. The standard dose group had a 71.4% response rate at a median of 1607 days. However, recurrence of disease has occurred in 4/5 in Cohort 1 at a median of 544 days (90-958) and 3/5 in cohort 2 at a median of 380 days (365-748) resulting in inferior relapse-free survival (Fig. 1). Estimated overall survival at one year was 100% for Cohorts 1 and 2, 80% for Cohort 3 and 86.1% for the standard dose arm.

Figure 1



Conclusions: The ASSURE trial has demonstrated that lower doses of Cy can be delivered safely to patients who previously were not eligible to receive HSCT. The ASSURE data suggests responses are similar between low and standard dose conditioning but recurrence may be higher. A larger, multi-centre study (2-ASSURE) is planned to explore conditioning regimens in this high-risk patient population who represent an unmet need in this field.

Clinical Trial Registry: ACTRN 12617000216314, www.anzctr.org.au

Disclosure: There are no conflicts of interest to declare

O025

Late complications after autologous HSCT for autoimmune diseases: a retrospective study from the EBMT autoimmune

diseases, transplant complications and paediatric diseases working parties

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Background: Over the past 20 years, autologous hematopoietic stem cell transplantation (aHSCT) has evolved as a treatment for severe autoimmune diseases (ADs) across all ages. Advances in transplant procedures and supportive care have led to improvements in long-term survival. Late complications are inevitable, with a potential impact on morbidity, quality of life and even mortality. However, the nature and frequency of 'late-effects' are largely unknown in the setting of ADs.

Methods: This is a retrospective multicenter study analyzing available EBMT registry data and additional information requested in a specifically self-designed questionnaire. The aim was to define the type, potential risk factors and cumulative incidence of non-infectious late effects after aHSCT for ADs, as well as their impact on overall outcome.

Results: Data were received for 500 patients (median of age 36.8 years, range 2.7–73.8), who received aHSCT for severe ADs between 1997 and 2016. Overall, 5% were children below 18 years. Median follow-up was 87.7 months (range 82.7–96.3). Indications included multiple sclerosis (MS, 47.2%), systemic sclerosis (SSc, 28.6%), Crohn's disease (CD, 11%), and systemic lupus erythematosus (SLE, 2.8%) and other ADs (10.4%). Graft source was PBSCs in 98% of cases, mainly mobilized with cyclophosphamide (Cy) and G-CSF ($n = 431$). Ex vivo graft manipulation was performed in 35.8% of cases. Conditioning was mainly based on Cy/ATG (49%) or BEAM/ATG (31%). ATG was given in 86.8% of patients (80% rabbit, 17.4% horse, 1.4% goat, 0.2% horse and rabbit, 1% unknown). The following late complications were reported: 11.5% secondary ADs (median time from aHSCT: 736 days), 5% malignancies (median time: 2358 days), 21.9% endocrine/bone complications (median time: 599 days), 13.9% cardiac complications (median time post-aHSCT: 920 days).

At 10-years the predicted cumulative incidence (CI) was 10.3% (95% CI: 7.6–13.4) for secondary ADs, 3.5% (95% CI: 2–5.8) for malignancies, 20.3% (95% CI: 16.3–24.6) for endocrine/bone complications, and 13.1% (95% CI: 10.1–16.4) for cardiac complications. Secondary ADs and endocrine/bone complications were more frequently reported in MS compared to SSc patients (9.1% vs 4.6%, $p = 0.04$ and 22.6% vs 12.1%, $p = 0.02$, respectively, while cardiac complications occurred at a higher frequency in SSc patients (32.7% vs 3.2%, p value $= 0.001$). Incidence of malignancies ($n = 20$) did not differ significantly between MS and SSc. Among secondary ADs ($n = 53$), autoimmune thyroid disease was reported in 29 patients. Endocrine/bone complications ($n = 87$) comprised gonadal/reproductive dysfunction in 30 patients, with osteoporosis/osteopenia in 19 and other thyroid diseases in 28 patients. Cardiac complications ($n = 66$) were heterogeneous, with dysrhythmia ($n = 17$), cardiac failure ($n = 11$) and "mixed" disorders ($n = 20$).

Overall, at 10 years, progression-free survival (PFS) was 42.2% (95% CI: 36.8–47.5), OS 83.7% (95% CI: 79.4–87.2) and non-relapse mortality (NRM) 5.1% (95% CI: 3.3–7.4).

Conclusions: Our study confirms that aHSCT for ADs in adults and children is associated with a cumulative burden of non-infectious late complications, including thyroid dysfunction, osteoporosis, cardiac complications, gonadal dysfunction, secondary ADs and subsequent malignancies. The study highlights the importance of routine screening, monitoring, and interventional treatment of late effects of aHSCT for ADs, supported by guidelines for standard of care.

Disclosure: Nothing to declare

O026

Longitudinal changes on quantitative chest high-resolution computed tomography in diffuse systemic sclerosis-related interstitial lung disease after autologous hematopoietic stem cell transplantation

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Background: Since Burt et al. first demonstrated in the ASSIST trial (1) that lung disease high-resolution computed tomography (HRCT) volumetric measurement decreased in autologous hematopoietic stem cell transplantation (aHSCT) recipients and increased in controls receiving cyclophosphamide iv one year after starting treatment, limited data have been reported concerning the evolution of Systemic Sclerosis-Interstitial Lund

disease (SSc-ILD) and its relationship with the evolution of esophageal volume is unknown. We therefore aimed to evaluate interstitial lung disease (ILD) and esophageal longitudinal changes on quantitative chest HRCT in early diffuse systemic sclerosis (dSSc)-patients before and after treatment by aHSCT.

Methods: Chest HRCT evaluation was performed before aHSCT and afterwards during yearly routine clinical and paraclinical follow-up in 33 consecutive dSSc-patients between January 2000 and January 2016. Two independent chest radiologist experts blindly assessed the extent of ILD on HRCT images, using the semi-quantitative Goh and Wells method (2), and the widest esophageal diameter and volume at each time point for all patients. Patients were retrospectively classified as radiological responders (A) or non-responders (B) according to stability or decrease of 5% or more of HRCT ILD extent at 24 months after aHSCT. Overall changes in chest-HRCT, lung function and skin score were compared before and after aHSCT. Survival rates were assessed for all patients.

Results: Significant improvement in HRCT median ILD and ground-grass opacities extent quantitative scores (–1.5 points ($p = 0.007$) and –2.0 points ($p = 0.07$) at 12 and 24 months, respectively) was observed after aHSCT. Eighteen patients were radiological responders at 2 years (probability of response 0.78, 95% CI (0.58; 0.90)), of whom ten (58.8%) had a decrease of 5% or more in overall ILD extent. The widest esophageal diameter and the esophageal volume increased from a median of 24.5 mm [18; 29] and 19 mm^3 [13; 33] before aHSCT to 28 mm [19; 33] and 30 mm^3 [13; 58] at 2 years respectively ($p = 0.005$ and $p = 0.01$). With a median follow-up of 65 [26; 142] months; four deaths occurred after aHSCT. Kaplan–Meier survival analyses showed that patients achieving a radiological response at 2 years had a trend towards better 5 years survival as compared with non-responder with respective rates of 100% versus 60% (HR 0.23, 95% CI 0.03–1.62, $p = 0.11$).

Conclusions: Real-world data confirmed significant improvement of SSc-ILD on chest HRCT (using the reference methodology) at 2 years after aHSCT, alhough esophageal volume constantly worsened.

(1)Burt RK, Shah SJ, Dill K, Grant T, Gheorghiade M, Schroeder J, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet Lond Engl. 2011;378:498–506.

(2)Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med. 2008;177:1248–54.

Disclosure: No conflict of interest

CAR-based cellular therapy—clinical

O028

Profiles of cytokines are associated with prolonged hematologic toxicities after BCMA targeted CAR-T cell therapy

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Background: Recently, a rising number of clinical trials have demonstrated the considerable efficacy of B cell maturation antigen (BCMA) targeted chimeric antigen receptor (CAR) T cell therapy in the treatment of relapsed or refractory multiple myeloma (RRMM). However, in clinic practice, prolonged hematologic toxicity (PHT), one of the most common toxicities, would extend the length of hospitalization, aggravate the economic burdens, and impair the quality of patients' life.

Methods: Here, we retrospectively reviewed 91 patients with RRMM who underwent BCMA CAR-T cell therapy in our center between July 2018 and July 2021. All patients were enrolled in an open-label single-center clinical trial of BCMA CAR-T cell therapy (ChiCTR1800017404). Neutropenia and thrombocytopenia were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Prolonged neutropenia (or thrombocytopenia) was defined as unrestored ≥grade 3 neutropenia (or thrombocytopenia) at day 30 following CAR-T cell infusion. Both prolonged neutropenia and thrombocytopenia were considered as PHT. Moreover, CRS was assessed according to a revised grading system. Grade 1–2 CRS was mild, while grade 3–4 CRS was severe. Stepwise multivariate regression were used to identify the independent risk factors for PHT.

Results: A total of 91 RRMM patients receiving BCMA CAR-T cell therapy between July 2018 and July 2021 in our center were followed. Before lymphodepletion regimen, their median serum lactate dehydrogenase and β2 microglobulin were 204 (range, 85–5600) U/L and 3715 (range, 1080–41,910) ug/L, respectively. Forty-two (46.15%) patients had extramedullary lesions, and 35 (38.46%) patients has experienced autologous stem cell transplantation.

After CAR-T cell infusion, 47 (51.65%) patients developed mild CRS, and 41 (45.05%) patients developed severe CRS. Besides, a high incidence of PHT (66/91, 72.53%) was observed, including prolonged neutropenia (36/91, 39.56%) and prolonged thrombocytopenia (56/91, 61.54%). After analysing the profiles of primary disease, CAR-T cell products, and cytokine release syndrome (CRS) by univariate analysis, we found that CRS was an important factor associated with PHT. Furthermore, the results of multivariable analysis showed that high maximum of IL-10 level and IL-17A level after CAR-T cell infusion were risk independent factors for prolonged neutropenia; low baseline IL-2 level and high maximum of IFN-γ level were risk independent factors for prolonged thrombocytopenia; high maximum of IFN-γ level were risk independent factors for PHT.

Conclusions: These findings discovered that the profiles of cytokines play a significant role in PHT following CAR-T cell infusion, which sheds light on the potential mechanism of PHT. More importantly, the profiles and risk factors of hematologic toxicities could facilitate early prediction and better clinical management when clinicians perform CAR-T cell therapy.

Clinical Trial Registry: ChiCTR1800017404.

Disclosure: No relevant conflicts of interest to declare.

O030

Treatment of adult all patients with third-generation CD19-directed chimeric antigen receptor (CAR) T cells – results of the Heidelberg Trial 1 (HD-CAR-1 trial)

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Background: Treatment with chimeric antigen receptor T cells (CARTs) has become standard of care in B-cell malignancies including patients with relapsed or refractory (r/r) acute lymphoblastic leukemia (ALL) younger than 26 years. However, no CART product for older r/r ALL patients is commercially available. Here, we present the preliminary results of the adult ALL patient cohort treated with third-generation CARTs within the Heidelberg CART trial 1 (HD-CAR-1).

Methods: HD-CAR-1 is an investigator-initiated phase I/II trial initiated in September 2018 designed to evaluate escalating doses of third-generation CD19-directed CARTs (1×10^6–2×10^8 CARTs/m^2) comprising the costimulatory domains CD28 and CD137 (4-1BB) after lymphodepletion with fludarabine and cyclophosphamide. Leukapheresis, CART manufacturing at the GMP Core Facility in compliance with EU GMP guidelines, administration of CARTs, patient monitoring and follow-up of HD-CAR-1 are performed in-house at the Heidelberg University Hospital. In addition to NHL patients, adult patients with r/r ALL are eligible.

Results: Until December 2021, 35 patients have been recruited for HD-CAR-1 and subjected to leukapheresis. For all patients, autologous CARTs were successfully manufactured, and 32 patients have received their respective HD-CAR-1 CART product. Three patients did not receive treatment due to progressive disease ($n = 2$) or death due to septic organ failure ($n = 1$) prior to CART administration. Of 35 patients, 13 patients with r/r ALL have been treated [10^6 CARTs/m^2 ($n = 3$), 5×10^6 CARTs/m^2 ($n = 3$), 20×10^6 CARTs/m^2 ($n = 4$) and 20×10^6 CARTs/m^2 ($n = 3$)]. Median age of treated r/r ALL patients was 42 years (range 21–67 years) and patients had received two to nine prior treatment lines. Eleven of 13 patients were treated after at least one prior allogenic stem cell transplantation (alloSCT). At the time of HD-CAR-1 enrollment, nine patients displayed active disease and four patients were positive for minimal residual disease (MRD). After treatment with CARTs no patient developed any grade of immune effector cell-associated neurotoxic syndrome (ICANS). No case of cytokine release syndrome (CRS) ≥III° was observed. Three patients developed CRS I°, and one patient CRS II° that resolved after management according to protocol. CARTs were detectable in the peripheral blood (PB) of all treated patients, with maximum CART copy numbers ranging between 12,983 and 563,332/µg PB mononuclear cell DNA.

Three patients died before reaching end-of-study (EOS) on day 90 due to progressive disease ($n = 2$) or sepsis due to gram negative infection ($n = 1$). Nine patients have reached the EOS. Of these nine patients, eight (83%) patients achieved a complete remission (CR), with four (44%) patients reaching MRD-negative CR.

As for hematotoxicity, three patients displayed prolonged >III° neutropenia for more than 28 days after CART treatment. Further evaluation of PB samples after CART administration for gene expression profiling of CART subpopulations, exhaustion markers and relevant genes for signal transduction on single-cell-based analysis is ongoing.

Conclusions: HD-CAR-1 product manufacturing was feasible for all patients enrolled in HD-CAR-1 so far. In adult patients with r/r ALL, third-generation HD-CAR-1 CAR T cells displayed an excellent safety profile as well as high clinical efficiency.

Clinical Trial Registry: NCT03676504 (www.clinicaltrials.gov); Institutional review board approval no.: AF-mu 405/2017; EudraCT-No. 2016-004808-60.

Disclosure: MLS: consultancy for Kite/Gilead, Janssen. Scientific presentation Kite/Gilead, Novartis. AS: travel grants from Hexal and Jazz Pharmaceuticals, research grant from Therakos/Mallinckrodt and co-founder of TolerogenixX LtD. PDe: honorarium for scientific presentation by MSD. CMT: consultancy Advisory Board for Pfizer and Janssen, and has received grants and research support from Pfizer, Daiichi Sankyo, BiolineRx and Bayer AG. PDr: consultancy for AbbVie, AstraZeneca, Gilead, Janssen, Novartis, Riemser, Roche; speakers bureau for AbbVie, Gilead, Novartis, Riemser, Roche; research support from Neovii and Riemser. MS: funding for collaborative research from Apogenix, Hexal and Novartis, travel grants from Hexal and Kite, financial support for educational activities and conferences from bluebird bio, Kite and Novartis, board member for MSD and (co-)PI of clinical trials of MSD, GSK, Kite and BMS, as well as co-Founder and shareholder of TolerogenixX Ltd. All other authors report no potential conflicts of interest.

O031

R/R B-ALL receiving haploidentical HSCT after CAR-T therapy achives comparable outcomes to B-ALL transplanted in CR1 after chemotherapy

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Background: Refractory/relapse(R/R) B-cell acute lymphoblastic leukemia (B-ALL) is associated with dismal survival. The efficacy and outcomes of consolidative allogeneic hematopoietic stem cell transplantation (allo-HSCT) in R/R patients achieving MRD-negative CR is also inferior to that in patients transplanted in first MRD-negative CR. How to decrease relapse rate and improve long-term survival after allo-HSCT in this population merits further attention.

Methods: Patients with R/R B-ALL who achieved MRD-negative CR after CAR-T therapy and bridged to haploidentical HSCT (haplo-HSCT) between January 2016 and August 2021 were assigned to the CAR-T group ($n = 28$). While patients with newly diagnosed B-ALL after chemotherapy and bridged to haplo-HSCT at CR were included in chemotherapy group. Moreover, the chemotherapy group was further divided into two cohorts: first CR at HSCT (chemo+CR1) group ($n = 118$) and second or more CR (chemo +≥CR2) group ($n = 22$), which were separately compared to the CAR-T group. Transplant outcomes were assessed between these cohorts.

Results: With a median follow-up of 31.0 months, the 2-year OS, LFS, NRM and relapse in the CAR-T group and the chemotherapy group did not differ significantly (OS, 87.9% vs 71.5%; LFS, 72.0% vs 66.8%; NRM, 3.9% vs 13.7%; relapse, 24.1% vs 19.4%; respectively). Multivariate analysis confirmed that ≥CR2 at transplantation following chemotherapy is an independent risk factor associated with poor OS (HR 4.22 [95% CI, 1.34–13.293], $P = 0.014$) and LFS (HR 2.57[95% CI, 1.041–6.343], $P = 0.041$).

We then divided patients in chemotherapy group into first CR at HSCT (chemo+CR1) group ($n = 118$) and second or more CR

(chemo+≥CR2) group ($n = 22$). Patients in the chemo+≥CR2 group had inferior OS (37.8%) and LFS (41.7%) than those in the chemo+CR1 group (OS, 76.0%, $P = 0.007$; LFS, 71.1%, $P = 0.004$) and in the CAR-T group (OS, 87.9%, $P = 0.007$; LFS, 72.0%, $P = 0.043$), respectively. The cumulative 2-year NRM incidences were 14.3%, 12.9% and 3.9% in the chemo+CR1 cohort, the chemo+≥CR2 cohort and the CAR-T cohort. No significant differences in the incidence of NRM were observed between groups. Patients in the chemo+CR1 group had a significantly lower relapse rate (14.6%) than those in the chemo+≥CR2 group (45.5%, $P < 0.001$), but no difference from those in the CAR-T group (24.1%, $P = 0.130$). There appeared to be a trend toward a higher relapse rate in the chemo+≥CR2 group compared with the CAR-T group, but this difference did not attain statistical significance ($P = 0.092$).

There were no differences in cumulative incidences of I–IV aGVHD, II–IV aGVHD and cGVHD between the two groups. Older donor age (≥36 years) was found to be a significant risk factor for incidence of II–IV aGVHD (HR = 2.66 [95% CI, 1.029–6.88], $P = 0.044$).

Conclusions: Our results demonstrated that patients with R/R B-ALL receiving haplo-HSCT after CAR-T therapy achieves comparable outcomes to newly diagnosed ALL transplanted after chemotherapy based CR1. Moreover, CAR-T therapy followed by haplo-HSCT in R/R B-ALL patients is feasible and does not increase the risk of transplant-related mortality and toxicity, greatly improving long-term overall survival in R/R B-ALL.

Disclosure: Nothing to declare

O032

Real-life experience with commercial CAR-T cells for lymphoma patients: early expansion kinetic predicts disease response and survival

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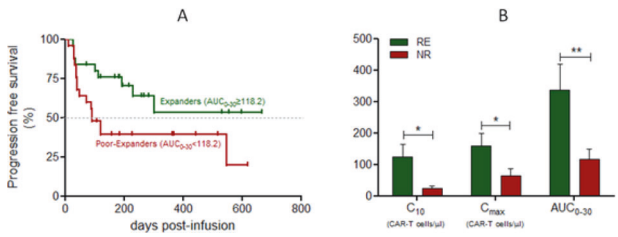
Background: Although Tisa-cel and Axi-cel are becoming widely used as standard-of-care therapy for lymphoma patients, key determinants of response are not well characterized. Clinical features such as poor PS, high systemic inflammatory state, tumor burden and LDH represent markers associated with lower efficacy in some studies. However, response and survival do not appear to be influenced by patients' characteristics in other reports and the role of CAR-T expansion in peripheral blood (PB) has never been prospectively investigated in a real-life setting. The aim of this study was to correlate Axi-cel and Tisa-cel in vivo expansion kinetics and lymphoma response, survival and toxicities.

Methods: This single-center prospective study evaluated 50 large B-cell lymphoma patients (26 DLBCL-NOS, 9 HGBCL, 7 tFL, 8 PMBCL) receiving Tisa-cel ($n = 23$; 46%) and Axi-cel ($n = 27$; 54%) and explored the prognostic role of monitoring CAR-T cells using flow cytometry. Data were acquired on MACSQuant® Analyzer (Miltenyi) and analyzed using the MACSQuantify Software.

Results: At a median follow-up of 325 days (range 33–667), the median PFS was 302 days and median OS was not reached. No statistically significant differences in PFS or OS were detected between patients treated with Tisa-cel and Axi-cel (PFS: median 192 vs 302 days; and OS: median 582 days vs not reached; *P* ns). The in vivo expansion kinetics of Tisa-cel and Axi-cel were similar. We then examined whether CAR-T cell expansion was associated with response and survival. Median time to peak expansion (T_{max}) was 10 days for both Tisa-cel and Axi-cel with no significant differences either in CAR+ cell/μl at day 10 (C_{10}: median 30.5 for Tisa-cel vs 23 for Axi-cel; *P* ns) or in the concentration of CAR+ cells at the T_{max} (C_{max}: median 52 CAR+ cell/μl for Tisa-cel vs 54 for Axi-cel; Pns) or in the magnitude of expansion up to 30 days (AUC_{0-30}: median 123 for Tisa-cel vs 113 for Axi-cel; *P* ns). When the median AUC_{0-30} (118.2) was used as a surrogate for CAR-T cell expansion and was set as the cut-off to discriminate "expanders" ($n = 25$, 50%) and "poor-expanders" ($n = 25$, 50%), expanders had a significantly longer PFS compared to poor-expanders (PFS median: not reached in expanders vs 93 days in poor-expanders; $P < 0.05$) (Fig. A). Of note, 14 (56%) patients with AUC_{0-30} <118.2 relapsed by day 90, as compared to 6 (24%) patients with AUC_{0-30} ≥118.2. Moreover, expanders exhibited significantly higher response rates than poor-expanders (OR 4.030; 95% CI 1.201–13.53; $P < 0.056$), whereas no significant correlation between grade ≥2 CRS and expansion was observed (OR 2.471; 95% CI 0.6339–9.629; *P* ns). Additionally patients in CR and PR (responders, RE; $n = 30$; 60%) by PET/CT by day 90, had significantly higher C_{10}, T_{max} and AUC_{0-30} when compared to non-responders (PD and SD, NR; $n = 20$; 40%) (C_{10}: median 43.7 in RE vs 13.7 in NR; $P < 0.05$; C_{max}: median 78.6 in RE vs 25.3 in NR; $P < 0.05$; AUC_{0-30}: median 161.9 in RE vs 61.1 in NR; $P < 0.01$) (Fig. B).



Conclusions: To the best of our knowledge, this is the first study demonstrating the clinical utility of CAR-T cell monitoring in lymphoma patients receiving standard-of-care therapy with Tisa-cel and Axi-cel.

Disclosure: PC—advisory boards: AbbVie, ADC Theraputics, Amgen, BeiGene, Celgene, Daiichi Sankyo, Gilead/Kite, GSK, Incyte, Janssen, KyowaKirin, Nerviano Medical Science, Novartis, Roche, Sanofi, Takeda. Honoraria for lectures: AbbVie, Amgen, Celgene, Gilead/Kite, Janssen, Novartis, Roche, Sanofi, Takeda. AC—advisory boards: Celgene-BMS, Clinigen, Gilead-Sciences, Janssen, Roche, Takeda. Honoraria for lectures: Astrazeneca, Celgene-BMS, Clinigen, Gilead-Sciences, Incyte, Janssen, Novartis, Roche, Takeda. AG—Honoraria for lectures: GSK; other from GILEAD.

This work has been supported by ACC (Alleanza Contro il Cancro), AIL (Associazione Italiana contro le Leucemie-Linfomi e mieloma) and Ministero della Salute.

O033

Development, safety and efficacy of locally produced novel BCMA CART cells for relapsed/refractory multiple myeloma

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Background: Excellent response achieved by B-Cell Maturation Antigen (BCMA)-targeted (Chimeric Antigen Receptor) CAR T cell therapy in multiple myeloma (MM) makes this treatment strategy of great promise. First anti-BCMA CART cell therapy for MM has been

approved by the FDA. Nevertheless, the broader application CART-based therapies faces several obstacles. Among these are the length of the manufacturing process, limited access and the excessive cost. With the world still facing a COVID-19 pandemic, there is an urgent need to develop in-house based CART treatments. To advance the treatment of MM in Israel, we have developed a novel CAR molecule for BCMA targeting. The sequence encoding this CAR was inserted into a MSGV1 retroviral cassette for the generation of a second-generation BCMA.CAR, with further development and generation of GMP-approved master cells and viral banks, required for clinical grade BCMA.CART cells. BCMA.CART cells were assessed for their activity against MM cells in vitro and in a mouse xenograft tumor model. Based on our favorable results pre-clinical novel CART-BCMA construct, Hadassah Medical Center has recently obtained approval from the Israeli Ministry of Health (MOH) to carry out a BCMA-targeted CART-based clinical trial relapsed refractory (R/R) MM patients.(NCT04720313).

Methods: At the beginning of 2021, a phase I a/b clinical trial, aimed at evaluating BCMA.CART safety and efficacy was initiated. The phase I first part of the trial consisted of three escalating cell doses. Twenty heavily pretreated relapsed/refractory (R/R) MM (including amyloidosis) patients were treated with BCMA.CAR+ cells produced onsite at HMC.

Results: The median age was 59.0 ± 12.4 and the median number of lines was 6 ± 3. Six patients were infused with 150 million BCMA.CAR+ cells, eight patients with 450 million, and six patients with 800 million cells. Only one patient had grade 3 cytokine release syndrome (CRS) at cell dose of 800 million. No grade 4 CRS was recorded. None of the patient had immune effector cell-associated neurotoxicity syndrome (ICANS). One patient died within 30 days of infusion secondary to disease progression. No other unexpected severe adverse effects (SAEs) have been observed at the three different doses, confirming that the BCMA.CAR T-based cellular therapy developed at HMC is well-tolerated. Overall response rate was found in 10/14 (71.4%) patients. Of the six patients treated with 150×10^6 CART cells—three responded one patient had a partial response (PR), one patient had a very good partial response (VGPR), and one patient had a complete response (CR). Of eight patients receiving 450×10^6 CART cells, seven responded. One had a progressive disease (PD), one patient had a PR, 5 patients had a VGPR, and one patient had a CR. Six patients were treated with 800×10^6 BCMA.CAR+ cells but response rates are too early to be assessed.

Conclusions: The anti-BCMA CART - cell therapy developed at HMC proves safe at the three cohorts, with manageable toxicities and evidence of initial favorable responses attesting to its efficacy in heavily pretreated R/R MM patients. These data are very encouraging and demonstrate the capability of single center local medical institution to develop, manufacture and deliver in-house CART.

Clinical Trial Registry: NCT04720313.

Disclosure: Nothing to declare

O034

Stem cell boost for persistent cytopenia after chimeric antigen receptor t-cell therapy: a German Lymphoma alliance (GLA) study

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Background: Chimeric antigen receptor T-cells (CAR-T) have shown dramatic efficacy in treating refractory aggressive B cell lymphomas leading to EMA approval of axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel). Persistent cytopenia is a frequently observed complication, including profound and prolonged neutropenia in approximately 60% of patients, which may subsequently further increase the risk for infection. No data exist on the value of hematopoietic stem cell boosts for persistent cytopenia after CAR-T therapy.

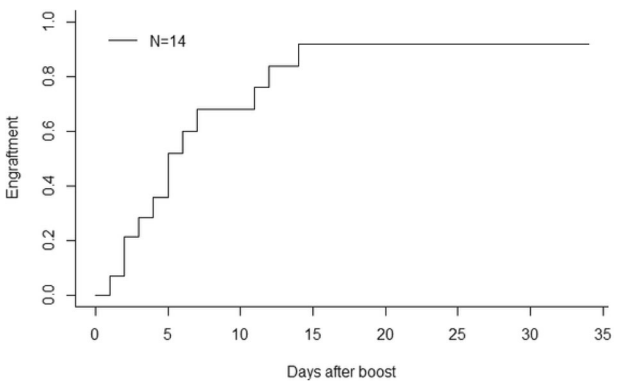
Methods: This is an ongoing multicenter cohort study of currently seven GLA centers. We present first results of patients who received stem cell boost between 2018 and October 2021 for persistent cytopenia after CAR-T therapy (either axi-cel or tisa-cel). Baseline patient, disease, and transplant data were collected in uniform fashion.

Results: As of December 13, 15 patients were included who received either axi-cel ($n = 9$) or tisa-cel ($n = 6$). Most patients had diffuse large B-cell lymphoma (DLBCL, $n = 12$). Median age was 61 years (range, 46-79 years). Most patients (60%, $n = 9$) had secondary International Prognostic Index 4 or 3 and an ECOG performance status of 0 or 1 at time of CAR-T infusion (80%, $n = 12$). 13/15 patients (87%) received bridging therapy. Seven patients (46%) achieved complete remission after CAR-T. 12/15 patients received GCSF before stem cell boost, with a median total of 9 (range, 0–51 injections). Median time from CAR-T infusion to first GCSF application was 13 days (range, 1–84 days).Median time between CAR-T infusion and stem cell boost was 1.4 months (range, 0.2–14.6 months). One patient received allogeneic CD34-selected stem cells from a matched related donor after having received allogeneic transplantation 1 year before CAR-T therapy, whereas all other products had been harvested for intended autoHCT before the decision to proceed with CAR-T therapy was taken. Median number of infused stem cells was 3.9×10^6/kg bodyweight (range, $1.4–11.5 \times 10^6$). Median absolute neutrophil count at time of boost was 0.29 (range, $0–1.88 \times 10^9$/L) and median platelet count was 19 (range, $6–30 \times 10^9$/L). Median time of neutrophil engraftment was 5 days (Fig. 1). Early application of boost (<2 months after CAR-T) correlated with sustainable blood counts.

In total, eight patients died. Treatment-related deaths due to sepsis occurred in two patients (one at day 4 after boost in neutropenia and one at day 14 after boost with engraftment). Both patients had neutropenia grade 4 for 2.7 and 2.8 months after CAR-T, respectively. The remaining six deaths were relapse-related, of which two occurred after subsequent allogeneic transplant.

Median follow-up time from CAR-T infusion was 15 months, median overall survival was 19.8 months and median progression-free survival was 14.3 months.

Conclusions:



This is the first multicenter cohort study on stem cell rescue for persistent cytopenia after CAR-T therapy. It demonstrates that stem cell boosts generally result in prompt resolution of cytopenia and is safe, thereby providing evidence that prolonged cytopenia after CAR-T therapy is due to dysfunction of hematopoietic stem or progenitor cells rather than to immunological or micro-environmental factors. Stem cell boosts should be considered for persistent cytopenia after CAR-T therapy.

Disclosure: Nothing to disclose

O035

Allogeneic CD19-CAR T cells: a promising treatment for pediatric patients with highly refractory BCP-ALL relapsing after allogeneic hematopoietic stem cells transplant (allo-HSCT)

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Background: Targeted immunotherapy with autologous CD19-CAR-T cell has shown an unprecedented efficacy in the treatment of children with relapsed/refractory (r/r) BCP-ALL. However, patients relapsing after an allo-HSCT and/or displaying a profound lymphopenia often cannot access autologous products for the failure of collecting and/or manufacturing a sufficient number of mononuclear cells with adequate fitness. Allogeneic, donor-derived CAR-T cells have the potential to overcome these hurdles but the risk of inducing GvHD has limited their development

Methods: At Ospedale Pediatrico Bambino Gesù in Rome, we tested donor-derived T-cells transduced with a 2nd generation (4.1BB) CD19-CAR for the treatment of pediatric patients with BCP-ALL relapsing after allo-HSCT, in a hospital exemption setting. Two manufacturing processes were explored, using either a retroviral construct incorporating inducible caspase-9 (iC9-CD19-CAR_ALLO) or a lentiviral construct and an automated, Prodigy®-based, manufacturing process (CD19-CAR-Lenti_ALLO). CD19-CAR-Lenti_ALLO cells were produced and released as fresh product.

All patients received a lymphodepleting regimen consisting of fludarabine and cyclophosphamide for 3 days.

Results: Four children/young adults received the ALLO-CAR T-cells between January and December 15, 2021; 2 additional patients will receive allogeneic products by the end of December. The characteristics of the patients, type of donor, cell product and doses are presented in Table 1.

Table 1. Pts characteristics. [a]Pt #3 had an HLA-identical sibling but could not receive an allo-HSCT because of the persistence of active disease.

ID	Gender	Age (y)	Cytogenetic anomalies	Previous autologous CD19-CAR-T	Disease phase at inclusion	Extramedullary disease (sites)	HSCT donor	CAR-T platform	CAR-T-cell dose
001	F	17	iAmp21 pos	No	Third relapse (<100 days after HSCT)	No	Unrelated, HLA-identical	iC9-CD19-CAR_ALLO	3×10^6/kg
002	M	11	t(12;21)	Yes	Fourth refractory relapse	Yes (bone – diffuse, kidneys, pancreas, CNS2)	HLA-identical sibling	CD19-CAR-Lenti_ALLO	1×10^6/kg
003	M	20	t(1;1)(q21;q22)-MEF2D/BCL9	No	Second refractory relapse	Yes (bone – diffuse, liver)	HLA-identical sibling[a]	iC9-CD19-CAR_ALLO	3×10^6/kg
004	M	6	None	Yes	Fourth refractory relapse (after 2 HSCTs)	Yes (kidneys, spleen)	HLA-partially matched relative	CD19-CAR-Lenti_ALLO	2×10^6/kg

The designed dose was successfully produced for all the patients, obtaining 3.87×10^9 (41.4% CAR^+) and 3.31×10^9 (41.5% CAR^+) total cells for iC9-CD19-CAR_ALLO and 6.92×10^9 (34.3% CAR^+) and 4.41×10^9 (57.3% CAR^+) total cells for the CD19-CAR-Lenti_ALLO. Interestingly, all the patients experienced the same toxicities observed in trials with autologous products, mainly cytopenia, CRS (maximum grade 2-Lee, 2014) and grade 2 ICANS. No case of new-onset aGVHD after ALLO-CAR T-cell infusion occurred in any of the treated patients, including the patient infused with ALLO-CAR-T-cells from the haplo-identical donor. In addition, pt #3, who received iC9-CD19-CAR_ALLO before HSCT, showed a significant expansion of CAR T cells (peak at day+10: 181,19CAR^+cells/mcl) without any sign of GvHD nor rejection of allogeneic cells.

All the patients obtained complete remission of the disease, with MRD negativity, in the BM. Pt #2 had an almost complete clearance of all extramedullary lesions, with persistence of only one single active spot of disease; also in pt #3, whose bone disease had shown strong resistance to all previous treatments, all the spots showed a massive response to the treatment, with only two residual lesions remaining 1 month after infusion. Interestingly, with a median follow-up of 2 months (range 0.5–9.5), all patients maintain B-cell aplasia.

Conclusions: Our data, although preliminary, suggest that allogeneic anti-CD19 CAR T cells can effectively treat highly refractory BCP-ALL relapsing after alloHSCT without showing increased toxicity as compared to autologous CAR T cells.

Disclosure: PM: scientific advisory: Sobi. MA: advisory board: Vertex. FL: research support: Bellicum; speaker's bureau: Miltenyi, Bellicum, Amgen, Medac, Neovii, Novartis, Sanofi, Gilead, bluebird bio; advisory board: Bellicum, Amgen, Neovii, Novartis, Sanofi.

CAR-based cellular therapy—preclinical

O036

Primary CD33-CAR-NK cells efficiently target acute myeloid leukemia

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Background: Acute myeloid leukemia (AML) represents a devastating disease for which novel therapies are urgently required. Previous studies already demonstrated the utility of CD33-targeting chimeric antigen receptor (CAR)-T cells for the treatment of AML. Yet clinical application of CD33-CAR-T cells remains challenging due to potential side effects including clonal expansion and persistence with long-term suppression of haematopoiesis as well as its restriction to autologous cell preparations. In contrast, natural killer (NK) cell preparations can be safely given to HLA-mismatched recipients without severe side

effects. Here, we report on the generation of primary CD33-CAR-NK cells, which are highly effective against AML in vitro and in AML xenograft models in vivo.

Methods: CD33-CAR-NK cells were generated by transduction of fresh blood-derived primary NK cells using baboon envelope pseudotyped lentiviral vectors (BaEV-LV). Genetically modified NK cells were expanded under feeder cell-free conditions and activated through addition of IL-15 and IL-2. CAR-expression and cytotoxicity towards $CD33^{+/-}$ AML cells were analyzed using flow cytometry. Finally, the efficacy of CD33-CAR-NK cell products was evaluated in OCI-AML2 (GFP^+, Luc^+) xenograft NSG-SGM3 mouse models by bioluminescence imaging (BLI) of the leukemic burden as well as flow cytometric and chimerism analysis of persisting (CAR-)NK and AML cells.

Results: Transgene integration by BaEV-LV resulted in 35-60% CAR-expression and CD33-CAR-NK cells displayed similar ex vivo-expansion, although fratricide of $CD33^+$ NK cells could be observed. CD33-CAR-NK cells were more potent in eliminating $CD33^+$ OCI-AML2 and primary AML cells in a short-term killing assay compared to untransduced (UTD)-NK cells. This was confirmed by IncuCyte-based life-cell imaging as well as in tumor rechallenge assays. Phenotypical and cytokine secretion assays revealed no major differences between UTD and CD33-CAR-NK cells, pointing to a CAR-mediated killing mechanism.

Following weekly injections (three in total) of 1×10^7 CD33-CAR-NK cells i.v., a significant reduction of leukemic burden by day 21 post AML cell-injection could be observed in an OCI-AML2 NSG-SGM3 xenograft mouse model ($n = 7$/group). BLI-analysis of femur, tibia and spleen on day 22 revealed impeded AML engraftment in CD33-CAR-NK cell-treated mice which was confirmed by flow cytometry analysis of isolated bone marrow (BM) (GFP^+ cells: untreated (UT): 17.6%, UTD: 9.1%, CAR: 0%) and splenocytes (GFP^+ cells: UT 7.6%, UTD 5.6%, CAR 0%). Additionally, NK cell-infiltration in the BM or spleen on day 22 was significantly increased in mice treated with CD33-CAR-NK cells ($CD56^+$ cells: BM: UT 0.2%, UTD 0.4%, CAR 1.1%; Spleen: UT 0.3%, UTD 2.1%, CAR 17.7%) and the majority of NK cells were identified as CAR-positive (>73%). Chimerism analysis of PB revealed higher persistence of NK cells and absence of AML cells in CD33-CAR-NK-treated mice (UTD: humanDNA 1.2% thereof 56% NK, 44% AML; CAR: humanDNA 17.9% thereof 100% NK). Behavior, weight and histological analysis of colon, liver and lung showed no signs of therapy-induced side-effects.

Conclusions: CD33-CAR-NK cells possess a strong anti-tumor efficacy and highly improved presence in BM, spleen and PB compared to UTD-NK cells and therefore constitute a promising treatment option for AML, especially for heavily pretreated patients who are not eligible for autologous cell products.

Disclosure: RP, MN, MQ, CZ, and NM are employees of Miltenyi Biotec. DS is an employee of Lentigen Technology, Inc., a Miltenyi Biotec Company.

O037

Enhancing SLAMF7 CAR T cell production by prevention of fatricide

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Background: The SLAMF7 antigen is highly and uniformly expressed on malignant plasma cells and under investigation as a target for antibody-based and cellular immunotherapy in multiple myeloma. We are pursuing the clinical development of SLAMF7 CAR T cell therapy in an ongoing phase I/IIa trial (CARAMBA EudraCT: 2019-001264-30).

A particular challenge with generating SLAMF7 CAR T cells is the physiologic expression of SLAMF7 on T cells which induces fratricide and submaximal SLAMF7 CAR T cell expansion during manufacturing. Here, we determined the effect of using an anti-SLAMF7 antibody (aSF7-mAb) to shield SLAMF7 on T cells on the yield and potency of SLAMF7 CAR T cells in preclinical campaigns.

Methods: We generated SLAMF7 CAR T cells following the cGMP-compliant manufacturing protocol of the CARAMBA trial. Different concentrations of aSF7-mAb were added to the culture medium after SLAMF7 CAR gene-transfer, replenished every 2nd day and removed either mid-way or at the end of the manufacturing process. We performed $n = 4$ manufacturing and release campaigns with extensive phenotyping and functional testing.

Results: We found that the addition of aSF7-mAb had a profound and consistent positive effect on SLAMF7 CAR T cell manufacturing. At the end of the manufacturing campaign, the total expansion factor of T cells treated with aSF7-mAB was 9.3 instead of 2.0 with the conventional process, and both methods resulted in a comparable gene transfer rate.

aSF7-ab addition exerted the strongest effect (in preventing fratricide) immediately after gene-transfer, evidenced by a higher proportion of viable T cells.

At the end of manufacturing, SLAMF7 CAR T cells had a SLAMF7-negative phenotype, suggesting that fratricide had still occurred but at a pace and extent that was compatible with productive proliferation and expansion. Phenotypic analysis showed that a sizeable fraction of SLAMF7 CAR+ T cells had lower expression of PD-1, TIM-3 and LAG-3 after treatment with aSF7-mAb.

Of particular note, we observed strong anti-myeloma efficacy of SLAMF7 CAR T cells that had been treated with aSF7-mAb.

In particular, we found greater proliferation of SLAMF7 CAR T cells after stimulation with multiple myeloma target cell lines, indicating substantially improved T cell fitness.

Conclusions: Taken together, the data show that the addition of aSF7-mAb to shield SLAMF7 on T cells substantially facilitates the manufacturing of SLAMF7 CAR T cells for adoptive therapy of multiple myeloma. The prevention (or rather: the steering of controlled fratricide) leads to increased yield, augmented phenotype and anti-myeloma function in pre-clinical models.

These data suggest that SLAMF7 CAR T cells produced with this improved protocol will also confer superior anti-myeloma efficacy in a clinical setting.

The aSF7-mAb is available in pharmaceutical grade and be seamlessly incorporated into cGMP manufacturing processes for the next generation of trials under the CARAMBA IND.

Disclosure: Nothing to declare

Cellular therapies other than CARs

O038

Off-the-shelf invariant natural killer T cell immunotherapy is feasible, safe and promotes regulatory and cytotoxic host immune cells in the dog

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Background: Allogeneic invariant natural killer T cells (allo-iNKT) are an attractive cancer immunotherapy platform as they do not

induce GVHD and suppress alloreactive cells, while promoting anti-tumor functions. Adoptive transfer of allo-iNKTs could also improve transplant outcomes by preventing graft rejection and providing anti-pathogen protection. Since murine systems cannot fully recapitulate human iNKT biology, the mechanisms of action of human allo-iNKTs, along with their safety and optimal protocols for therapeutic use, remain poorly understood. Dogs have proven a valuable translational model, historically superior to rodents in developing protocols for human allo-transplant. Hence, we investigated the feasibility, safety, and effects of allo-iNKT adoptive transfer in the dog as a means to inform human trial design.

Methods: We established a protocol to detect, isolate and expand canine iNKTs ex vivo. We comparatively evaluated the phenotype and function of canine and human iNKTs by flow cytometric immunoassays and single-cell RNA-sequencing (scRNA-seq). We generated a bank of cryopreserved iNKTs from 9 healthy dogs. A trial was designed to evaluate the safety of allo-iNKT transfer into unrelated canine recipients by clinical, hematological and biochemical parameters. Effects on host immune populations were monitored by flow cytometry.

Results: Purified iNKTs from nine dogs were successfully expanded to clinical scale within 3–4 weeks (mean: 4.95×10^8, SEM: 9.45×10^7, min: 2.09×10^8, max: 9.56×10^8). Immunophenotypic and functional characterization revealed that canine and human iNKTs have comparable phenotype, CD1d-specific proliferative response and cytotoxic activity against $CD1d^+$ targets. In addition, scRNA-seq demonstrated that iNKT immunomodulatory and metabolic profiles were also similar in both species. For adoptive transfer, we selected an iNKT product from a female donor with excellent ex vivo expandability (nearly 10^6-fold increase in 3.5 weeks) and cytotoxic potential (predominant $CD8^+$ subset and killer and Th1 features over Th2). 4×10^8 unedited allo-iNKTs were infused into an unrelated, 30 kg male dog after non-lymphodepleting preconditioning (cyclophosphamide 250 mg/m^2). The treatment was well tolerated, with no side effects or cytokine release syndrome. Within 24 h, peripheral blood (PB) iNKTs showed more than 5-fold increase. Neutrophils and monocytes decreased over the next 10 days while lymphocytes steadily increased. Lymphoblast-like cells appeared 7 days after allo-iNKT therapy, consistent with expansion of autologous NK cells, as assessed by flow cytometry. Blood counts and flow cytometry also showed expansion of $CD8^+$T, Treg and MDSC cells. Bone marrow (BM) assessment 2 weeks after infusion revealed a higher frequency of natural $Helios^+$ Tregs, while persisting signs of lymphoid activation and expansion of $NKp46^+$ cells were observed 1 month later. Another dog treated with the iNKT agonist alpha-GalactosylCeramide instead of allo-iNKTs showed only mild and transient iNKT and Treg increases in the PB.

Conclusions: For the first time, we have shown that canine iNKTs recapitulate human iNKT biology, making dogs suitable for clinically relevant iNKT studies. Off-the-shelf canine iNKTs can be generated to scale, cryopreserved and safely transferred. Allo-iNKTs induced autologous regulatory and killer cells in vivo, consistent with simultaneous anti-GVHD and pro-GVT potential, paving the way to evaluate allo-iNKT protocols and mono/combination therapies in canine patients to inform human clinical use.

Disclosure: Nothing to declare

O039

Multistate analysis of allogeneic HSCT in patients ≥70 years compared to population mortality based on the German Registry for Stem Cell Transplantation (DRST)

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Background: Hematologic diseases curable by allogeneic hematopoietic stem cell transplantation (alloHSCT) often occur at higher ages. Outcomes data in this situation are scarce.

Methods: Epidemiology and outcomes of patients ≥70 years undergoing alloHSCT in Germany 1999–2019 and registered with the DRST/EBMT database were analyzed retrospectively. Baseline data were collected from MED-A forms. For calculation of baseline mortality, the human mortality database was used (1 November 2021).

Results: Between 1999 and 2019, 1648 patients aged ≥70 years (median 72, range 70–79.7; 585 female) were transplanted in 50 German centers. More than 90% of these were transplanted 2010–2019. Centers transplanted 2–192 patients, with 14 centers contributing <10 and 4 centers contributing >100 patients each. Most patients suffered acute leukemia ($n = 1084$, 65.8%) or MDS and MPN ($n = 410$, 24.9%). Karnofsky index before start of conditioning was 80-100% ($n = 1361$, 90.1%) and <80% ($n = 149$, 9.9%). Myeloablative conditioning was chosen in 27.1% ($n = 420$). Total body irradiation was used for 18.6% ($n = 305$). Conditioning contained antithymocyte-/lymphocyte-globulin in 70.2%. Donors were unrelated for 85.6%. Median donor age was 34.3 (18–79) years. Patient CMV IgG was positive in 64.1%, the constellation 'negative donor, positive patient' was present in 20.5%. Frequency of acute graft versus host disease (GvHD) until day 100 was 46.9% and chronic GvHD until end of follow-up 27.9%.

Median overall (OS) and disease-free survival (DFS) was 408/295 days. With a median follow-up of 1088 days [95% CI 1011–1184, reversed Kaplan–Meier, completeness of follow-up 54.3%], Kaplan–Meier estimates of OS/DFS were 52.6%/46.2% and 40.9%/36.6% at 1 and 2 years. In a competing risk analysis, cumulative incidence of non-relapse-mortality (NRM)/relapse (RI) was 32.84%/20.95% at 365 days. Hazard exceeding that of a stratified healthy German control population was plotted after kernel smoothing within an additive model. Since hazard values were stably low after 2 years, multistate models with respect to population mortality were built not only for the first 2 years after HSCT but also in a landmark fashion after 2 years without an event in disease-free survival. One/two years after HSCT, 46.3%/36.8% remained alive+relapse-free, 6.5%/4.4% were alive in relapse, 1.6%/2.6% died due to population mortality while 13.5%/19.7% had died after relapse. Thus, NRM excluding population mortality is 32.0%/36.3%. Population mortality after relapse was estimated to be 1.3‰/2.6‰. The course of the patients that were alive +relapse-free at 2 years (36.7%) was modeled similarly. One/two years after landmark (three/four years after HSCT), 88.1%/76.3% were alive+relapse-free, 4%/7.1% were alive in relapse, 2.5%/5.3%

died due to population mortality, 4.3%/7.7% had died of NRM excluding population mortality while 1.1%/3.4% had died after relapse.

Conclusions: AlloHSCT is increasingly used to treat elder patients in Germany during the last decade. OS and DFS is fair in an elder cohort but NRM raises concerns. With extending disease-free survival time, the contribution of baseline population mortality to mortality increases. Further studies on the influence of age should include relative survival.

Ethic consent no. 291/2021BO2 (University of Tuebingen).

Disclosure: Nothing to declare

O040

A phase 1/2a study of decidual stromal cells for the treatment of COVID-19 ARDS

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Background: Acute respiratory distress syndrome (ARDS) in COVID-19 is associated with high mortality. Decidual stromal cells (DSC) are known to exert immunomodulatory and anti-inflammatory effects and could yield beneficial effects in COVID-19 ARDS. The objective of this study was to determine safety and explore efficacy of DSC infusions in ventilated subjects with COVID-19 ARDS. Here we provide a preliminary report on our phase 1/2a single arm trial conducted between December 2020 and May 2021.

Methods: Nineteen subjects received 1×10^6 DSC/kg intravenously within 72 h of initiation of mechanical ventilation along with best standard of care. Primary endpoint was safety (adverse events [AEs]) and efficacy. Secondary endpoints included survival at Day 28, ventilator free days at day 28, length of ICU stay and duration of hospitalization.

Results: Seven patients received a second infusion of DSCs between Day 5 and 8 while 12 could not receive a second dose (transfer to another hospital, $n = 10$, or need for ECMO, $n = 3$). Median age was 54 years (25–70) and 11/19 (57%) were male; comorbidities included obesity ($n = 8$), asthma ($n = 7$), diabetes mellitus ($n = 4$) and hypertension ($n = 4$). Baseline median P/F ratio at first DSC infusion was 118.7 (68–200). One patient experienced a transient hypoxic event that was judged as probably related to the DSC infusion; other possibly related grade 3–4 SAEs included ARDS, transient hypoxia, pulmonary embolism and hypoxemia. SAEs that were deemed unrelated included bacteremia ($n = 4$), ventilator-associated pneumonia ($n = 2$) and pneumonia ($n = 3$). SARS-CoV-2 viral RNA was positive in plasma of one patient. Overall, DSC infusions in COVID-19 ARDS were found to be safe. P/F ratio increased from median 123 (95% CI: 113.8–144.8) to 160 (95% CI: 136.8–205.9) from D-1 to D+5 post DSC, $p = 0.03$. Overall survival was 84.2% (95% CI: 58.7–94.6%). All 7 patients that received 2 doses survived vs 75% (40.8–91.2) survival for one dose. Seven patients treated within 48–72 h of intubation had 100% survival vs those treated within 48 h, $n = 12$, 75% (40.8–91.2) survival.

Conclusions: In conclusion, DSC infusion was shown to be safe in patients with severe COVID-19 ARDS and could be beneficial in treating severe disease.

Clinical Trial Registry: https://clinicaltrials.gov/ct2/show/NCT04451291

Disclosure: We have no conflicts of interest to declare

Chronic leukaemia and other myeloproliferative disorders

O041

Outcomes of allogeneic hematopoietic cell transplantation for chronic neutrophilic leukemia: a combined CIBMTR/EBMT analysis

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Background: Chronic neutrophilic leukemia (CNL) is an aggressive myeloproliferative neoplasm. Limited information is available about the role of allogenic hematopoietic cell transplantation (allo-HCT) in CNL.

Methods: The study aimed to assess the outcomes of allo-HCT in CNL. We analyzed the outcomes of patients aged ≥18 years with CNL who underwent allo-HCT from 2004 to 2018 in two transplant registries.

Results: Twenty-nine patients were included: CIBMTR ($n = 16$), EBMT ($n = 13$). The median patient age was 58 (range: 33–72) years. Pre-transplant disease status was stable disease in 11 (38%), hematological improvement in 6 (21%), complete remission in 4 (14%) and progressive disease or relapse in 3 (10%) of patients. Data on somatic mutations were available in a subset of patients. Presence of the following mutations was reported in the database: *CSF3R* ($N = 9$), *ASXL1* ($N = 3$), *DNMT3A* ($N = 1$), *IDH2* ($N = 1$), *SETBP1* ($N = 3$), *SRSF2* ($N = 2$), *CUX1* ($N = 1$), *SF3B1* ($N = 2$), *RUNX1* ($N = 1$). The median follow-up was 71 (range: 25–161) months and the median time from diagnosis to transplant was 11 (range: 3–65) months. Splenomegaly was reported in 8 (28%) and 16 (66%) pts received pre-transplant hydroxyurea.

Most patients ($N = 27$, 93%) received peripheral blood stem cell graft from an HLA matched sibling ($N = 12$, 41%) or HLA 8/8 unrelated ($N = 10$, 34%) donor with myeloablative ($N = 19$, 66%) conditioning. Calcineurin-inhibitor-based GVHD prophylaxis was used in 22 (76%) patients. Neutrophil engraftment was achieved in 27 pts at a median of 16 days (range: 1–34). The non-relapse

mortality was 10.5% (95% CI: 2–24.1%) at 1 year and 13.8% (95% CI: 3.7–28.9%) at 4 years. The relapse incidence was 31% (95% CI: 15.5–49.2%) at 1 year and 34.5% (95% CI: 18.2–52.9%) at 4 years. The estimated disease-free survival and overall survival were 58.6% (95% CI: 40.5–75.6%) and 69% (95% CI: 51.3–84.2%) at 1 year and 51.7% (95% CI: 33.8–69.4%) and 55.2% (95% CI: 37.1–72.5%) at 4 years, respectively (Fig. 1).

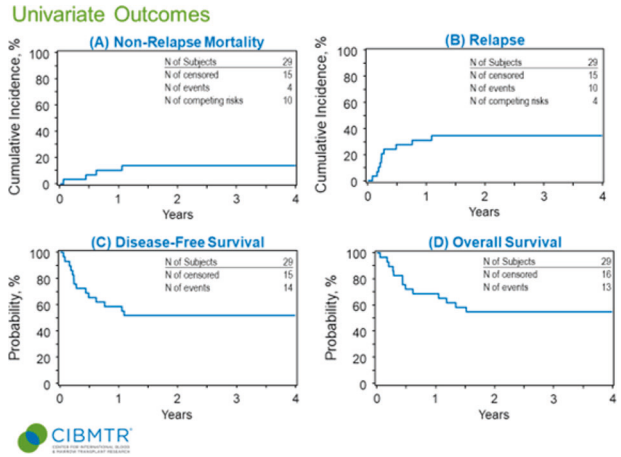

Figure 1. Non-relapse mortality (**A**, NRM), relapse incidence (**B**, RI), disease-free survival (**C**, DFS), and overall survival (**D**, OS).

Conclusions: In this registry-based, retrospective study, allo-HCT resulted in significant long-term disease-free and overall survival with acceptable nonrelapse mortality among patients with CNL. These results confirm allo-HCT as a potentially curative therapy in CNL.

Clinical Trial Registry: NA.

Disclosure: BD: institutional research funding: Takeda, Janssen, Angiocrine, Pfizer, Poseida, MEI, Sorrento.

Consultancy: Jazz, Celgene, Gamida Cell.

Conditioning regimens

O042

TBI/fludarabine versus busulfan/fludarabine as a myeloablative conditioning for adults with acute myeloid leukemia treated with allo-HCT. A study from the ALWP of the EBMT

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Background: Allogeneic hematopoietic cell transplantation (allo-HCT) is widely used for the treatment of patients with acute myeloid leukemia (AML) who are at high risk of relapse. Standard myeloablative regimens include the use of either busulfan (Bu) or total body irradiation (TBI) in combination with cyclophosphamide (Cy). More recently, Cy is frequently substituted with fludarabine (Flu) to reduce regimen toxicity. The goal of this retrospective study is to compare TBI at a dose of 12 Gy combined with Flu (FluTBI12Gy) versus intravenous Bu at a dose of 12.8 mg/kg (4 days) plus Flu (FB4) as a myeloablative conditioning before allo-HCT in AML patients.

Methods: Overall, 121 and 3082 adult patients with AML transplanted in first or second complete remission (CR) receiving FluTBI12Gy or FB4, respectively, between years 2009 and 2020 met the inclusion criteria. Statistical analysis was restricted to populations matched according to donor type (matched sibling/unrelated), disease status at allo-HCT (CR1/CR2), cytogenetic risk group, and stem cell source (bone marrow/peripheral blood). A final matched-pair analysis included 109 patients treated with FluTBI12Gy and 213 patients given FB4.

Results: Patient, donor, and transplant-related characteristics were comparable between the two conditioning groups. Median patient age was 41 years in both groups. The proportion of patients treated in CR1/CR2 was 78%/22%. Unrelated donor-HCT was performed in 78% of patients. The probabilities of leukemia-free survival (LFS) and overall survival (OS) at 2 years in FluTBI12Gy and FB4 groups were 65% vs. 60% ($p = 0.64$), and 70% vs. 72% ($p = 0.87$), respectively. The cumulative incidence of relapse (RI) was 19% vs. 29% ($p = 0.11$), while non-relapse mortality (NRM) was 16% vs. 11%, respectively ($p = 0.13$). There were no statistically significant differences between the FluTBI12Gy and FB4 groups with respect to the incidence of grade 2–4 and grade 3–4 acute graft-versus-host disease (GVHD) (18% vs. 24%, and 8% vs. 6%, respectively). The incidence of overall chronic GVHD was 42% vs. 34% ($p = 0.2$) and the incidence of extensive chronic GVHD was 16% in both study groups. The probability of GVHD-free, relapse-free survival (GRFS) was 49% for both groups.

Conclusions: FluTBI12Gy and FB4 are associated with similar RI, NRM, LFS, OS and GRFS in patients with AML in CR1 or CR2 before allo-HCT. Survival rates are encouraging for both regimens. These results do not provide evidence for advantage of one regimen over another.

Disclosure: Nothing to declare

O044

GVHD and GFRS in patients with AML undergoing allogeneic transplantation with treosulfan- versus busulfan-based conditioning: a subgroup analysis of the randomized phase III MC-FludT.14/L trial

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Background: The randomized phase III trial MC-FludT.14/L (NCT00822393, Beelen et al., Lancet Haematol. 2020) prospectively compared a conditioning regimen with treosulfan/fludarabine (FT10) in elderly and/or comorbid AML and MDS patients with the reduced-intensity conditioning regimen busulfan/fludarabine (FB2). In this post hoc subgroup analysis for AML patients in the full analysis set, graft-versus-host disease (GvHD) and GvHD- and relapse-free survival (GRFS) are presented.

Methods: In the MC-FludT14/L Trial AML patients with a comorbidity index (HCT-CI) of >2 and/or age ≥50 years were stratified based on cytogenetic/molecular risk group, donor type, and transplant center. Patients were randomized to receive either 10 g/m^2 BSA intravenous (IV) treosulfan (days –4, –3, –2) or 3.2 mg/kg IV busulfan (days –4, –3), both combined with 30 mg/m^2 IV fludarabine (days –6 to –2). Primary endpoint was event-free survival (EFS; events: disease recurrence, graft failure, or death). Secondary endpoints included engraftment, completion of donor chimerism, overall survival (OS), relapse/progression incidence (RI), non-relapse mortality (NRM), GvHD, GRFS and safety. The composite endpoint GRFS was recorded as the time from HSCT to the incidence of acute GvHD of at least grade III, extensive chronic GvHD, relapse/progression, or death (whatever comes first).

Results: Median age of the 352 AML patients in the full analysis set (184 FT10, 168 FB2) was 60 years (range 31-70 years). Primary neutrophil recovery at day +28 was comparable for both groups (97%), while the rate of complete donor-chimerism (day +28) was numerically higher after FT (94.5% vs. 87.5%). At 2 years, the differences between FT10 and FB2 in Kaplan–Meier estimates of EFS and OS were significantly in favour of treosulfan (64.7% vs 53.3%; $p = 0.01$, and 72.8% vs 64.7%; $p = 0.03$, respectively).

The incidences of acute GvHD (all grades, up to 100 days) and for acute GvHD grade III-IV were similar in the FT10 and FB2 treatment arms (51.6% vs 53.6% and 2.7% vs 5.4%). While cGvHD was comparable in both groups (61.1% for FT10 vs. 54.9% for FB2), the cumulative incidence of extensive cGvHD at 2 years was significantly lower in patients receiving FT10 compared to FB2 (15.1% vs. 28.1%, $p = 0.01$). This difference was especially pronounced in high risk patients or patients in CR >1 (12.9% vs. 30.9%; $p = 0.02$). NRM favoured the treosulfan treatment group (8.4% vs. 14.7%; $p = 0.13$), with mortality attributed to GvHD occurring in 2.7% of patients who received FT10 vs 6.5% for FB2. GRFS at 2 years was significantly in favour of treosulfan (52.9% vs. 39.6%, $p = 0.02$).

Conclusions: Our subgroup analysis of AML patients included in this prospective phase III trial favours FT10 conditioning treatment before alloHCT in adult AML not eligible for myeloablative conditioning. The rate of extensive chronic GvHD and for the composite endpoint GRFS significantly favoured FT10 over FB2. Overall, the AML subgroup analysis demonstrated a clinically relevant benefit for the new treosulfan conditioning regimen in elderly and/or comorbid AML patients.

Clinical Trial Registry: NCT00822393. https://clinicaltrials.gov/ct2/show/NCT00822393

Disclosure: FS received travel grants from medac and has served on ad boards for medac. DB received honoraria for consultancy, a grant for study patient documentation, speaker fees, and travel support from medac. EMWD received travel grants from medac. WB received travel grants from medac.

O045

Treosulfan-based compared to thiotepa-busulfan-fludarabine conditioning for haploidentical transplant in patients with acute myeloid leukemia. A study from the Acute Leukemia Working Party of the EBMT

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Background: A treosulfan-based conditioning regimen has been associated with reduced non-relapse mortality (NRM) and promising outcome in patients with acute myeloid leukemia (AML) in the setting of transplantation (HSCT) from matched sibling or unrelated donors.Nevertheless, little data is available in the context of haploidentical transplant.

Methods: We included adult AML patients who had received treosulfan-based (Treo) or thiotepa-busulfan-fludarabine (TBF) conditioning as the preparatory regimen for haploidentical transplantation in first or second complete remission (CR1 or CR2) between 2010 and 2020. Only patients who received post-transplant cyclophosphamide as graft-versus-host disease (GVHD) prophylaxis were included in the analysis. Myeloablative conditioning (MAC) was defined as a busulfan dose of 9.6 mg/kg for TBF (TBF-MAC) and a treosulfan dose of 42 g/m^2 for Treo (Treo-MAC).Reduced intensity conditioning (RIC) was defined as a busulfan dose of 6.4 mg/kg for TBF (TBF-RIC) and a treosulfan dose less than or equal to 36 mg/m^2 for Treo (Treo-RIC). A 1:1 matched-pair analysis was performed using the main patient characteristics as matching factors.

Results: A total of 1123 patients met the inclusion criteria (155 received Treo and 968 TBF).

The matched pair analysis was performed on 142 Treo and 142 TBF patients. Median follow-up was 18 and 15 months in the Treo and TBF groups, respectively. Engraftment rate was 95% in both groups. We

observed a trend towards lower incidence of grade II-IV acute (a) GVHD in the Treo group (20 ± 6%) as compared to TBF (29 ± 8%, $p = 0.08$), while incidence of grade III-IV aGVHD did not differ. Similarly, the 2-year incidence of chronic (c) GVHD and severe cGVHD was not statistically different, being 41 ± 10% vs 32 ± 9% ($p = 0.14$) and 12 ± 6% vs 13 ± 6% ($p = 0.9$) in Treo vs TBF, respectively.

The 2-year relapse incidence (RI) was 18 ± 6% in Treo and 16 ± 7% in TBF ($p = 0.9$). The 2-year non-relapse mortality (NRM) was 14 ± 6% in Treo and 19 ± 6% in TBF ($p = 0.4$). Leukemia-free survival (LFS) and overall survival (OS) were 68 ± 10% vs 65 ± 8% ($p = 0.6$) and 76 ± 8% vs 73 ± 10% ($p = 0.5$) in Treo vs TBF, respectively.The 2-year GVHD-free, relapse-free survival (GRFS) was 53 ± 9% in Treo and 54 ± 10% in TBF ($p = 0.8$). Among patients who received a MAC regimen,RI was 17 ± 13% in Treo-MAC and 19 ± 8% in TBF-MAC ($p = 0.9$). NRM was the same in both groups, being 15 ± 7% ($p = 0.9$).LFS and OS were 68 ± 11% vs 66 ± 9% ($p = 0.8$) and 75 ± 8% vs 77 ± 8% ($p = 0.8$) in Treo-MAC vs TBF-MAC, respectively.

Among patients who received a RIC regimen, RI was 20 ± 13% in Treo-RIC and 13 ± 7% in TBF-RIC ($p = 0.7$), while NRM was 13 ± 7% in Treo-RIC and 24 ± 10% in TBF-RIC,respectively ($p = 0.2$).LFS and OS were 67 ± 10% vs 64 ± 8% ($p = 0.6$) and 77 ± 8% vs 68 ± 10% ($p = 0.3$) in Treo-RIC vs TBF-RIC, respectively.

Conclusions: These data confirm that TBF represents a valid preparatory regimen for haploidentical transplant in patients with AML in remission, providing acceptable NRM and good survival.-Treosulfan-based conditioning seems to provide a valid alternative which is associated with similar outcomes to TBF and warrants further investigation in this setting.

Disclosure: Nothing to declare

O046

Graft-versus-host disease (GVHD) and GVHD-free/relapse-free survival (GRFS) in patients with myelodysplastic syndrome (MDS) after treosulfan- versus busulfan-based conditioning and allogeneic hematopoietic cell transplantation (alloHCT)

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Background: To date, alloHCT is the only treatment with a curative potential for patients with MDS; however, the optimal conditioning regimen has not yet been defined. The phase III study NCT00822393 (Beelen et al. Lancet Haematol. 2020) prospectively compared a conditioning regimen with treosulfan/fludarabine (FT10) in elderly and/or comorbid AML and MDS patients with the RIC regimen busulfan/fludarabine (FB2). This post hoc subgroup analysis for MDS patients assesses the influence of risk group on outcome parameters.

Methods: In the MC-FludT.14/L trial MDS patients with a comorbidity index (HCT-CI) >2 and/or age ≥50 years were stratified according to disease risk (IPSS-R), donor type, and participating institution. Patients with matched related or unrelated donor were randomised to receive either 10 g/m^2 BSA intravenous (IV) treosulfan (day −4, −3, −2) or 3.2 mg/kg IV busulfan (day −4, −3), both combined with 30 mg/m^2 IV fludarabine (day −6 to −2). Primary endpoint was event-free survival (EFS; events: disease recurrence, graft failure, or death). Secondary endpoints included overall survival (OS), relapse/progression incidence (RI), non-relapse mortality (NRM), chimerism, GvHD, GRFS, and safety.

Results: Median age of the 199 MDS patients in the full analysis set (84 FT10, 115 FB2) was 61 years (range: 41–70). No significant difference of patients or disease characteristics between the FT10 and FB2 group observed. A total of 53% of the patients were at high/very high risk (HR/VHR), 27% intermediate risk (IR) and 20% low/very low risk MDS, respectively. Overall, the Kaplan–Meier estimate of EFS at 2 years was significantly better for FT10 compared to FB2 in (68.1% vs 48.2%; $p = 0.048$). OS, GvHD-free and relapse-free survival, cumulative incidences of relapse/progression and NRM showed a trend (n.s.) towards a more favourable outcome in the FT10 group (72.8% vs 53.7%, 44.5% vs. 33.6%, 10.8% vs 19.6%, and 19.9% vs 28.7%). The cumulative incidence of acute GvHD (all grades, up to 100 days) was similar in the two treatment groups, as was cGvHD after 2 years.

Analysis by IPSS-R showed that particularly high/very high risk patients revealed a significantly improved EFS for treosulfan (67.2% vs 30.5%; $p = 0.013$) and compared favourable for GRFS (43.0% vs 22.2%, $p = 0.055$) as well as chronic GVHD-free/relapse-free survival (cGRFS; 47.4% vs. 22.1%; $p = 0.013$).

Conclusions: MDS patients included in this prospective phase III alloHCT trial showed a better survival outcome after FT10 compared to FB conditioning. Overall rates of acute and chronic GvHD were roughly comparable, while FT10 especially in high and/or very high-risk patients was significantly in favour regarding GRFS as well as cGRFS. The subgroup analyses in MDS support the meaningful clinical benefit for the new FT10 regimen in elderly and/or comorbid MDS patients.

Clinical Trial Registry: NCT00822393.

Disclosure: MS: speaker fees, and travel support from medac GmbH. DB: honoraria for consultancy, a grant for study patient documentation, speaker fees, and travel support from medac GmbH. WB: travel grants from medac GmbH. FS: travel grant und speaker fee from medac GmbH. FC: speaker fee from medac GmbH.

Experimental transplantation and gene therapy

O047

Hematopoietic stem cell transplant for Krabbe disease is augmented by addition of intravenous AAV gene replacement therapy

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Background: Early Infantile Krabbe disease is an aggressive, monogenic neurodegenerative disorder leading to death by the age of 2 if left untreated. The standard of care for patients is

allogeneic hematopoietic stem cell transplantation (HSCT) which can stabilize cognitive decline and significantly improve long-term outcomes, but is ultimately not curative due to peripheral neuropathy that continues to worsen over time.

Methods: We have developed an AAV (galactosylceramidase, GALC) gene replacement therapy, FBX-101, that is delivered by intravenous administration after allogeneic HSCT. This complementary HSCT/AAV approach has been evaluated in safety and efficacy studies in various naturally occurring animal models of the disease as well as in a long-term rat GLP toxicology study. Conditioning protocols similar to those used in humans were developed for immunosuppression and allogeneic HSCT in murine and canine models of Krabbe disease or for wildtype rat.

Results: **Murine** Compared to untreated GALC-knockout mice, intravenous AAV or transplant alone increased median survival by 61% and 86% respectively (both $p < 0.0001$ compared to untreated groups). Treatment with both transplant and AAV together increased survival by 697% ($p < 0.0001$ compared to either treatment alone), demonstrating superiority of the combination of the treatments. The dose dependence was determined over a 400-fold range from 4×10^{11} to 1.6×10^{14} gc/kg. Age of administration and timing interval between transplant and AAV were also explored in this murine model.

Canine Naturally occurring GALC-knockout canines received transplant with AAV gene replacement and were compared to dogs receiving either treatment alone. Dogs receiving transplant alone survived 9–13 weeks and dogs receiving AAV alone survived 23–55 weeks. Dogs receiving transplant followed by AAV survived 82–104 weeks of age. Dogs receiving transplant with AAV showed improvement in survival and promising disease correction compared to untreated dogs: lack of hind limb ataxia/paralysis, incontinence, hearing loss as well as reduced brain demyelination (by MRI) and correction of peripheral nerve conduction velocities to the normal range.

Rat safety of unrelated donor transplant with FBX-101 AAV at several dose levels was evaluated in a 6-month GLP safety study in rat.

Conclusions: The preclinical studies demonstrate that the administration of AAV (FBX-101) following HSCT is a safe and highly effective approach to address both of the CNS and PNS manifestations of Krabbe disease.

Clinical Trial Registry: RESKUE (ClinicalTrials.gov NCT04693598) is active and enrolling pre-symptomatic children with early infantile Krabbe Disease from birth to 1 year old that are candidates for HSCT. Two cohorts of three children each will test intravenous 3×10^{13} vg/kg (Cohort 1) and 8×10^{13} vg/kg (Cohort 2). Follow-up will be 2 years, with primary endpoints including safety and HSCT incidence of engraftment and secondary time to independent sitting and gross motor function improvements.

Disclosure: The University of Pittsburgh and two investigators, ME and PS, have financial interests in Forge Biologics, the company that is sponsoring this study. Therefore, both are sub-investigator of the trial with limited responsabilities defined by a Conflict of Interest Management Plan (CMP) developed by the University of Pittsburgh Conflict of Interest Committee (COIC).

O048

Glycolytic enzyme PFKFB3 determines bone marrow endothelial progenitor cell damage post chemotherapy and irradiation

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Background: Chemotherapy, irradiation and allogeneic hematopoietic stem cell transplantation (allo-HSCT) are commonly utilized in patients with hematopoietic cancers. However, many patients who undergo the therapies will suffer poor hematopoietic function characterized by delayed hematopoiesis recovery, resulting in prolonged cytopenia and increased risk of infections, bleeding and hospitalization. Due to the unclear pathogenesis of poor hematopoietic function, the optimal therapeutic approaches have not been well established. Endothelial cells (ECs), a key component of BM microenvironment, plays an essential role in regulating hematopoietic stem cell (HSC) homeostasis. Except to the malignant cells, chemo-radiotherapy also damages HSCs and their supportive BM microenviroment, especially ECs. Previous murine studies combined with our serial translational researches (2013 BBMT, 2015 BMT, 2016 Blood, 2019 Blood Advances, 2020 EBM) reported that BM EC damage contributes to impaired hematopoiesis recovery after chemo-radiotherapy and allo-HSCT, whereas improvement of BM ECs promotes hematopoietic reconstitution. Considering that repair of BM ECs is a prerequisite for hematopoietic recovery, it is critical to identify the mechanism underlying BM EC damage to promote hematopoietic recovery.

Methods: To determine the glycolysis status of damaged BM endothelial progenitor cells(EPCs) derived from PGF, a clinical model of EPC damage-associated poor hematopoiesis after allo-HSCT, the expression of key glycolytic enzyme PFKFB3 was analyzed by flow cytometry. Glycolysis levels were measured by glucose consumption and lactate production assays. To further validate the role of defective metabolism in BM EPC damage and the underlying mechanism, well-established BM EPC damage models in vitro and in vivo and in a BM EC-specific PFKFB3 overexpression murine model were used. To investigate therapeutical potential of glycolysis inhibitor to damaged BM EPCs, glycolysis inhibitor was administrated to the BM EC-specific PFKFB3 overexpression murine model and cultivated BM EPCs derived from PGF and patients with acute leukemia post chemotherapy.

Results: Enhanced glycolytic enzyme PFKFB3 was demonstrated in the damaged BM EPCs of patients with poor graft function (PGF). Moreover, glycolysis inhibitor 3PO alleviated the damaged BM EPCs of PGF in vitro. Consistently, PFKFB3 overexpression triggered BM EPC damage after 5FU treatment and impaired hematopoiesis-supporting ability in vitro. Mechanismly, PFKFB3 facilitated pro-apoptotic transcription factor FOXO3A and its downstream gene expressions, including P21, P27, FAS after 5FU treatment in vitro. Moreover, PFKFB3 induced NF-κB activation and its downstream adhesion molecule E-selectin expression, while reduced hematopoietic factor SDF-1 expression, which could be rescued by FOXO3A silence. Highly expressed PFKFB3 was found in damaged BM ECs of chemo-radiotherapy-induced myelosuppression murine models. Furthermore, the BM EC-specific PFKFB3 overexpression murine model demonstrated that PFKFB3 aggravated BM EC damage, and impaired hematopoiesis recovery after chemotherapy in vivo, which could be improved by 3PO, indicating a critical role of PFKFB3 in regulating BM EC damage. Clinically, PFKFB3-induced FOXO3A expression and NF-κB activation were confirmed to contribute to the damaged BM EPCs of patients with acute leukemia after chemotherapy. 3PO repaired the damaged BM EPCs by reducing FOXO3A expression and phospho-NF-κB p65 in patients after chemotherapy.

Conclusions: Therefore, our studies suggest a critical role of PFKFB3 in triggering BM EPC damage and indicate that endothelial-PFKFB3 may be a potential therapeutic target for myelosuppressive injury.

Disclosure: Nothing to declare

O049

Comparison of fludarabine plus reduced versus myeloablative dose busulfan in patients with non-Hodgkin lymphoma

undergoing allogeneic hematopoietic stem cell transplantation

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers a possible cure for some patients with Non-Hodgkin lymphoma (NHL); however, it is associated with high non-relapse mortality (NRM). Fludarabine and a reduced dose of busulfan (FB2), and fludarabine and a myeloablative dose of busulfan (FB4) are commonly used in allo-HSCT. Several studies have compared the use of FB2 and FB4 in the treatment of patients with hematological malignancies. However, little data is available on their use in patients with NHL. Therefore, this study aimed to investigate how the dose of busulfan affects the outcome by comparing FB2 and FB4 in patients with NHL undergoing allo-HSCT.

Methods: This study included 415 adult patients with NHL who received allo-HSCT following FB2 or FB4 for the first time between January 2008 and December 2019. FB2 consisted of fludarabine (125–180 mg/m^2) and intravenous busulfan (6.4 mg/kg), and FB4 consisted of fludarabine (125–180 mg/m^2) and intravenous busulfan (12.8 mg/kg). Additional total body irradiation at a low dose was permitted.

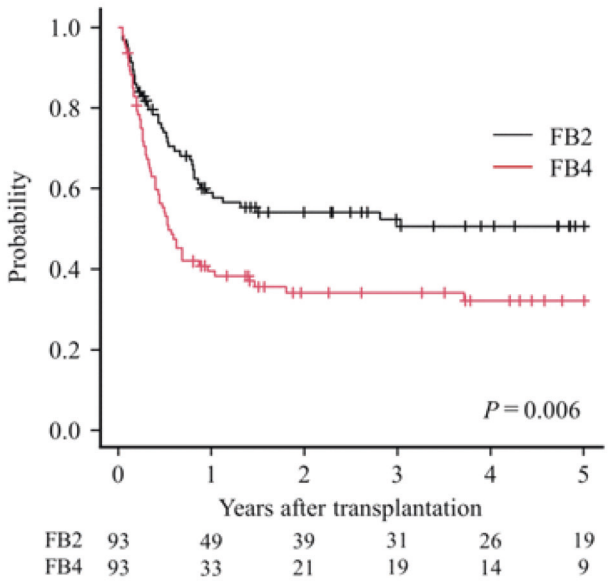
Missing data were imputed by the single imputation method using the "missForest" package. We performed the propensity score (PS) matching analysis to adjust the patient background characteristics and eliminate potential confounders. The PS was calculated by logistic regression using the confounding factors, which were selected clinically according to previous studies. PS matching was applied with the nearest neighbor matching method using calipers of width equal to 0.2. All analyses were performed using the PS matching cohort.

The primary endpoint was the 5-year overall survival (OS), and secondary endpoints were the 5-year progression-free survival (PFS), 5-year cumulative incidence of relapse, and 5-year cumulative incidence of NRM. OS and PFS were evaluated using the log-rank test. Other endpoints were evaluated using Gray's method.

Results: A total of 415 patients, consisting of 315 who received FB2 and 100 who received FB4, were analyzed. Among them, 93 patients were classified into each of the FB2 and FB4 groups after PS matching, and the patient characteristics were well-balanced between the groups. The median age was 55 years (interquartile range, 47–60), and 110 patients (59%) were male. Of the total NHL patients, 114 (61%) belonged to the B cell type. At the time of allo-HSCT, 67 patients (36%), 46 patients (25%), and 73 patients (39%) presented with complete response, partial response, and no response, respectively. The 5-year OS was 50.6% (95% confidence interval [CI], 39.4–60.8%) and 32.2% (95% CI, 22.4–42.4%) in the FB2 and FB4 groups, respectively ($P = 0.006$) (Fig. 1). The adjusted hazard ratio was 2.13 (1.30–3.50, $P = 0.003$). The FB2 group had higher 5-year PFS (41.1% in FB2 group vs 27.5% in FB4 group, $P = 0.022$), similar 5-year cumulative incidence of relapse (38.2% vs 41.3%, $P = 0.581$), and lower cumulative incidence of 5-year NRM (15.7% vs 31.9% $P = 0.043$) compared to the FB4 group in the PS-matched cohort.

Conclusions: In the present study, the 5-year OS was higher with FB2 than FB4, owing to lower NRM.

Figure 1. Overall Survival



Disclosure: Nothing to declare

Graft-versus-host disease—clinical

O051

Ruxolitinib versus best available therapy in patients with steroid-refractory acute graft-versus-host disease: a comparison of response by organ class from the randomized, phase 3 REACH2 study

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Background: The multicenter, randomized, phase 3 REACH2 study (NCT02913261) demonstrated that ruxolitinib improved overall response rate (ORR) at Day 28 (primary endpoint; 62.3% vs 39.4%) and durable ORR at day 56 (key secondary endpoint; 39.6% vs 21.9%) vs best available therapy (BAT) in patients with steroid-refractory acute graft-versus-host disease (SR-aGVHD). In addition, day 28 ORR was superior with ruxolitinib regardless of aGVHD grade (Figure). Here we report a post hoc analysis of response by organ class.

Methods: Patients aged ≥12 years with grade II–IV SR-aGVHD were randomized to receive ruxolitinib 10 mg twice daily ($n = 154$) or investigator-selected BAT ($n = 155$). Crossover from BAT to ruxolitinib was allowed on or after day 28. Outcomes of interest in this analysis included (1) day 28 ORR (complete response plus partial response) by organ class and (2) percentage of patients with ≥1-stage improvement from baseline by organ class at days 28 and 56, excluding those with stage 0 disease at baseline. Odds ratio, 95% CI, and P values were calculated using the Cochran–Mantel–Haenszel test.

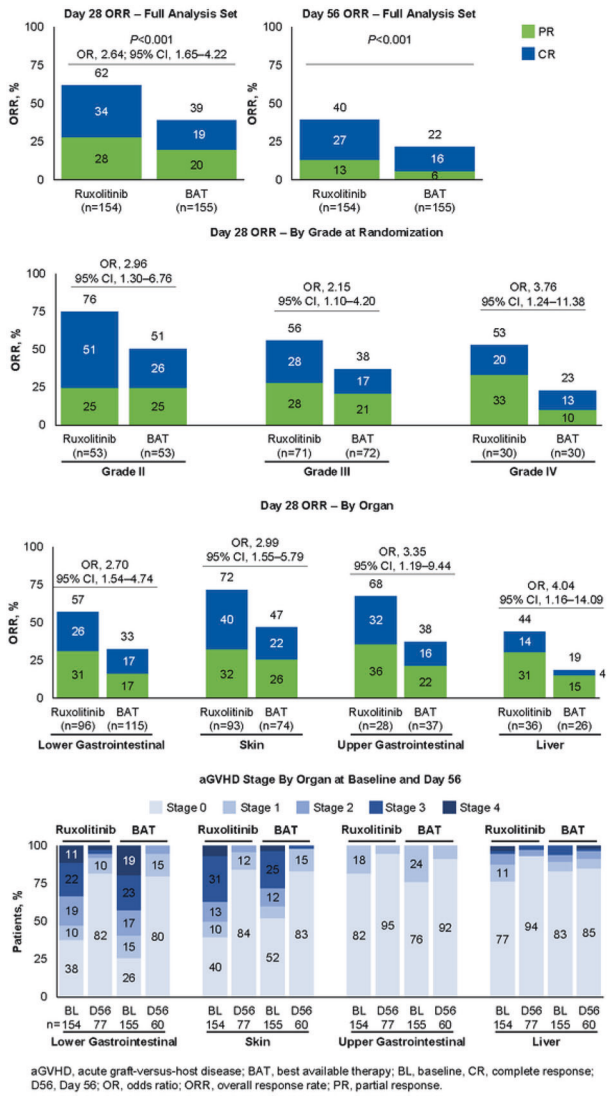
Results: Baseline characteristics are presented in the Table. Four organ classes were evaluated for response to therapy (lower gastrointestinal, $n = 211$; skin, $n = 167$; upper gastrointestinal, $n = 65$; liver, $n = 62$). All organ classes showed improvement in

day 28 ORR for patients treated with ruxolitinib vs BAT (Figure). An improvement of ≥1 stage from baseline in the ruxolitinib vs BAT groups was observed in 60.4% vs 49.6% with lower gastrointestinal involvement, 78.5% vs 59.5% (skin), 60.7% vs 56.8% (upper gastrointestinal), and 38.9% vs 23.1% (liver). At Day 56, an improvement of ≥1 stage from baseline in the ruxolitinib vs BAT groups was observed in 36.5% vs 28.7% with lower gastrointestinal involvement, 57.0% vs 43.2% (skin), 46.4% vs 35.1% (upper gastrointestinal), and 27.8% vs 15.4% (liver; Figure).

Table. Baseline characteristics

	Ruxolitinib ($n = 154$)	BAT ($n = 155$)
Age, median (range), y	52.5 (12–73)	54.0 (13–71)
Male, *n* (%)	92 (59.7)	91 (58.7)
aGVHD grade, *n* (%)		
Grade II/III/IV	53 (34.4)/71 (46.1)/30 (19.5)	53 (34.2)/72 (46.5)/30 (19.4)
Organ involvement, *n* (%)		
Lower gastrointestinal	96 (62.3)	115 (74.2)
Skin	93 (60.4)	74 (47.7)
Upper gastrointestinal	28 (18.2)	37 (23.9)
Liver	36 (23.4)	26 (16.8)

Figure. ORR and aGVHD Stage



aGVHD, acute graft-versus-host disease; BAT, best available therapy; BL, baseline, CR, complete response; D56, Day 56; OR, odds ratio; ORR, overall response rate; PR, partial response.

Conclusions: These data suggest that response rates are higher with ruxolitinib compared with BAT regardless of lower gastrointestinal, skin, upper gastrointestinal, or liver organ involvement, or aGVHD grade.

Clinical Trial Registry: ClinicalTrials.gov NCT02913261.

Disclosure: MM received grant support, lecture fees, and consulting fees from Janssen, Sanofi, and Jazz Pharmaceuticals; lecture fees from Celgene, Bristol Myers Squibb, and Takeda; lecture fees and consulting fees from Amgen; grant support from Roche; and advisory board fees from Novartis. JG, CT, and VB are employees and stockholders of Incyte Corporation. CW is an employee and stockholder of Novartis.

O052

Minnesota acute GvHD risk score defines survival at onset of acute GvHD after PTCY prophylaxis

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Background: Graft-versus-host disease (GvHD) still represent one of the major unmet needs of allogeneic stem cell transplantation (HSCT). Early identification of patients at higher risk to develop steroid-refractory acute (a-) GvHD and moreover patients at higher risk of GvHD-related-mortality is a paramount. The Minnesota group has provided a risk score model for a-GvHD classifying patients into HR (high risk) or SR (standard risk) at a-GvHD onset. Minnesota a-GvHD risk score offers a reliable stratification of patients with reference to both probability of a-GvHD overall response and transplant related mortality.

The aim of our study was to confirm the efficacy of the Minnesota risk score as a valid tool to identify patients at higher risk of mortality at onset of a-GvHD in the setting of post-transplant cyclophosphamide (PTCy).

Methods: Our analysis consisted in a prospective single-center study, involving all HSCT performed in San Raffaele Hospital who received a PTCy-based GvHD prophylaxis, for any disease in indication according to EBMT guideline, and with any donor type, between January 2016 and June 2020. Acute GvHD and chronic GvHD were graded according to MAGIC criteria and NIH 2014 criteria.

Results: Overall, 315 patients (median age 52.7 years, range 15.3–75.6) with a median follow-up of 2.4 years (range 1.4–3.5) were evaluated. The 2-year probability of OS was 66.2% (95% CI 60.4–71.4), the 2-year probability of PFS was 62.5% (95% CI 56.6–67.8). The 2-year cumulative incidence of relapse was 20% (95% CI 15.6–24.8) while the 2-year cumulative incidence of TRM was 17.5% (95% CI 1.4–22.1).

Cumulative incidences of a-GvHD grade II–IV and a-GvHD grade III–IV at day 100 were 24.8% (95% CI 26.5–37.4) and 14.9% (95% CI 11.2–19.1) respectively. The 2-year cumulative incidence of chronic GvHD was 31.9% (95% CI 26.5–37.4)—moderate/severe chronic GvHD 20%.

In multivariate analysis donor source [match related vs mismatch related HR 0.27 (95% CI 0.13–0.57, $p = 0.001$); match unrelated vs mismatch related HR 0.54 (95% CI 0.30–0.99, $p = 0.047$)] and donor age [>35-year vs ≤35-year HR 2.75 (95% CI 1.59–4.76, $p < 0.001$)] independently associate with a-GvHD grade II–IV.

Overall, 87/93 patients with SR and 29/46 patients with HR a-GvHD reached a significant overall response by day 28. In

multiple regression analysis, adjusting for clinically significant variables, the 2-year OS were lower in HR versus SR GvHD patients [57% (95% CI, 37.8–72.4) for Minnesota SR and 30.7% (95% CI, 17.4–45) for Minnesota HR, p value 0.003], conversely the 2-year TRM were higher in HR versus SR GvHD patients [20.6% (95% CI, 9.5–34.7) for Minnesota SR, 52.7% (95% CI, 36.3–66.7) for Minnesota HR, $p = 0.001$].

Conclusions: In our study, the Minnesota Risk Score was confirmed to be an excellent prognostic score for a-GvHD, providing stratification for both TRM and probability of OS, irrespective of donor source within the frame of PTCy GvHD prophylaxis.

Notably, day 28 overall response rate with current available treatment is significantly better in SR a-GvHD patients than in HR patients, strengthening the indication to candidate high-risk patients to clinical trials where possible.

Disclosure: Nothing to declare

O053

Overlap chronic graft-versus-host disease (GvHD) is associated aith an adverse prognosis: secondary analysis of the ABA2 trial

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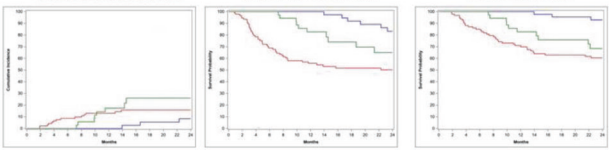
Background: The 2005 National Institute of Health GvHD consensus conference defined overlap chronic GvHD [cGvHD] as the presence of both acute and chronic GvHD features; however, there is limited and inconsistent data regarding outcomes in patients with overlap compared to classic cGvHD.

Methods: We performed a secondary analysis to evaluate overlap cGvHD using data from the ABA2 trial (NCT01743131) that enrolled children and adults undergoing hematopoietic cell transplantation (HCT) for hematologic malignancies. Patients were enrolled under two strata: a randomized, double-blind, placebo-controlled stratum (8/8 HLA-matched unrelated donor), comparing calcineurin inhibitor [CNI] and methotrexate [MTX] plus 4 doses of abatacept versus CNI/MTX plus placebo (8/8 Aba $n = 73$, 8/8 placebo $n = 69$, respectively), and a single arm stratum (7/8-HLA mismatched unrelated donor) receiving CNI/MTX plus Aba (7/8 Aba, $n = 43$).

Results: As previously published, the NRM and OS were similar among the 3 groups (Watkins et al., JCO 2021;39:1865). The 1-year cumulative incidence of cGvHD was 58.3% (95% CI: 49.9%, 65.8%), with 37.6% classified as overlap cGvHD. There was no difference in incidence of cGVHD among the 8/8 placebo, 8/8 Aba and 7/8 Aba cohorts ($p = 0.42$), and no difference in the distribution of overlap to classic chronic presentation ($p = 0.6$). Further, organ involvement and GvHD global severity score were similar among the cohorts ($p = 0.5$ at presentation, $p = 0.7$ at maximum within the first year post HCT), thus the groups were combined for analysis. Overlap cGvHD was associated with higher presenting and maximum global cGvHD severity score compared to classic cGvHD ($p = 0.001$ at presentation, $p = 0.003$ at maximum). As expected, overlap was more likely to have skin or gastrointestinal organ involvement as presentation, however skin involvement was more likely to have a higher score (2–3 vs 0–1, $p = 0.002$ at presentation, <0.001 at maximum).

Two-year non-relapse mortality [NRM] was highest for overlap cGvHD (26.1%) versus classic cGvHD 8.3%) and patients without cGvHD (13.0%, $p = 0.048$, Fig. 1A), with early death observed for overlap cGvHD but not classic cGvHD (1-year NRM 17.4% and 0.0% respectively). 2-year disease-free survival [DFS] was 65.0% (overlap cGvHD), 83.2% (classic cGvHD) and 50.2% (no cGvHD, $p \le 0.002$, Fig. 1B); 2-year overall survival [OS] was 68.5% (overlap cGvHD) 92.9% (classic cGvHD) and 60% (no cGvHD, $p < 0.001$, Fig. 1C). The difference between overlap and classic cGvHD outcomes was statistically significant ($p = 0.01$, 0.02, 0.002 for NRM, DFS and OS, respectively). To evaluation the impact of abatacept, we restricted the analysis to the 8/8 cohorts. The differences observed in NRM, DFS, OS were consistent when examining overlap versus classic cGvHD in the 8/8 placebo group. However, in the 8/8 Aba group, there was no difference in NRM (overlap 7%, classic 10%, $p = 0.89$), DFS (overlap 84%, classic 74%, $p = 0.57$), or OS (overlap 84%, classic 89%, $p = 0.59$), at 2 years suggesting that abatacept treatment may mitigate the risks associated with overlap cGvHD.

1A. NRM for patients with overlap cGvHD (green), classic cGvHD (blue) and no cGvHD (red) B. Disease-free survival C. Overall survival



Conclusions: Overlap cGvHD has a more severe presentation and course than classic cGvHD within the first year post HCT and is associated with worse 2-year NRM, DFS and OS. GvHD prophylaxis with Abatacept in 8/8 MUD transplantation may be protective.

Clinical Trial Registry: NCT01743131.

Disclosure: Nothing to declare

O054

Biomarker analysis in patients with steroid-refractory/dependent chronic graft-vs-host disease treated with ruxolitinib or best available therapy in the randomized phase 3 REACH3 study

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Background: Inhibition of the Janus kinase 1 [JAK1]/JAK2 pathway modulates various biomarkers associated with chronic graft-vs-host disease [GVHD]. Ruxolitinib, a JAK1/JAK2 inhibitor, demonstrated superior efficacy over best available therapy [BAT] in the phase 3, randomized clinical trial REACH3 in patients with steroid-refractory/dependent chronic GVHD. This exploratory analysis of REACH3 assessed whether baseline levels of proinflammatory cytokines, chronic GVHD biomarkers, and immune cell subsets were predictive of response to treatment.

Methods: Patients aged ≥12 years with moderate or severe steroid-refractory/dependent chronic GVHD were randomized 1:1 to receive ruxolitinib 10 mg twice daily ($n = 165$) or investigator-selected BAT ($n = 164$). A total of 316 patients had valid biomarker levels at baseline.

Blood samples were collected at baseline, cycle 1 day 1 [C1D1], C1D8, C1D15, C2D1, and C7D1. Biomarkers assessed are summarized in the Table.

Patients were stratified by response (complete response [CR], partial response [PR], no response [NR]) to ruxolitinib or BAT at C7D1; biomarker levels were assessed by disease severity and key patient characteristics, including organ involvement at screening and history of acute GVHD.

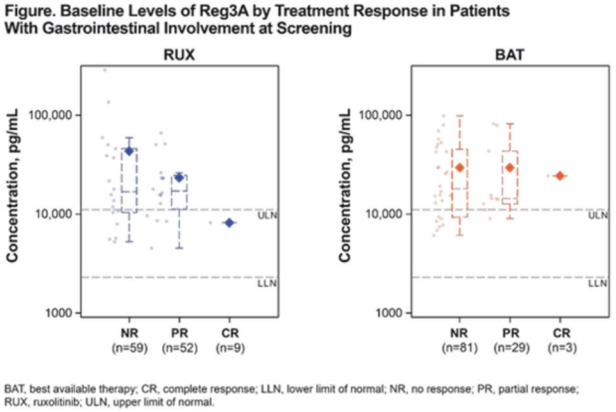
Changes in biomarker levels over time were analyzed using ANOVA methods.

Results: In patients with steroid-refractory/dependent chronic GVHD, baseline levels of proinflammatory cytokines, chronic GVHD disease markers, and immune cell markers did not predict overall and organ-specific responses, regardless of disease severity. Given the heterogeneity of chronic GVHD, the predictive value of these biomarkers was assessed while accounting for the impact of patient baseline characteristics on biomarker expression. Most findings were consistent with the prior analysis; however, among patients with baseline gastrointestinal involvement, those with lower baseline levels of Reg3A, a marker indicative of gastrointestinal involvement in acute GVHD, were more likely to respond to ruxolitinib treatment than patients with higher baseline Reg3A levels (Figure). No substantial changes in most biomarker levels were observed over time in either treatment arm.

Conclusions: Baseline inflammatory biomarker, chemokine, and immune cell levels in patients with steroid-refractory/dependent chronic GVHD in REACH3 did not predict response to treatment. However, a positive finding was seen among patients with baseline gastrointestinal involvement, for which response to ruxolitinib was predicted by lower baseline Reg3A levels. Overall, this analysis underscores the heterogeneity and complexity of chronic GVHD and suggests that, although known blood biomarkers are of limited value for predicting treatment response, patients might derive benefit from ruxolitinib treatment regardless of their baseline inflammatory biomarker levels.

Table. Summary of biomarkers assessed

Group	Biomarkers assessed
Inflammatory cytokines	IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12P70, IL-13, IFNγ, TNF-α
Chemokines	CXCL9, CXCL10, CXCL11, TNFSF13B (BAFF)
Immune cells	B cells, Tregs
Soluble cytokine receptors	IL-2RA, ST2, TNFRSF1A
Organ-specific markers	
Skin	Elafin/trappin-2
GI tract	Reg3A, TIM-3, osteopontin/SPP1
Liver	HGF



Clinical Trial Registry: ClinicalTrials.gov NCT03112603.

Disclosure: FL has participated in speakers bureaus for Amgen, Jazz Pharmaceuticals, Medac, Miltenyi, Novartis, and Takeda and has been a member of the board of directors or advisory committee for Amgen, Bellicum Pharmaceuticals, Neovii, and Novartis. RZ has received honoraria from Incyte, Mallinckrodt, and Novartis. TT has received grant funding from Astellas, Chugai, Fuji Pharma, Kyowa Hakko Kirin, Novartis, Nippon Shinyaku, Sanofi, and Teijin Pharma; honoraria from Bristol Myers Squibb, Kyowa Hakko Kirin, MSD, Novartis, Pfizer, and Takeda; and has been a member of advisory boards for Novartis and Takeda. AP is an employee of Novartis. KS and TS are employed by and have equity ownership in Novartis Pharma AG. SJL has received research funding from Amgen, AstraZeneca, Incyte, Kadmon, Novartis, Pfizer, Syndax, and Takeda, is a member of a steering committee at Incyte, and has consulted for Mallinckrodt and Amgen.

O055

Deciphering the effects of graft Tregs on chronic graft-versus-host disease: results from a multicenter study of patients with acute leukemia undergoing allogeneic PBSCT

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Background: In allogeneic hematopoietic stem cell transplant (allo-HSCT) acute graft versus host disease (aGvHD) may depend on known factors such as: human leucocyte antigen (HLA) and/or sex mismatch, source of stem cell, disease stage at diagnosis, CMV match-risk and, in addition, higher Tregs graft content which might be correlated and eventually determine a protection from aGvHD onset and severity. On the contrary, the Tregs reduction seems to be associated with lower chronic GvHD (cGvHD)

incidence. Of note, this later correlation was demonstrated in peripheral blood (PB) at the time of cGvHD onset, while no evaluation was performed on allo-graft content at the time of infusion so far. The aim of this sub-analysis of our published report regarding the correlation between graft Tregs and aGvHD onset and severity [Delia et al. Transplant Cell Ther. 2021;27:918e1–9)] was to investigate the possible correlation between graft content Tregs and the cGvHD incidence rate.

Methods: We prospectively enrolled 94 consecutive patients at 9 italian centers belonging to the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) affected by AML or ALL in complete remission (CR) who underwent MRD ($n = 35$, 37%) or MUD PBSCT ($n = 59$, 63%), with a myeloablative conditioning regimen. The graft content CD3/Tregs ratio (gCD3/TregsR) value associated with aGvHD onset was also used in the current cGvHD evaluation to subdivide the study population in two groups, the low ratio (LR, gCD3/TregsR <70) and high ratio (HR, gCD3/TregsR≥70) one, thus permitting to obtain conclusive effects by gCD3/TregsR both on aGvHD and on cGvHD, respectively. Cox regression model was performed in order to estimate the effect on the incidence of cGvHD by patient age, donor-recipient CMV serostatus, donor-recipient gender combination, donor type, disease type and stage at transplantation, HLA-match, time dependent aGvHD [i.e., the corresponding event can occur at different points in time after transplantation] in addition to the gCD3/TregsR.

Results: The 3-years cumulative incidence (CI) rate of cGvHD according to any (18 events), mild (1 event), moderate (10 events) and severe (7 events) global severity score was of 40, 2, 29 and 16%, respectively. Two-years statistically significant difference of cGvHD-CI rate was found between LR and HR (37 vs 15%, $p = 0.021$), with and without grade II-IV aGVHD (54 vs 17%, $p = 0.045$) and HLA-matched and HLA-mismatched pairs (14 vs 81%, $p < 0.001$) patients' group, respectively. No correlation between type and stage of disease, low CMV risk, female donor/male recipient, ATG usage, type of donor, recipient age and cGvHD (or aGvHD) incidence was documented. In multivariate analysis, HLA mismatch (antigenic and/or allelic) and LR group were correlated both with cGvHD (HLA-mismatch: hazard ratio (HR) = 5.33; 95% CI:1.65–17.18, $p = 0.005$; LR group: HR = 2.99; 95% CI:1.05–8.29, $p = 0.04$) and with aGvHD (HLA-mismatch: HR = 4.43; 95% CI: 1.63–12.09, $p = 0.04$; LR group: HR = 0.25; 95% CI: 0.08–0.77, $p = 0.016$) incidence rate, respectively.

Conclusions: Our data seem to confirm the value of Tregs in preventing aGvHD (HR = 0.25), while favoring cGVHD (HR = 2.99). Larger studies should be performed to confirm our initial report.

Clinical Trial Registry: Not applicable.

Disclosure: There are no conflicts of interest to report

O057

Deciphering antigen specificity of protective regulatory T cell clones in patients after allogeneic stem cell transplantation

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Background: Regulatory T cells (Treg) play an important role in controlling immune homeostasis after allogeneic hematopoietic stem cell transplantation (HSCT). Recently, we detected specific clonal expansion of Treg by bulk T cell receptor (TCR) β-chain sequencing in patients not developing acute graft-versus-host disease (GVHD). Thus, it is of major interest to identify the antigen specificity of such presumably protective Treg clones.

Methods: One hundred and seventy-seven patients who underwent HSCT for the treatment of AML were recruited for this prospective clinical study. We excluded patients with CMV reactivation or other known immune-altering infections. To date, 12 patients with or without acute GVHD were analyzed in greater detail using single-cell analyses. To obtain the exact sequences of both TCRαβ chains (*TRA* and *TRB*) of presumably protective Treg clones, single-cell transcriptome libraries and TCRαβ libraries were generated from $CD3^+CD4^+CD25^{hi}CD127^{low}$ lymphocytes with 10x genomics™ 5′ kits on average 30 days post-HSCT. To identify Treg specificity, TCR pairs of highly expanded Treg clones (expanded TCR pairs: composite >2% of the repertoire) were lentivirally transduced into the TCRαβ deficient Jurkat cell line J76 (presenter); while IL2-capturing antibody on the cell surface, along with patient-originated MHC-II genes and CD74-peptide fusion were lentivirally transduced into HEK293T cell line (reporter). After co-culturing both modified cell lines, IL2 is released by presenter upon successful peptide-MHC-TCR complex formation. The reporter cell presenting the specific antigen captures the IL2 enabling the identification of Treg specificity.

Results: Patients without GVHD showed a focused Treg-TCR repertoire. Of note, in one patient clonal expanded Treg dominated the $CD4^+$ population, and the most abundant clone accounted for more than 15% of the entire Treg repertoire. Of note, expanded Treg clones were not observed in the control group without GVHD. Transcriptome analysis of expanded Treg clones revealed high expression of FOXP3, RTKN2, FCMR, CD27 and TIGIT, which are key regulatory factors or important immune checkpoints. Top Treg TCR pairs from this study were not found in VDJdb database or other published sequencing data.

Next, we aimed at the identification of corresponding antigens of these expanded Treg, using the above-described reporter system. For proof of principle experiments, we introduced a known CMV epitope and designated MHC-II/TCR combinations. This system was then adapted for screening of Treg antigens.

Conclusions: This study has identified paired and complete TCR sequences from clonally expanded Treg in patients not developing GVHD after HSCT. Single-cell transcriptome analyses suggest their suppressive capacity. Our reporter system will enable us to identify the specific (allo)antigen of such Treg clones. The identification of antigen recognized by protective Treg clones might open up new therapeutic strategies for the prevention and treatment of acute GVHD.

Disclosure: Nothing to declare

Graft-versus-host disease—preclinical and animal models

O058

Ex vivo *generate D* through pharmacological hypomethylation HLA-G+T-regulatory cells, do not induce alloreactivity

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Background: Graft-versus-host disease (GvHD) is a frequent and life-threatening complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Adoptive transfer of T cells with immunosuppressive properties, the so-called T-regulatory cells (Tregs), stands as a very promising alternative strategy for the prevention and treatment of GvHD. However, the low numbers of

naturally occurring regulatory FOXP3+ Tregs in the circulation and the lack of specific cell surface markers for efficient purification, limit their clinical use. Recently, it has been shown that exposure of human peripheral T-cells to hypomethylating agents induces the expression of HLA-G and converts them to regulatory cells (iG-Tregs). The HLA-G molecule is expressed in placenta and protects the "semi-allogeneic" fetus from maternal immune attack. We here, aimed to explore the safety of iG-Tregs both in vitro and in vivo in a humanized mouse model of GvHD.

Methods: Human mononuclear cells were stimulated with anti-CD3/CD28 for 3 days (OKT3 cells) and subsequently treated with 10 μM Decitabine for 4 days (iG-Tregs) or left untreated (untreated OKT3), in the presence 50 U/mL interleukin-2. The generated iG-Tregs were characterized for HLA-G expression and their in vitro alloreactivity against CFSE-labeled allogeneic blasts stimulated with phytohemagglutinin (PHA), by flow cytometry. A total of 3×10^6 of either iG-Tregs or untreated OKT3 were infused in sub-lethally irradiated NSG mice, which were evaluated for GvHD by a 5-parameter sickness score.

Results: Decitabine treatment induced the expression of HLA-G in iG-Tregs compared to untreated OKT3 cells ($8.19 \pm 0.21\%$ vs $1.19 \pm 0.53\%$, $p < 0.0001$) and importantly, the generated iG-Tregs were not alloreactive in vitro against allogeneic PHA blasts as compared to untreated OKT3, (% lysis at 40:1 ratio: 49 ± 4 vs 1.8 ± 1, respectively, $p < 0.0001$). To confirm the lack of alloreactivity in vivo, iG-Tregs were infused into sub-lethally irradiated mice. In contrast to the recipients of untreated OKT3 cells ($n = 5$) developing high GvHD score from day 21 onwards and succumbing all by day 35 from clinically confirmed GvHD, 50% (3/6) of iG-Treg-mice survived until sacrifice (day 84). T-cell engraftment was confirmed in the spleen of iG-Treg-treated, GvHD-free survivors.

Conclusions: Overall, HLA-G-expressing T cells generated ex vivo through pharmacological hypomethylation present a safe profile, both in vitro and in vivo. Whether adoptive transfer of iG-Tregs could advance the treatment of GVHD after allo-HSCT, will be ultimately determined in clinical trial.

Disclosure: Nothing to declare

O059

Donor plasmacytoid dendritic cells regulate GVHD and GVL activities of donor T cells in allogeneic hematopoietic stem cell transplantation

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Background: We previously reported that more donor plasmacytoid dendritic cells (pDC) in 5/6 and 6/6 HLA-matched marrow grafts from related donors led to more relapse among CML or AML patients (Waller Blood 2001). In contrast, MDS and AML patients randomized to receive marrow versus G-CSF blood stem cell grafts from 7/8 or 8/8 unrelated donors (BMT CTN 0201) showed that more donor pDC in marrow grafts reduced the incidence and severity of chronic graft-versus-host disease (GvHD) without affecting the graft-versus-leukemia (GvL) activity of donor T cells (Waller JCO 2014). Vasoactive intestinal polypeptide (VIP) expressed by marrow pDC is an immuno-suppressive peptide that limits GvHD in murine models of allo-HSCT (Wang Blood 2018). Here we compared the activation profiles of T cells in the presence or absence of wild type or VIP knock-out pDC, and the effects of wild-type versus VIP knock-out donor pDCs on gene expression, GvL, and GvHD activity of donor T cells in MHC mis-matched murine allo-HSCT recipients.

Methods: T cells negatively selected from mouse splenocytes or human blood were activated in vitro by surface-bound anti-CD3 antibody and expression of VIP receptors VPAC1 and VPAC2 were assessed by western blots of cell extracts. The effects of donor pDC on T cell alloreactivity, GvHD, and GvL was assessed in C56BL/6◄DBA/2J or C57BL/6◄B10.BR MHC mis-matched models. Tumor burden was assessed by serial bio-luminescence imaging in irradiated DBA/2J recipients inoculated s.c. with luciferase+ P815 (DBA/2J) then transplanted with the combination of $1 \times 10E5$ purified donor T cells, $3 \times 10E6$ c-kit+Sca-1+lin- HSC, and either no added donor pDC, 50,000 wild-type donor pDC or 50,000 VIP knock-out donor pDC.

Results: Activated murine T cells co-cultured with wild-type pDC showed decreased proliferation and lower levels of inflammatory cytokines compared to T cells activated in the presence of VIP knock-out pDC. Activation of both murine and human T cells induced expression of the VPAC1 receptor consistent with the immuno-suppressive action of VIP on T cells. Tumor-bearing DBA/2 mice transplanted with VIP KO donor pDC had a significantly lower tumor burden with an increased proportion of tumor free-mice compared to recipients of wild-type pDC or no pDC. Nanostring analysis of RNA expression in T cells from recipients of VIP KO donor pDC showed higher levels of *bhlhe40* transcripts during the first two weeks post-transplant, and higher levels of *Cyclophilin A* transcripts at day 15 than T cells from recipients of wild type pDCs, consistent with increased activation of allo-reactive T cells in the absence of VIP production by donor pDC.

Conclusions: Consistent with clinical data from recipients of related and unrelated donor marrow grafts, GvL and GvHD activities of donor T cells are augmented by fewer donor pDC or donor pDC that lack expression of VIP. With evolving technologies that support sophisticated graft engineering, the use of grafts containing more donor pDC may enhance survival in patients with non-malignant and low-risk hematological malignancies, while reduction of donor pDC for patients with high-risk disease may lead to better transplant outcomes.

Disclosure: EKW is supported by NIH NCI/NHLBI/NIAID R01 AI145231-01A1. There are no relevant financial conflicts of interest

Haematopoietic stem cells

O060

International differences in baseline characteristics and practice patterns in newly diagnosed multiple myeloma (MM) patients undergoing upfront autologous stem cell transplantation

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Background: MM patients undergoing upfront autologous stem cell transplantation (ASCT) have different characteristics worldwide, likely due to variances in transplant activity, health economic factors and access to new myeloma therapies. The goal of this retrospective study was to analyze outcomes of MM patients across different regions

Methods: Data were provided to the Worldwide Network for Blood and Marrow Transplantation (WBMT) through the European Society for Blood and Marrow Transplantation (EBMT), the Center for International Blood and Marrow Transplantation (CIBMTR), the Asian Pacific Blood and Marrow Transplant Group (APBMT), the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), the Eastern Mediterranean Blood and Marrow Transplant Group (EMBMT), the Latin American Bone Marrow Transplant Group (LABMT), and the Ottawa Canadian Registry. This study focused on patients undergoing ASCT between 2013 and 2017

Results: Information on 61,937 patients were available: 37,662 (61%, EBMT), 16,217 (26%, CIBMTR), 3,820 (6%, APBMT; 3127 from Japan, 524 from Taiwan and 169 from Malaysia), 3166 (5%, ABMTRR), 545 (0.9%, EMBMT), 339 (0.5%, LABMT) and 188 (0.3%, Ottawa). Patients were of Caucasian (73%), Asian (16%) or African American (11%) descent, 52% were male and the median age at diagnosis was 59.9 years (IQR: 53.6–64.9). 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%) (data available for 54%) and cytogenetic risk was standard in 70% and high in 30% of patients (data available for 44%). The median time from diagnosis to transplant was 7 months (IQR: 5.5–9.9). Transplant activity/year increased from 18.3% in 2013 to 21.9% in 2017 ($p < 0.001$), the biggest increase being from 10.6% to 32.2% in LABMT. The median age at transplant was 60.8 years (IQR: 54.6–65.8) with 5.0% of patients older than 70 years (3.5% in EBMT and 9.8% in CIBMTR) and the lowest value in the EMBMT group (53.7 years). The HCT-CI at transplant was reported as low risk (0) in 52%, intermediate (1–2) in 25% and high risk (≥3) in 23% of cases (28.3% missing). The% of patients with a low risk was lowest in Malaysia (3.8% vs 51.9% in the pooled registry, $p < 0.0001$). At ASCT, the Karnofsky score was 100 in 40% and ≤90 in 60% (9.7% missing) and disease status CR (19%), VGPR (38%), PR (36%), MR/SD (5%) or refractory (2%) (9.7% missing). The most frequent preparative regimen was melphalan 200 mg/m^2 (82%), 140 mg/m^2 (14%) or other (4%). Tandem ASCT was reported in 7%. The source of stem cells was peripheral blood in 99.8%. Of the 11% reported with post-ASCT maintenance treatment, 51% received lenalidomide. The median follow-up was 35.46 months (95% CI: 35.29–35.61, IQR: 12.75–52.4)

Conclusions: This novel comparative study of MM patients treated with upfront ASCT revealed marked regional differences in transplant activity and patient characteristics. ASCT increased between 2013 and 2017 and the preferred preparative regimen was melphalan 200. Transplant outcomes will be presented.

Clinical Trial Registry: Not applicable.

Disclosure: The authors have no conflict of interest

O062

Humoral immune response and kinetics following dual vaccination with BNT162b2 in patients after allogeneic blood stem cell transplantation

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Background: Immunocompromised patients are at particular risk for a severe course of SARS-CoV-2 infection and therefore should receive special attention with regard to antibody formation following active immunization.

Methods: We analysed humoral immune responses in 88 patients who had received 2 doses of the Biontech/Pfizer vaccine BNT162b2 after allogeneic blood stem cell transplantation (aBSCT). Median age was 60 years (range 23–79) and 40% were female. Diagnoses were AML (50%), MDS (16%), MPN (11%), ALL (8%), NHL (8%) and others (7%). Thirty-one patients (35%) had cGvHD, 28 (32%) were on immunosuppressants, 5% had active disease and 2% received chemotherapy for relapse. Twenty-four patients (27%) received the vaccine within the first year after aBSCT.

Median interval from aBSCT to first vaccination was 707 days (103–7673) and median interval from first to second vaccination was 28 days (12–57) days. Median interval from second vaccination to first blood sample was 41 days (13–76). A second sample was analysed 3 months later from 77 patients (88%). Samples were tested for antibody (AB) titers against SARS-CoV2 spike S1 subunit antigen (Euroimmun Anti-SARSCoV-2-QuantiVac-enzyme-linked immunosorbent assay) and an "in-house" serial dilution endpoint neutralization test with the infectious SARS-CoV-2 isolate (EPI_ISL_425126) was performed in a biosafety level 3 facility to determine neutralization capacitiy. Previous infection

was ruled out by measuring the anti-nucleocapsid AB titer (Abbott). AB titers were correlated with neutralization and various patient, disease and transplant variables (Spearman-Rho, Mann–Whitney *U*).

Results: We observed a highly significant and positive correlation between anti-SARS-CoV2-Spike-IgG formation and neutralizing capacity ($r = 0.908$, $p \leq 0.001$). Median Anti-Spike-IgG after 2 vaccinations was 891.8 BAU/ml (3.2–12.934). Variables correlating positively with AB titer height included CD3+ CD4+ cell count ($r = 0.61$, $p < 0.001$), interval between aBSCT and first vaccination ($r = 0.51$, $p < 0.001$), number of CD19+ cells ($r = 0.44$, $p \leq 0.001$) and the number of CD16+ CD56+ cells ($r = 0.35$, $p \leq 0.001$). Active disease and immunosuppression with Ruxolitinib tended to negatively impact antibody response. In 63% of patients vaccinated in the first year after aBSCT antibody response (median 100.14 BAU/ml, range 3.2–1040) was considered insufficient (<200 BAU/ml) compared to 15% in patients vaccinated at later time points ($p < 0.05$). In the second analysis after 3 months, we observed that AB-titers had dropped by 73% (median, −95%–40%) from 891.8 to 335.09 BAU/ml. These titer reductions were seen even in patients with extraordinary good primary immune responses and in patients vaccinated in the first year after aBSCT as well as those vaccinated at later time points.

Conclusions: Humoral vaccine responses to Biontech/Pfizer (BNT162b2) were highly variable in patients after aBSCT, with particularly poor titers achieved by patients vaccinated within the first year after aBSCT and those with low T-, B- and NK-cell numbers. Even those patients who had high primary antibody titers showed a dramatic decline over a period of 3 months. These data support the general recommendation for titer measurement after vaccination as well as vaccine booster for all patients after aBSCT and argue for passive immunization strategies early after transplant.

Disclosure: Nothing to declare.

O063

Late relapse after hematopoietic stem cell transplantation for acute leukemia – a retrospective study from the French Society for Stem Cell Transplantation (SFGM-TC)

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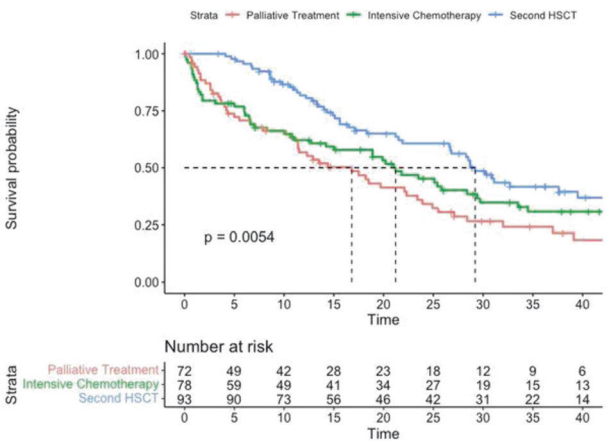
Background: Late relapse (LR) after hematopoietic stem cell transplantation (HSCT) for acute leukemia is a rare event (near 4.5% of relapses) and raises the question of prognosis, salvage therapy and risk factors. The aim of this study was to describe survival after LR.

Methods: A multicentric retrospective study was performed by considering data from the French national retrospective register ProMISe, from the SFGM-TC. The study periods covered from January 2010 to January 2017. We included patients (pts) presenting LR, defined as relapse occurring at least 2 years after HSCT. We used Cox model to identify risk factors associated with LR.

Results: During the study period, 7582 AHSCT were performed, and 2565 relapses were reported in 30 centers. Among them, 319 (4.2%) were considered as LR. Data analysis was available for 290 patients. The mean age of pts was 47 years (SD 14.5). Acute myeloid leukemia was the most common indication of HSCT (77.6%), followed by Philadelphia-negative acute lymphoblastic leukemia (13.4%), therapy-related acute leukemia (5.2%) and Philadelphia-positive lymphoblastic leukemia (3.8%). Myeloablative conditioning was performed for 42.6%, and peripheral stem cells was the main source of hematopoietic stem cells (75.8%). In most cases, pts were in complete response at transplant (88.2%). Regarding graft versus host disease (GVHD), 44% and 43.4% developed acute and chronic GVHD respectively before LR.Median delay of LR was 38.8 months (36.5–40.7) and 27.2% of pts had extramedullary involvement at LR (17.2% exclusively and 10% associated with medullary involvement). Most of pts (62.6%) lost complete chimerism at LR.Median overall survival (OS) after LR was 19.9 months (15.1–24.9) with a median follow-up of 55.8 months (52.2–60.1).

With regard to salvage therapy, most common was induction regimen (57.9%), followed by hypomethylating agents with donor lymphocytes infusion (DLI) for 29.8%. Complete remission was obtained for 43.9% and 36.6% were refractory to first line salvage therapy. Ninety-three pts (38.8%) underwent second HSCT. Relapse free survival (RFS) and OS were significantly higher compared to chemotherapy alone ($p = 0.00011$ and $p = 0.0054$, respectively) when pts had second HSCT as seen in the Figure below, with median of 17 months (11.1–35.6) and 20.4 months (14.4–37.2), respectively. We did not observe excess of toxicity related to second HSCT with incidence of acute GVHD in 42.1% of pts and of chronic GVHD in 22.1% of pts. Non-relapsed mortality was at 18.2%. We identified in Cox model, association between LR and having adverse cytogenetics (OR 1.6, 1.2–2.2, $p = 0.0026$), use of cyclophosphamide (OR 1.7, 1.1–2.7, $p = 0.045$). Myeloablative conditioning appeared to be a protective factor (OR 0.7, 0.5–0.9, $p = 0.028$).

Figure. Overall survival (in month) and salvage therapy after LR



Conclusions: LR after HSCT for acute leukemia occurred in 4.2% of relapses, with a median OS of 19.9 months. Salvage therapy with second HSCT appeared feasible, without excess of toxicity.

Clinical Trial Registry: No.

Disclosure: Nothing to declare

O065

The impact of donor-specific antibodies presence on the outcome post allogeneic hematopoietic stem cell transplantion: a survey from a single center

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Background: Donor-specific antibodies (DSAs) refer to anti-HLA antibodies that specifically correspond to a mismatched antigen of the donor. The role of DSAs in solid organ transplantation is well established, where their presence is associated with solid organ rejection. DSA role in allogeneic stem cell transplantation is controversial. Several studies reported that DSAs have been associated with primary graft failure (PGF) after either MUDT, UCBT or haploidentical SCT. The aim of our retrospective study is to evaluate the impact of DSA presence on the outcome post transplant, focusing our attention on engraftment

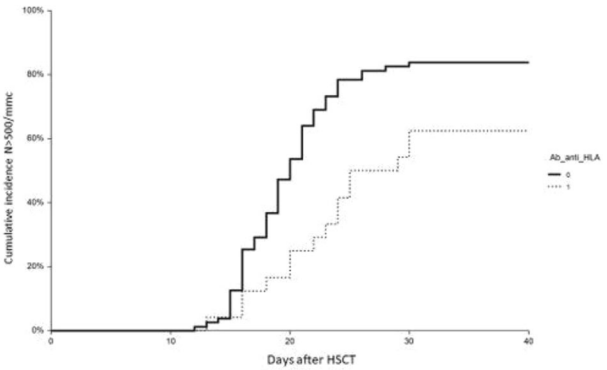
Methods: We collected DSA recipient of allogeneic stem cell transplantation (allo SCT), performed at our institution from March 2019 to August 2021. A total of 103 patients, with a median age of 55 years (range 19–73 years), received a median dose of CD34+ cell of 6.8×10^6/kg (range 1.6×10^6–10.2×10^6/kg). Patients' characteristics are summarized in Table 1.

Results: A total of 84 patients (81.5%) achieved sustained myeloid engraftment. The median times to neutrophil engraftment and platelet engraftment were 21 days (range 12–160 days) and 20 days (range 10–57 days), respectively. PGF occurred in 3/103 patients (2.9%). Twenty four patients (23.3%) were DSA positive. Sixteen patients had antibodies against HLA class I antigens, nobody had antibodies against HLA class II, and 8 against classes I and II. Among 15 patients with sibling donors, two (13%) were positive for DSA. Acute and chronic GvHD was present respectively in 26/103 (25%) and 15/103 (14%) patients. We found that DSA positivity directly correlates with neutrophil engraftment failure at 30 days after allo SCT ($p = 0.007$). There is no correlation with platelets and red blood cell engraftment.

Univariate analysis showed that factors, including DSAs positivity ($p = 0.006$), disease type ($p = 0.009$), disease status ($p = 0.0001$), donor-recipient HLA match ($P = 0.057$) were correlated with neutrophil engraftment delay at 30 days after allo SCT. Patient with DSA negativity, with acute leukemia, in complete response at time of transplant, with a sibling donor have a reduced risk of neutrophil engraftment failure. Patient's age, stem cell source, condition regimen and Gvhd prophylaxis have no effect on neutrophil engraftment.

Multivariate analysis demonstrated that two factor were associated with primary GR: the presence of DSAs (HR 0.41 (95% CI 0.22–0.73) ($p = 0.003$) and donor-recipient HLA matching (sibling vs MUD 8/8 $p = 0.02$; sibling vs MUD 7/8, $p = 0.01$; sibling vs haplo, $p = 0.002$).

Patients	103
Age	Median age 55 years (range 19–73 years)
Sex	M/F = 58/45
Diagnosis	
Acute leukemia/MDS	59 (57.2%)
Lymphoproliferative disease	9 (8.7%)
Chronic myeloproliferative disease	29 (28.1%)
Aplasia	6 (5.8%)
Disease status before HSCT	
Stable disease	36 (34.9%)
Complete remission	50 (51.5%)
Progressive disease	15 (14.6%)
HCST frontline	2 (1.9%)
Conditioning regimen	
TBF	72 (69.9%)
Baltimore	17 (16.5%)
Flu-TBI	13 (12.6%)
CTX	1 (0.9%)
Donor	
MUD 7/8	22 (21.4%)
MUD 8/8	38 (36.9%)
SIB	15 (14.6%)
APLO	25 (24.3%)
CB	3 (2.9%)
GvHD prophylaxis	
CSA, CTX, MMF	88 (85.4%)
CSA, C TX, MMF, ATG	14 (13.6%)
CSA, MTX, ATG	1 (0.9%)
Presence of anti HLA antibodies	24 (23.3%)



Conclusions: We confirmed the association of DSAs with primary GF,as previously reported, in the setting of MUD and haploidentical transplant.

Disclosure: No disclosure to declare

O066

The histone demethylase KDM6A regulates hematopoietic stem and progenitor cells emergence and its loss causes myeloid-biased differentiation in zebrafish

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Background: KDM6A, also known as UTX, is a H3K27me2/3-specific demethylase and belongs to the KDM6 family. KDM6A can derepress expression of diverse genes through the catalytic JmjC domain and is also a component of the COMPASS-like complex, which is important for global alterations in chromatin accessibility. Recurrent somatic loss-of-function mutations in UTX occur in human cancers, such as CMML, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL), and are proposed to be "driver" mutations. To elucidate the role of KDM6A in normal and malignant hematopoiesis, numerous mouse models of aberrant KDM6A expression have been described. Even with these models and their different phenotypes, the role of KDM6A in hematopoiesis is still largely unknown. Zebrafish are an excellent model to study

hematopoiesis, especially in early embryogenesis. To elucidate the function of KDM6A in hematopoiesis and the leukemogenic mechanisms, we established an endogenous of kdm6a-loss-of-function mutants in zebrafish.

Methods: CRISPR/Cas9 was used to create *kdm6a* mutants, Cas9 protein was injected along with sgRNA targeting exon10 (Transcript ID: ENSDART00000144623.3). Antisense Morpholinos (MOs) used in this study was purchased from GeneTools and 4 ng for *kdm6a* MO was injected into 1-cell-stage zebrafish embryos at the yolk/blastomere boundary.

Results: We engineered a zebrafish *kdm6a*-null mutant by introducing a 10-bp deletion using CRISPR/Cas9 genome editing method and characterized its phenotype. Homozygous progeny from heterozygous incrossed were viable to adulthood and females were fertile, which differed from $UTX^{-/-}$ female embryos (died between E11.5 and E13.5) reported by Sebastian Thieme et al. The *kdm6a*-null embryos that were produced by homozygous parents exhibited a significant reduction in body size compared to wild-type fish at 3 days post-fertilization. To explore the role of *kdm6a* in hematopoiesis, whole-mount in situ hybridization (WISH) was performed. The aorta–gonad–mesonephros (AGM) expression of *runx1*, which is a well-known HSPCs marker in vertebrates, was drastically reduced in *kdm6a*-null homozygous at 28 h post-fertilization. Consistently, the decreased expression of *cmyb* was also observed in the *kdm6a*-null mutants at 36 h post-fertilization. Further, we observed increased expression of lineage-specific markers (erythroid- *hbae1*, neutrophil- *mpx/lyz*, macrophage- *mfap4*), while decreased expression of T lymphocyte marker *rag1* at 3–4 days post-fertilization. To further confirm the pivotal role of *kdm6a* in hematopoiesis, morpholino was used, the phenotypic alterations were also recapitulated in this *kdm6a* morphants. Additionally, the number of *cmyb*:GFP/*kdrl*:mCherry double-positive HSPCs in the AGM region was significantly reduced in *kdm6a*-morphant embryos, compared with control embryos. These data indicate that loss of *kdm6a* leads to emergence defects in HSPCs and causes myeloid-biased differentiation.

To reveal the mechanisms of *kdm6a* regulationg HSPCs generation and differentiation, cd41-GFP^{low+} HSPCs were sorted for smart-RNA-sequencing analysis. Our data showed 261 differentially expressed genes (FDR <0.05, 107 upregulated genes, 154 downregulated genes) between MO and control HSPCs. GSEA revealed positive enrichment for E26 transformation-specific (Ets) transcription factors and negative enrichment of inflammatory signaling pathway signatures in morphants compared to controls.

Conclusions: *kdm6a* is required for HSPCs emergence and lineages differentiation in zebrafish embryos. Our $kdm6a^{-/-}$ zebrafish model will be a helpful tool to understand the process of hematopoiesis.

Disclosure: Nothing to declare

Haemoglobinopathy

O067

Decision-making about HSCT in patients with hemoglobinopathies, a PDPW/IEWP scenario-based survey on physicians' perspectives

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Background: Choosing HSCT in hemoglobinopathy patients remains difficult in clinical practice. It is unclear which disease-, treatment- or patient-related factors HSCT physicians take into account, and who they think should be involved in the decision-making process. We aimed to describe relevant factors influencing decision-making for hemoglobinopathy patients from the perspectives of HSCT physicians.

Methods: EBMT-centers transplanting hemoglobinopathy patients were invited to complete a scenario-based survey. The survey consisted of:

1. demographic questions,
2. 3–5 hypothetical scenarios reflecting realistic clinical patients' situations, accompanied by questions asking what a physician would do if actually presented with the patient,
3. two open-ended questions asking about aspects considered important to decision-making.

The following factors were systematically assigned as categorical variables: phenotype sickle cell disease (SCD) or transfusion-dependent thalassemia (TDT), complications, donor type, and patient age as a continuous variable. Descriptive statistics were used to describe demographics. A mixed-effects logistic regression model with a random effect for respondents was used to analyze the influence of the scenarios' factors on the decision to transplant. Open-ended questions were analyzed qualitatively.

Results: Between August 2020 and April 2021, 93 professionals from at least 54 centers in 27 countries responded. In total, 387 responses were analyzed, and when asked if an HSCT would be chosen in the given scenario, 63% (SCD 58%, TDT 68%) answered positively. There was a significant interaction between phenotype and complication ($p < 0.001$), as respondents were less likely to choose HSCT for SCD patients without complications compared to SCD patients with complications (OR = 0.03, 95% CI: 0.01–0.10, $p < 0.001$). In contrast, no difference was found between TDT patients with or without complications ($p = 0.756$). Regarding donor type, HSCT was less likely to be chosen if only a haplo-identical donor was available, compared to if a MUD donor (OR = 0.11, 95% CI: 0.05–0.29, $p < 0.001$) or an HLA-identical donor (OR = 0.02, 95% CI: 0.01–0.06, $p < 0.001$) was available. HSCT was also less likely with a MUD donor only compared to an HLA-identical donor only (OR = 0.17, 95% CI: 0.07–0.4, $p < 0.001$). Patient age was not associated with choosing HSCT ($p = 0.716$). Concerning the timing for HSCT: 'as young as possible' (236 scenarios) was most often chosen, followed by 'depending on patient's preferences' (89 scenarios), and 'waiting for better therapies' (84 scenarios). Answers to the open-ended questions about important aspects to include in the decision-making process reflected that various pros and cons needed to be balanced, such as possible complications and outcomes post-HSCT, disease complications without HSCT, quality of life, disease burden, prognosis, donor availability, and fertility.

Conclusions: This exploration of HSCT decision-making shows that physicians in realistic hypothetical scenarios choose HSCT in more than 50% of the scenarios. In SCD, but not TDT, the existence of complications influences decisions. Availability of an HLA-identical donor over a MUD over a haplo-identical donor increased the likelihood of choosing HSCT. Current developments such as the use of post-transplant cyclophosphamide in MUD or haplo-identical donors could influence decision-making in the future. In summary, this survey shows that choosing HSCT in hemoglobinopathy patients clearly requires a delicate balance of weighing risks and benefits together with patients and their families.

Disclosure: Nothing to declare

O069

Impact of including abatacept for graft-versus-host disease prophylaxis in allogeneic stem cell transplantation for hemoglobinopathy

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Background: Abatacept, based on efficacy against acute graft-versus-host disease (GVHD) in malignant disorder transplants was recently approved for use in the United States (PMID: 33449816). In 2020 we reported on phase I portion of a trial using abatacept prophylaxis in sickle cell disease transplants (grade I–II and III–IV aGVHD rates 28.6% and 7%, respectively) (PMID: 32813873). Chronic GVHD (57%) was mild/limited in all but one patient that received longer duration abatacept. The goal of this report is to compare reduced-intensity transplant/GVHD outcomes in hemoglobinopathies with and without abatacept for acute and chronic GVHD prophylaxis.

Methods: We compared hemoglobinopathy transplant outcomes between June 2011 and June 2021 (current era) on NCT 03128996, a multi-center trial. Conditioning included hydroxyurea, proximal/early alemtuzumab (days −21 to −18) (48 mg), fludarabine (150 mg/m^2), and melphalan (140 mg/m^2) in patients with 8/8 HLA-matched (-A, -B, - C and -DRB1) donors. Thiotepa (8 mg/kg) was added in 7/8 HLA-matched transplants. GVHD prophylaxis included a calcineurin inhibitor, methotrexate (marrow) or mycophenolate (cord), +/− prednisone. In 2017, prednisone was replaced by early abatacept (10 mg/kg) and subsequently extended to days −1, +5, +14, +28, +60, +100, +180, +270 and +365. The latter three doses were omitted in cord transplant recipients. Median follow-up was 102 months (5–125) in the no abatacept group and 32 months (6–87) in the abatacept group.

Results: Children (1–20 years) were transplanted for symptomatic sickle cell disease (50) or thalassemia (8). Median recipient age in the no abatacept group ($N = 40$) was 7 (range 1–20) years (Group A); 12.5 years (range 2–20) in the abatacept group ($N = 18$) (Group B). In Group A, 23 received matched sibling/unrelated transplants and 17 received mismatched unrelated marrow/cords. In Group B, 10 received matched sibling/unrelated transplants and 8 received mismatched marrow/cords. Three (5%) had primary graft rejection and autologous recovery (2/3 were in Group A). In all patients, neutrophils engrafted at 13 days (range 10–24), platelets at 26 days (range 11–71 days). Median donor myeloid chimerism was 98% (range 41–100), lymphoid chimerism 96% (range 25–100), and whole blood 100% (range 48–100) on day 100. Median myeloid chimerism was 99% (range 29–100), lymphoid 97% (range 23–100) and 99.5% (range 22–100) in whole blood at 1 year. The day +100 incidence of grade III–IV acute GVHD in Groups A and B was 30% and 5%, respectively. The 1-year incidence of extensive chronic GVHD in Groups A and B was 30% and 11%, respectively. In Group B, two patients with extensive cGVHD received mismatched unrelated transplants, were ≥13 years of age, and one got short-course abatacept. Virus replication (CMV/adenovirus) was detected in 22/40 patients in Group A (55%) and 12/18 patients in Group B (66%). Mortality was 12% in group A (GVHD related), and 0% in Group B despite similar transplant/GVHD risk factors for age, HLA mismatch, and infections.

Conclusions: In this comparison analysis, the addition of abatacept resulted in favorable and desired outcomes attributable to a lowered GVHD risk (and early immune reconstitution) in hemoglobinopathy transplants, the majority from alternate donors (55% in Group A, 77% in Group B).

Clinical Trial Registry: NCT 03128996.

Disclosure: SC—advisory board: Bristol Myers Squibb. SS—honoraria: Takeda, Janssen, Bristol Myers Squibb, Graphite. DSMC – NHLBI, Aruvant. No conflict of Interest for the remaining authors

O070

100 Hematopoietic cell transplants for sickle cell disease: lessons learnt

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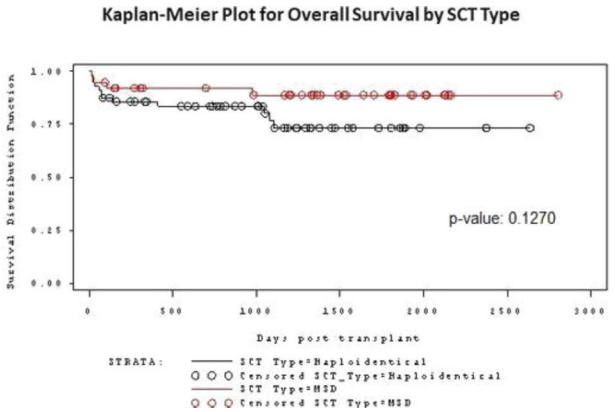
Background: Sickle cell disease (SCD) remains associated with high risks of morbidity and mortality. Even best of supportive care fails to improve quality of life considerably. Awaiting gene therapy, hematopoietic cell transplant (HCT) is the only curative option for selected group of patients who continue to worsen on optimal supportive care. Here we share our experience of 100 HCT's for SCD over a period of 7 years.

Methods: Hundred consecutive patients suffering from SCD who underwent HSCT between January 2015 and October 2021 were enrolled in the study. It was retrospective data collection. All patients met one or other laid down criteria for HCT. Forty-four patients underwent HLA identical donor HCT (38: MSD, 4: MRD, 1: CBT, 1: MUD), whereas 56 underwent haploidentical family donor HCT (HFD-HCT). Conditioning and GvHD prophylaxis are highlighted in Table 1.

Conditioning-Regimen		
HLA-Identical	Busulfan based	30
	Thiotepa based	14
HFD	Thio-Flu-Cy-ATG-TBI	54
	Others	2
GvHD-Prophylaxis		
HLA-Identical	CSA based	36
	PTCy/TCD-Sirolimus±MMF	8
HFD	PTCy-Sirolimus-MMF	45
	PTCy-Tacrolimus-MMF	11

Results: Hundred patients (median, 7 years, range, 9 months to 32 years) underwent 100 HCT, 61 males, 39 females. Graft failure was seen in 5 (2 primary, 3 secondary). Median time to neutrophil and platelet engraftment was 13 days (range, 6–20 and 8–48, respectively). At a median follow-up of 1064 days (range, 12–2806) the overall-survival and disease-free survival of the entire cohort is 83% and 79%, respectively. The OS in HLA identical donor HCT is (39/44) 88.64% with a mortality of (5/44) 11.36%. In HFD-HCT, the OS is (44/56) 78.57%, DFS is (40/56) 71.43%, rejection was seen in (5/56) 8.93%, whereas the mortality was (12/56) 21.43%. Although HLA identical donor HCT's fared better but this difference was not significant statistically (Fig. 1, $p = 0.127$). In the HFD-HCT cohort, OS/DFS were better in APOLLO protocol, 80.65% vs rest 76% (OS) and 60% (DFS) but this was not significant statistically ($p = 0.943$). However, the rejection free survival was better in APOLLO protocol (100% vs 75%, $p = 0.0133$). Grade III–IV acGvHD was seen in 8 patients (8.33%) and chGvHD was seen in 11 (9 limited, 2 extensive). CMV was the commonest viral reactivation in (54/100) 54% patients but no CMV related mortality was seen. The OS was superior in patients ≤13 years at time of HCT (87.18% vs 68.18%) (Fig 2, $p = 0.0426$) and also in patients who received HCT after 2018 (87.18% vs 80.33%).



Conclusions: Our study highlights that HCT remains a reasonable curative option for select group of SCD patients. It also highlights that overtime the outcomes of HFD-HCT are improving and matching HLA identical donor HCT. Patients ≤13 years at the time of transplantation do better than patients >13 years old. The rates of rejection and GvHD have gone negligible but infection related morbidity and mortality still needs to be addressed.

Disclosure: None.

O071

HLA identical related cord blood transplantation for patients with transfusion-dependent thalassemia and sickle cell disease

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Background: Allogeneic hematopoietic cell transplantation (alloHCT) is a potentially curative treatment for patients with transfusion-dependent thalassemia (TDT) and sickle cell disease (SCD). Currently, due to genetic counselling and lack of HLA identical HCT donors for genetic disorders, many parents of affected children are seeking information on cord blood transplantation (CBT) specially knowing that embryo selection of an HLA identical-disease-free donor child may be possible with in vitro fertilization.

Methods: With this aim, we performed an analysis of HLA identical related CBT for TDT ($n = 230$) and SCD ($n = 112$), reported to Eurocord/EBMT.

Results: Median age at CBT in patients with TDT was 6.4 years and median follow-up (FU) was 6 years. Most patients received a myeloablative conditioning (MAC), mainly cyclophosphamide (CY) + busulfan(BU) ± other (53%) others with Thiotepa (TT) containing regimens (38%) and 9% other combinations. Anti-thymocyte globulin (ATG) was used in 50%. Bone marrow (BM) from the same donor were added to CB in 50% ($n = 116$). Neutrophil recovery was successful in 95%. Chimerism within the first 100 days of CBT (day-100 chimerism) was available for 121 patients and was full donor in 65% and mixed in 25%, while 10% had autologous reconstitution. A second transplant was performed in 16 patients, mostly due to primary graft failure; 15 of these patients were alive at last FU. Grade II–IV acute GVHD was observed in 10% (II = 16, III = 7, IV = 1) and only 7% had chronic GVHD. Seven patients died, mostly of infections. At 5Y, overall surviva (OS) and GVHD-rejection-free survival (GRFS) were 97% and 82%, respectively. The 5-year OS according to day-100 chimerism was 99% for full donor chimerism; 97% for mixed chimerism and 89% for autologous reconstitution.

Regarding patients with SCD ($n = 112$), median age at CBT was 7.4 years and median FU was 5.4 years. Most of the patients received a MAC regimen, mainly CY + BU ± other (76%). ATG was used in 88%. In 32% ($n = 36$), BM from the same donor was added to the CB graft. Neutrophil recovery was observed in 98%. Day-100 chimerism analysis were available for 74 (66%); mixed chimerism was observed in 64% and 34%, respectively, and 2% had autologous reconstitution. Two patients received a second transplant with BM; one was alive at the last FU.

Grade II–III acute GVHD was observed in 10% (II = 9, III = 2) and only 8% had chronic GVHD. Two patients died, one of infection and the other of SCD-related complications. OS at 5Y and GRFS were 98% and 87%, respectively. The 5Y OS according to chimerism was 98% for patients with full donor chimerism and 96% for those with mixed chimerism. Whether CB or CB + BM cell dose is associated with mixed chimerism should be further investigated.

Conclusions: In conclusion, CB, supplemented or not with BM of the same HLA identical sibling, is a valuable source for alloHCT for patients with TDT or SCD. Despite high frequency of mixed chimerism after CBT, survival was excellent, suggesting that mixed chimerism does not affect final outcomes. More chimerism data, in particular split chimerism analyses in mixed chimera are pivotal to understand the role of mixed chimerism and to develop novel strategies, if needed, in patients with hemoglobinopathies receiving related CBT.

Disclosure: no conflict of interest

Immunodeficiency diseases and macrophages

O074

Alternative donor stem cell transplantation with post-transplantation cyclophosphamide in 37 children with severe combined immunodeficiency (SCID)

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Background: Severe combined immunodeficiencies (SCID) lead to early death from overwhelming infection, usually in the first year of life. Alternative donor (AD) transplantation using post-transplantation cyclophosphamide (PTCY) as graft versus host disease (GVHD) prophylaxis allows immediate donor availability in these time-sensitive transplants, where any delays may result in catastrophic results.

Methods: Retrospective study including all patients with SCID receiving first AD transplantation using PTCY in three pediatric centers. Statistics were performed using the EZR program.

Results: Thirty-seven SCID patients were transplanted between January 2012 and September 2021 at a median age of 9.8 months (range 1.9–109). Seventy percent were male, 67% were malnourished. All but 5 were vaccinated with BCG and 59% had BCGitis/osis before transplant. 40% had a first-grade relative dying from infection at an early age, 64% had comorbidities and/or active infections at admission. Bone marrow was the stem cell source in 98% and the father was the donor in 75%. A total of 35 had haploidentical donors, one had a matched unrelated and one a mismatched related donor (9/10). Most regimens were Busulfan-based (81%), 7 patients received low-dose TBI-based conditioning, and the median total nucleated cell infused was 7.1×10^7/kg. Since most patients were already infected or had severe comorbidities during transplant, ICU transfer, mechanical ventilation, and dialysis were frequent (in 35%, 27%, and 19%, respectively). Severe and very severe hepatic sinusoidal obstruction syndrome (SOS) was observed in almost a third of the cases (27%), all in the busulfan group. The 28- and 60-day cumulative incidence (CI) of neutrophil and platelet recovery was 81% and 75%, respectively. At 100 days, CI of acute GVHD grades II–IV was 21.6% and, at 2 years, CI of chronic GVHD was 12.4%. The CI of CMV reactivation was 40% at a median of 25 days after transplant. BCG infection reactivation occurred in 34% of the vaccinated patients. The median length of inpatient stay was 58 days (range 21–245). With a median follow-up of 31 months, 3-year overall survival (OS) was 74.6% and, although not statistically significant, there was a trend to an inferior OS when comparing patients with or without comorbidities (65.2% vs. 92.3% $p = 0.09$). Nine patients died at a median of 22 days after HCT (range 8–308), with 6 very-early deaths (five due to severe infection, and one due to SOS). There were no graft failures, but mixed chimerism was frequent (34%) and led to an inability to stay off IGIV after transplant in 21% of patients. The median CD4+ count at 100 days was 144 (range 4–741) and did not impact survival.

Conclusions: This is one of the largest series of SCID patients receiving AD Transplantation using PTCY and, although most of our patients were referred at an older age, with severe infections and multiple comorbidities, OS was good. SCID patients should be referred to specialized centers as these transplants are very challenging and need an experienced multidisciplinary team. Newborn screening programs may allow these children to be diagnosed with better clinical conditions and have even better outcomes.

Disclosure: Nothing to declare

O075

HSCT outome in hypomorphic rag deficiencies: an IEWP/PIDTC study

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Background: Biallelic hypomorphic RAG 1 and 2 mutations are responsible for combined immune deficiencies with a broad clinical and immunological phenotype including susceptibility to infections and frequent immune dysregulation such as autoimmunity and granuloma. The later manifestations may prevail and mask the underlying disease. Hematopoietic stem cell transplantation (HSCT) is potentially curative for patients with hypomorphic RAG deficiencies; however, data on clinical and immunological characteristics at HSCT and the course thereafter scarce.

Methods: We conducted an international retrospective multicenter study of patients with hypomorphic RAG mutations (excluding Omenn syndrome and classical SCID) who underwent HSCT using the EBMT and Primary Immune Deficiency Treatment Consortium (PIDTC) data bases. Data on disease manifestations, HSCT characteristics and outcome were collected. Endpoints were overall survival (OS), event-free-survival (death, chronic GVHD, post-HSCT autoimmunity) and quality of immune reconstitution with a focus on naïve T-cells. For descriptive statistics, Kaplan–Meier estimates and log rank test were used: Cox models were applied to determine hazards ratios (HR) with forward selection of covariables.

Results: In this cohort of 60 patients transplanted from 2004 to 2019, the median age at first symptoms was 1.4 years (range 0–15 years). Age at genetic diagnosis was 3.3 years (range 0–40 years), with 12% diagnosed via newborn screening (NBS). Prior to HSCT, infections were documented in 78% of patients (29% with active infection at HSCT), autoimmunity or granulomata in 78% (58% active at HSCT) resulting in frequent end organ damage documented in 57% of patients, mostly affecting the lungs (28%) or liver (10%). Median age at HSCT was 3 (0–43) years. Donors were MUD, MSD/MFD and MMFD in 48%, 22% and 18%, respectively. T-cell depletion was performed in 15 cases (25%). There was an equal distribution between myeloablative vs. reduced toxicity vs. reduced intensity conditioning (32% vs. 37% vs 30%). Graft failure was rare (8%); mixed chimerism was documented in 12%. OS was 70% at 2 years post HSCT. Ongoing pre-HSCT complications (infection, organ impairment) as well as T-cell depletion were major predictors for early death (HR = 8.06 and HR = 6.71, respectively), while age at HSCT was not. Cumulative incidence of acute GvHD and extensive chronic GVHD was 47% and 19%, respectively. De novo autoimmunity within 6 months post HSCT was observed in 8 patients (20%). Immune reconstitution, particularly naïve T cell counts was faster and more robust in patients undergoing HSCT before age 4 years.

Conclusions: Pre-HSCT clinical status (infection and organ damage) as well as T-cell depletion of the graft but not age at HSCT predicted an unfavorable HSCT outcome. Naïve T cell count recovery was better in patients transplanted at a younger age. These findings advocate for early HSCT in patients with hypomorphic RAG 1/2 deficiencies and continued efforts to minimize the toxicity of HSCT for these patients to make earlier hSCT referrals more acceptable. NBS may facilitate an earlier diagnosis in these patients. In addition, high probability of de novo autoimmunity observed in this series might be related to thymic damage pre/during HSCT and a persistence of a central tolerance defect early after HSCT.

Disclosure: The authors declare no conflict of interest

Inborn errors, granulocyte and osteoclast disorders

O076

Pilot study on memory T-cell addback after TCRAB/CD19 depleted haploidentical hematopoietic cell transplantation in children with non-SCID inborn errors of immunity

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Background: In this pilot study, we explored the safety and potential of adoptive immunotherapy with donor T cells enriched for memory cells (addback) after TCRab/CD19-depleted haploidentical hematopoietic cell transplantation (TCRab-HaploSCT) in children with non-SCID inborn errors of immunity (IEI), to reduce the barriers of delayed immune reconstitution and increased viral infection after TCRab-HaploSCT.

Methods: Eight children with non-SCID IEI were included in the pilot study from March 2020 to July 2021. All patients were conditioned with fludarabine (160 mg/m^2), treosulfan (30–42 g/m^2), thiotepa (10 mg/m^2), ATG (Grafalon, 5 mg/kg/dose on day −4, −3, −2) and Rituximab (200 mg/m^2 on day-1). All received TCRab/CD19 depleted PBSC graft on day 0 and CD45RO+ memory T-cell addback (maximal dose of 1×10^6/kg CD45RO+ was given within the limit of CD45RA+ $<2.5 \times 10^4$/kg) on day +1.

Results: Median age of transplant was 2.4 years (range, 1.1–11.3). The primary diagnoses were MHC class II deficiency ($n = 3$), CGD ($n = 1$), IL2RB deficiency ($n = 1$), XLP ($n = 1$), ZAP70 deficiency ($n = 1$) and LAD ($n = 1$). All except one (LAD; second HCT) were first transplants. All patients had active infection within 100 days prior to transplant. All had viraemia (3 CMV, 1 adeno+HHV6+EBV, 1 adeno, 3 HHV6). Three had active viral enteritis at HCT (2 norovirus; 1 parechovirus, norovirus, salmonella and cryptosporidium). Two had fungal chest infection. For TCRab/CD19 depleted PBSC graft, median CD34+ cell dose was 18.2×10^6/kg (10.4–34.2) and median TCRab was 3.5×10^4/kg (0.5–4.9). Median CD45RO+ cell dose was 1×10^6/kg (0.2×10^4–1×10^6/kg) and median CD45RA+ cell dose 1.1×10^4/kg (0.3–2.5×10^4/kg). All engrafted with median neutrophil and platelet recovery of 15 days (9–23) and 12 days (7–17). None had VOD or TMA. Four had grade 2 cutaneous aGvHD. None had visceral GvHD, Grade III–IV aGvHD or cGvHD. Three had CMV viraemia (duration of viraemia was 19, 21 and 29 days; highest viral load log 4.4; none had CMV disease); one had adenoviraemia (highest viral load log 4.0; duration of viraemia, 5 days); 3 had HHV6 viraemia

(duration of viraemia, range 7–52 days); none had EBV viraemia. Mean time of CD3+ >200 cells/mL was 68 ± 49 days (range 14–123 days), which was shorter than historical TCRab-HaploSCT cohort ($n = 28$, mean 115 ± 77 days) ($p = 0.08$) (Fig. 1). CD3+ lymphocyte reconstitution was variable even among patients received CD45RO+ add back of 1×10^6/kg (Fig 2). Figure 3 shows deep immunophenotyping of patient 1 with MHC class II deficiency. All patients except one (IL2RB deficiency) had 100% donor chimerism at last follow-up. The patient with IL2RB deficiency had secondary autologous reconstitution at 4 months post-HCT and underwent a successful second transplant.

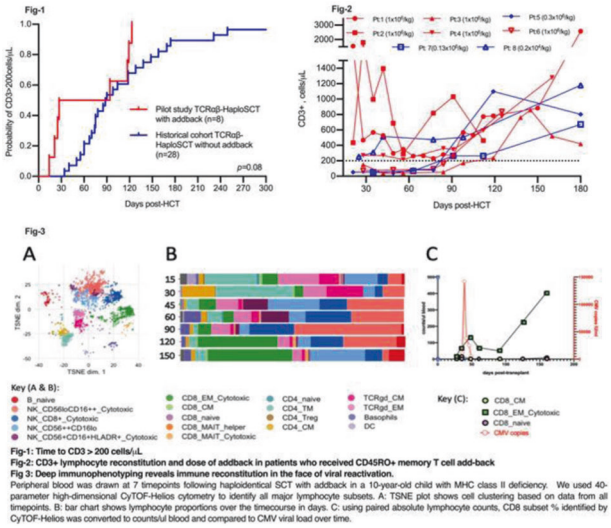

Fig-1: Time to CD3 > 200 cells/μL
Fig-2: CD3+ lymphocyte reconstitution and dose of addback in patients who received CD45RO+ memory T cell add-back
Fig 3: Deep immunophenotyping reveals immune reconstitution in the face of viral reactivation.
Peripheral blood was drawn at 7 timepoints following haploidentical SCT with addback in a 10-year-old child with MHC class II deficiency. We used 40-parameter high-dimensional CyTOF-Helios cytometry to identify all major lymphocyte subsets. A: TSNE plot shows cell clustering based on data from all timepoints. B: bar chart shows lymphocyte proportions over the timecourse in days. C: using paired absolute lymphocyte counts, CD8 subset % identified by CyTOF-Helios was converted to counts/ul blood and compared to CMV viral load over time.

Conclusions: We demonstrated that CD45RO+ memory T-cell addback is safe in children with non-SCID IEI. T-lymphocyte reconstitution is unpredictable, this is potentially attributed to proximity of the addback to ATG infusion. In our upcoming prospective phase I/II trial, three escalating doses of addback (0.3, 0.6 and 1×10^6/kg) will be studied, and the addback will be infused on day+7. This trial will recruit prospective TCRab-HaploSCT without addback and MUD recipients for comparison and ATG/alemtuzumab pharmacokinetic studies will be performed.

Disclosure: None

O077

In depth immune profiling of IL2RG deficient patient 50 years after hematopoietic stem cell transplantation reveals a diverse naive but oligoclonal memory T cell compartment

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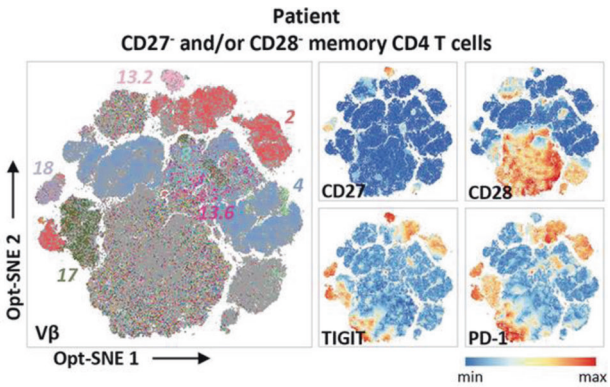
Background: The first successful European hematopoietic stem cell transplantation (HSCT) was performed without conditioning in 1968 as treatment in a newborn with IL2RG deficiency using an HLA identical sibling donor. Because of declining numbers of naive T cells and NK cells, and persistent human papilloma virus (HPV)-induced warts, he received an unconditioned peripheral stem cell boost at the age of 37 years.

Methods: The unique long-term follow-up of this patient gave us the opportunity to assess the T cell compartment in peripheral blood before and up to 14 years after the boost by flow cytometry. To simultaneously analyze the T cell phenotype and T cell receptor (TCR) repertoire, a set of TCR Vβ antibodies was combined with antibodies specific for T cell differentiation and activation. A single-cell analysis pipeline was applied to visualize and quantify the TCR Vβ repertoire at distinct T cell maturation stages. TRB sequencing was applied on sorted T cell subsets from blood and on T cells from skin biopsies.

Results: Before the boost, the TCR Vβ diversity of the naive T cells of the patient was comparable to his healthy donor, despite a low absolute number of naive CD4 and CD8 T cells. After the boost, the numbers of naive T cells were increased to normal levels, and the TCR diversity as assessed by TRB sequencing was indistinguishable from an age-matched healthy control. Interestingly, before and after the boost, memory CD4 and CD8 T cells that lost CD27 and/or CD28 represented at least 40% of the T cells, while these cells were nearly absent in his donor. Within the $CD27^-$ and/or $CD28^-$ memory compartment, multiple clusters with persistence of at least 14 years were identified with a homogenous phenotype of TIGIT and PD-1, and only one dominant TCR Vβ. TRB sequencing confirmed the clonality of these T cell expansions. Detailed phenotypical analysis by spectral flow cytometry revealed a chronic CMV-associated phenotype of these expansions: $CD57^+KLRG1^+CX3CR1^+$. Since the patient is seronegative for CMV, this finding suggests that the phenotypic imprint is caused by another chronic virus infection, i.e., HPV. To study the link with HPV, we performed TRB sequencing of T cells from HPV-induced skin lesions and healthy skin. Interestingly, abundant $CD27^-$ and/or $CD28^-$ CD8 memory clonotypes found in blood, were also present in wart enriched skin tissue, but not in healthy skin of the patient. Although we could not confirm specificity of the clonal expansions using a selection of HPV2-derived peptides, the presence of overlapping clonotypes in blood and skin lesions is strongly suggestive for a link with HPV.



Conclusions: In an IL2RG deficient patient we demonstrate a diverse and lasting naive T cell compartment, supported by a stem cell boost, and an oligoclonal memory compartment half a century after HSCT.

Disclosure: Nothing to declare

O078

Targeted, myeloablative busulfan is well tolerated in infants with Hurler syndrome

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Background: Haematopoietic cell transplantation (HCT) serves to change the natural history and ameliorates multi-system disease in Hurler syndrome (HS). Reduced-intensity protocols are associated with increased graft failure. Outcomes depend on age at transplant and, with newborn screening (NBS), then the age at transplant will fall. We review our experience of using Busulfan (Bu) pharmacokinetics (pk) targeted myeloablative conditioning (MAC) in infants with HS at our centre for the last 16 years.

Methods: We retrospectively analysed data of 48 infants with HS undergoing MAC with Bu at our centre performed between 2005 and 2021.

Results: The median age at HCT was 7.2 months (range, 3.9–12.4 months), male:female 22:26. All received Busulfan in MAC doses either intravenously or orally with pK monitoring; target AUC being 90 mg/L/h. The conditioning protocols were either Bu/Cyclophosphamide (Cy) [$n = 12$] or Bu/Fludarabine (Flu) [$n = 36$], with serotherapy [Anti-Thymocyte Globulin (ATG)-19, Alemtuzumab-19 and ATG/Rituximab in 10 patients, respectively]. Donors were matched unrelated donors (MUD) [$n = 25$], mismatched unrelated donors (MMUD) [$n = 8$], mismatched family donor ($n = 1$) and matched family donor (MFD) [$n = 14$]. Cord blood (CB) [$n = 28$], peripheral blood (PB) [$n = 7$] and bone marrow (BM) [$n = 13$] were stem cell sources.

The median total nucleated cell (TNC) dose for CB was 16×10^7/kg body weight (range, 1–28.39) and the median CD34 cell doses were 9.6×10^6/kg (range, 10–42.6×10^6) and 10×10^6/kg (range, 8.4–14.2×10^6) for PB and BM, respectively.

Median neutrophil engraftment was at 14 days (range, 11–31 days) post HCT and platelets were engrafted at 22.5 days (range, 12–45 days). A total of 27% ($n = 13$) of patients developed veno-occlusive disease (VOD) managed conservatively or with Defibrotide and there was no multi-organ failure associated with VOD. Acute graft versus host disease (GvHD) of skin grade I ($n = 10$), grade I–II ($n = 3$), grade II ($n = 4$), or grade IV ($n = 2$) and liver GvHD ($n = 1$), lung GvHD ($n = 1$) were noted while 1 patient had chronic GvHD of skin (limited). Viral reactivation was seen in 37.5% patients (adenovirus 12,CMV-4, EBV-2).

Five patients experienced graft failure (primary 3 with cord blood, and secondary with autologous reconstitution in 2), and 4 had undergone a second HCT and are alive and engrafted, and 1 received donor lymphocyte infusion (DLI). A total of 44 patients are alive and engrafted (including 4 who had a second transplant,1 who received DLI, and 1 with persistent, adequate mixed chimerism). Four patients experienced transplant-related mortality (TRM) [immune cytopenia, chronic lung GvHD, respiratory syncytial virus (RSV) pneumonitis and cardiorespiratory disease]. Event free survival (EFS) at 1year was 81.3%, events being graft failure and death as demonstrated in Fig. 1 and the overall survival (OS) at 2 years was 91.7% as depicted in Fig. 2. Full donor chimerism was observed in 75%($n = 36$) patients after the first HCT.

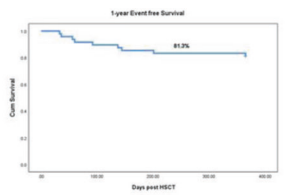

Figure1: 1- year Event free Survival (Events=Death and graft failure).

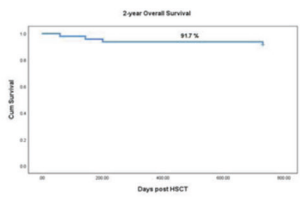

Figure2: 2-year Overall survival

Conclusions: Incorporating Bu in MAC with pk-guided dose monitoring for HS is well tolerated in infants, with no death related to conditioning therapy, and high rates of donor-derived engraftment. These results are similar to older children transplanted in our centre, and give confidence that similar MAC-Bu can be given to infants, including in gene therapy protocols, and after NBS.

Disclosure: Nothing to declare

O079

CD3+ TCRαβ/CD19+ depleted haploidentical haematopoietic cell transplantation as a salvge strategy for graft failure or refractory graft versus host disease in inborn errors of immunity

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Background: This single-centre retrospective case series reports the feasibility and outcomes of CD3+ TCR αβ/CD19 depleted haploidentical haematopoietic cell transplantation (TCRαβ-HaploSCT) for 11 children with inborn errors of immunity (IEI) who developed graft failure or refractory aGvHD between 2013 and 2021.

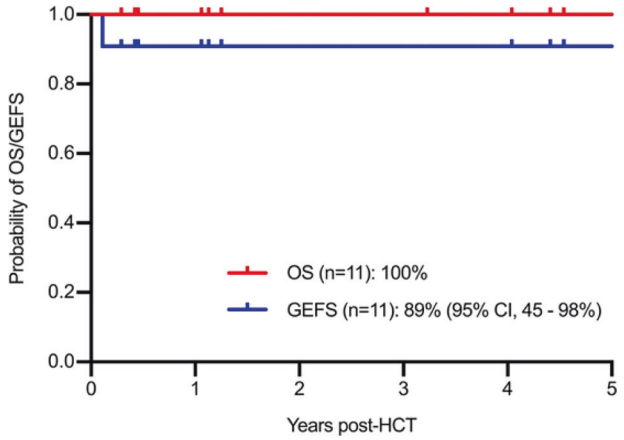
Methods: Data on patient and transplant characteristics, indications of salvage TCRαβ-HaploSCT and outcomes were collected. Outcomes of interest were overall survival, GvHD-free, event-free survival (GEFS; survival without graft failure, grade III–IV aGvHD and cGvHD), toxicities, GvHD, viraemia and long-term graft function.

Results: The median age at first HCT was 0.73 years (range: 0.21–6.13 years) and the median age at salvage TCRαβ-HaploSCT was 3.46 years (1.2–11 years). The median interval between first and salvage TCRαβ-HaploSCT was 1.7 years (3 months to 9 years). The primary diagnoses were SCID ($n = 4$), CGD ($n = 2$), APDS ($n = 1$), LAD ($n = 1$), MSMD ($n = 1$), WAS ($n = 1$) and perforin deficiency ($n = 1$). For the first HCT, the donor type and stem cell source were MFD (marrow, $n = 1$; PBSC, $n = 1$), MUD (PBSC, $n = 3$; CB, $n = 3$), MMUD (marrow, $n = 1$) and T depleted HaploSCT ($n = 2$; 1 CD3/19 depletion; 1 TCRαβ/CD19 depletion). All except one (SCID) received conditioned HCT (9 had Flu-Treo (FT) and alemtuzumab ($n = 8$) or ATG ($n = 1$); one FT-thiotepa (FTT)-ATG). Indications for salvage HaploSCT were primary graft failure ($n = 1$), secondary autologous reconstitution ($n = 6$), refractory aGVHD ($n = 3$) and secondary leukaemia ($n = 1$, RAG-SCID). Median whole blood donor chimerism ($n = 5$) immediately prior to salvage HSCT was 19% (7–100%). In patients where split cell chimerism was available ($n = 8$), the median myeloid, B-lymphocyte and T-lymphocyte chimerism was 4% (0–20%), 9% (0–78%) and 39% (27–93%), respectively. Donors were haploidentical parental donors ($n = 9$; one had the same donor as first TCRαβ-HaploSCT) and MMUD ($n = 2$). All but one conditioned with FTT and ATG ($n = 9$) or alemtuzumab ($n = 1$); one had FT and alemtuzumab (SCID). All received TCRαβ/CD19 depleted PBSC with CD34+ 9.5×10^6/kg (2.8–32.3) and TCR αβ dose 4×10^4/kg (1.3–19.2). One patient received iCasp suicide gene-modified T cell addback and two received CD45RO+ memory T cell addback. All except one engrafted with median day to neutrophil and platelet recovery of 15 (12–27) and 12 (9–19). None had veno-occlusive disease or transplant-associated microangiopathy. Four (36%) had grade II aGvHD and none had grade IIII–IV aGvHD or cGvHD. Two had CMV, 5 adeno and 3 HHV6 viraemia; none had EBV viraemia. One patient (TCRαβ/CD19 depleted MMUD) had primary aplasia and received a successful third MUD PBSC transplant from the first donor.

The median duration of follow-up was 1.3 years (0.3–8.0 years). The 1-year OS and GEFS were 100% and 89% (95% confidence interval, 45–98%) (Fig. 1). All patients with successful salvage HaploSCT ($n = 10$) had 100% donor chimerism. The RAG-SCID patient with high-risk B acute lymphocyte leukaemia (KMT2A-

LARS2 fusion and MRD positive after induction) remained in remission 15 months post-HCT.

Figure 1. Overall survival (OS; red) and GvHD-free, event-free survival (GEFS; blue) of the study cohort.



Conclusions: This retrospective case series shows that salvage therapy using TCRαβ-HaploSCT is a safe alternative donor transplant strategy for patients without a suitably matched donor or if an urgent transplant is needed.

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to declare

O080

Autoimmune cytopenia after haematopoietic cell transplantation for children with inborn errors of immunity: a multicentre retrospective cohort analysis

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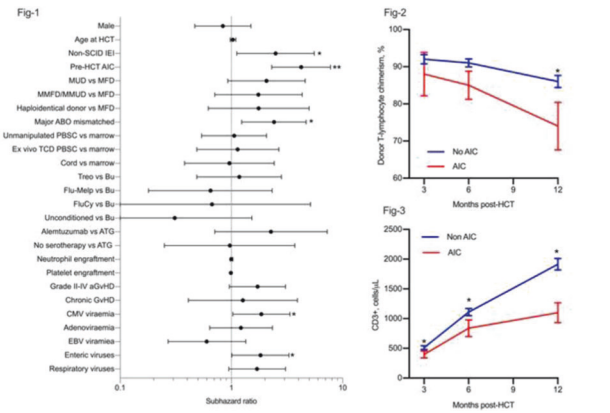
Background: In this study involving two supraregional transplant centers for inborn errors of immunity (IEI), we conducted an analysis of incidence, risk factors, outcome of post haematopoietic cell transplantation (HCT) autoimmune cytopenia (AIC) in children with IEI.

Methods: Between January 2009 and December 2018, 536 IEI patients who underwent first allogeneic HCT at the Great North Children's Hospital or Great Ormond Street Children's Hospital were included in the study. Cumulative incidence (CNI) of post-HCT AIC was calculated using a competing risk analysis, considering death and graft failure as competing events. Risk factors included for analysis were gender, age at transplant, indication for HCT, pre-HCT AIC, donor type, donor-recipient ABO matching, stem cell source, conditioning, conditioning type, serotherapy, graft-versus-host disease (GvHD) prophylaxis, neutrophil and platelet engraftment, acute GvHD, chronic GvHD, viraemia, respiratory and enteric viral infections. All factors associated with a p value <0.10 by univariate analysis were included in a multivariate analysis using subdistribution hazard model of Fine-and-Gray.

Results: Forty-nine children (CNI, 9%, 95% CI 8–13%) developed post-HCT AIC, with median onset at 6.5 months (range, 0.7 months to 4.2 years). Types of AIC were autoimmune haemolytic anaemia (AIHA, $n = 28$, 58%), immune thrombocytopenia (ITP, $n = 9$, 18%), autoimmune neutropenia (AIN, $n = 3$, 6%), AIHA + ITP ($n = 5$, 10%), AIHA+AIN ($n = 1$, 2%), AIHA+ITP+AIN ($n = 1$, 2%) and ITP +AIN ($n = 2$, 4%). Twenty-four (49%) were on immunosuppressive therapy (CSA/tacrolimus ± steroids/others, $n = 19$; steroids ± others, $n = 5$) at the onset of post-HCT AIC. On univariate analysis (Fig. 1), non-SCID IEI ($p = 0.02$), pre-HCT AIC ($p < 0.001$), major ABO mismatched ($p = 0.007$), CMV viraemia ($p = 0.04$), enteric viruses ($p = 0.04$) were significantly associated with post-HCT AIC. After multivariate analysis, pre-HCT AIC (SHR 3.99, 95% CI, 2.21–7.21, $p < 0.001$), major ABO mismatched (SHR 2.37, 1.27–4.45, $p = 0.007$) and grade II–IV aGvHD (SHR 2.01, 1.18–3.63, $p = 0.01$) were independently associated with post-HCT AIC. Patients with post-HCT AIC had significantly lower donor T-lymphocyte chimerism at month 12 post-HCT compared to patients without post-HCT AIC ($p = 0.009$, Fig. 2). Median T cell chimerism at 12 months post-HCT was 76% (10–100%) in patients with post-HCT AIC and 96% (7–100%) in patients without post-HCT AIC. Donor myeloid chimerism at month 3, 6 and 12 post-HCT had no association with risk of AIC. CD3+ (Fig. 3) and CD4+ CD45RA+ CD27+ lymphocyte count was significant lower in patients with post-HCT AIC at month 3, month 6, and month 12 after HCT.

Corticosteroid ± high-dose IVIg achieved remission in 33% ($n = 16$) and the remaining patients required multimodal therapies including rituximab, bortezomib, sirolimus and MMF. Median follow-up of 4.6 years (range, 0.4–10.0) showed that 37 of 46 survivors (80%) were in complete remission, 6 (15%) were in remission with immunosuppressive therapy including sirolimus, low dose steroids or MMF, and 2 (5%) required a second HCT (1 refractory aGvHD and 1 persistent aplasia after AIHA). The transplant related mortality (TRM) in patients with post-HCT AIC was 6% (4 deaths: 3 TRM and one due to underlying disease).



Figures: 1) Univariate analysis of risk factors for development of post haematopoetic cell transplantation (HCT) autoimmune cytopenia (AIC) using Fine-and-Gray model with death and graft failure as competing eventsLeiden University Medical Centre. 2) Impact of donor T-lymphocyte chimerism on post-HCT AIC. 3) CD3+ lymphocyte reconstitution in patients with and without post-HCT AIC
* indicates $p<0.05$ and ** indicates $p<0.001$

Conclusions: Strategies to reduce GvHD and improve T-lymphocyte chimerism and immune reconstitution may reduce the incidence of potentially life-threatening post-HCT AIC.

Disclosure: None

O081

Prepad: predicting patient death after alloHSCT for inborn errors using machine learning, an IEWP study

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Background: Survival models after allogeneic hematopoietic stem cell transplantation for inborn errors remain inaccurate. By creating a machine learning model that integrates all inborn errors and estimates general and disease-specific effects, we aimed to improve survival predictions both within and across different diagnoses.

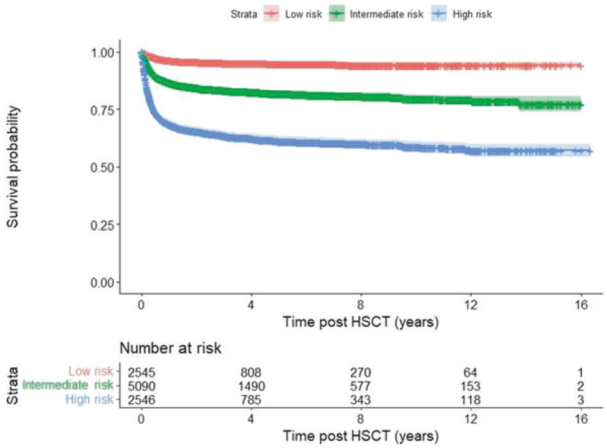
Methods: In this retrospective megafile study survival of 10,261 patients who received a first allogeneic transplant between 2003 and 2018 for an inborn error was modelled. We evaluated the impact of patient, donor and transplant characteristics on survival using survival curves and Cox models, and modelled effects within different diseases and donor types. We evaluated predictive performance using the cross validated area under the ROC curve (AUC). In this analysis 0.5 indicates the prediction is not more accurate than chance alone while 1 indicates perfect predictions. To integrate all predictors, we used XGBoost, which can handle missing data and model deep nonlinear interactions.

Results: In univariate analysis, the best predictor of survival was categorized diagnosis (AUC 0.643), closely followed by exact diagnosis (AUC 0.636) and donor type (AUC 0.635). Hemoglobinopathies had the best 1-year survival at 93% (92–94%), while histiocytic disorders had the least favourable 1-year survival (74%, 71–77%). Identical siblings had the most favourable 1-year survival at 92% (92–91%), while this was 71% (68–74%) with mismatched related donors.

In congenital bone marrow failure (CBMF), hemoglobinopathies and inborn errors of immunity and metabolism (IEIM) donor type was most predictive, favouring matched sibling donors, with a 1-year survival difference vs an unrelated donor between 3.7% in hemoglobinopathies and 11.8% in CBMF. In histiocytic disorders, however, CMV matching was more predictive, with a 15.9% survival difference between a negative patient with positive donor and a positive patient with negative donor.

We determined a risk score using XGBoost, which was highly predictive of survival (AUC 0.725, 0.711–0.739). We assigned each transplant to be low, intermediate or high risk if they were below, within or above the IQR respectively. The low-risk group had a 1-year survival of 97% (96–97%) while this was 68% (66–70%) in the high-risk group.

Within disease and donor type, we compared the risk score with the best predictor. The risk score was substantially more predictive in each subgroup with less variance. Hemoglobinopathies, CGD and identical sibling transplants were overrepresented in the low-risk group, while histiocytic disorders were overrepresented in the high-risk group.



Conclusions: By integrating diagnoses and using machine learning to account for deep nonlinear interactions, mortality risk can be determined accurately, both globally and within disease and donor subgroups.

Disclosure: Nothing to declare

O082

Clinical trial update: ex vivo autologous stem cell gene therapy in MPSIIIA

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Covariate	Category	N	Survival at 1 year	AUC strongest predictor	AUC risk score	Risk group (low/intermediate/high)
Disease	CBMF	130	80.5% (73–88%)	Donor type: 0.559 (0.448–0.670)	0.681 (0.553–0.808)	3.8/59/37%
	Hemoglobinopathies	4090	93.2% (92–94%)	Donor type: 0.603 (0.578–0.639)	0.695 (0.660–0.730)	58/40/1.9%
	Histiocytic disorders	874	75.0% (71–78%)	CMV matching: 0.541 (0.503–0.568)	0.606 (0.560–0.652)	0.0/40/60%
	IEIM	5088	79.3% (78–81%)	Donor type: 0.602 (0.575–0.627)	0.672 (0.653–0.692)	3.4/59/37%
Donor type	Identical sibling	4512	91.6% (91–93%)	Disease: 0.631 (0.603–0.684)	0.707 (0.679–0.735)	49/44/6.3%
	Matched relative	854	87.3% (85–90%)	CMV matching: 0.596 (0.477–0.651)	0.606 (0.544–0.669)	5.7/77/17%
	Mismatched relative	1159	71.7% (69–75%)	CMV matching: 0.593 (0.552–0.654)	0.668 (0.631–0.705)	0.9/38/61%
	Unrelated	3612	79.4% (78–81%)	Stem cell source: 0.578 (0.548–0.596)	0.663 (0.641–0.686)	7.1/54/39%

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Background: Ex vivo autologous haematopoietic stem cell gene therapy (HSC-GT) is emerging as a viable and potential treatment option for refractory and monogenic metabolic diseases such as Mucopolysaccharidosis type IIIA (MPSIIIA). MPSIIIA is a lysosomal storage disorder where pathogenic variants in the *SGSH* gene leads to accumulation of glycosaminoglycans (GAGs) including heparan sulphate (HS). This accumulation leads to cell inflammation and ultimately cell death. Affected children typically present around 2 years of age with developmental delay and deterioration in cognitive skill set; the disease then progresses with profound behavioural disturbance, eventual physical disability and premature death occurring usually in the late teenage years.

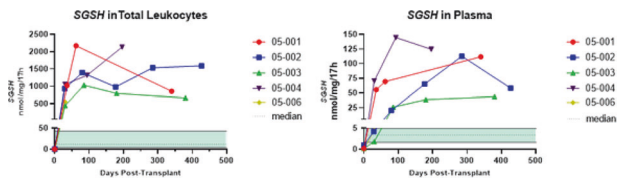
Unlike other lysosomal storage disorders, MPSIIIA does not respond to allogeneic stem cell transplant, and there is currently no effective enzyme replacement therapy.

Here we provide updates on a phase I/II clinical trial treating patients with MPSIIIA with ex vivo autologous HSC-GT.

Methods: In this phase I/II, open label, safety and tolerability study, mobilised $CD34^+$ stem cells are collected via apheresis. Cells are transduced ex vivo with a lentiviral vector containing a myeloid promoter CD11b and the *SGSH* gene to create the investigational medicinal product (IMP). The CD11b drives overexpression of the SGSH protein in myeloid derived cell lines. Patients receive myeloablative conditioning and the IMP is then infused.

Results: A total of five patients have received the IMP; the infused vector copy number (VCN) ranged from 1.19 to 8.91 copies/cell and cell dose between 4.3 and 22.7×10^6 $CD34^+$/kg. Engraftment was successfully achieved in all five patients—median time to neutrophil, platelet and red cell engraftment was 19, 28 and 25 days, respectively. In patients with available follow-up, engraftment is sustained; supra-physiological levels of SGSH enzyme was seen in leukocytes (see Fig. 1a) and was 38–91-fold above normal (median) at 1 month post-transplant, plateauing from 3 months post-transplant. Significant SGSH levels were also rapidly detected in $CD15^+$ lineages, plasma and bone marrow. CSF SGSH levels were within or above normal range by six months post-transplant. Substrate reduction was shown by a substantial fall from baseline in GAGs and heparan sulphate in both urine (>90%) and plasma (82%) samples post-transplant. Neurocognitive outcomes for these patients continue to be assessed and plotted against the age-matched natural history.

Data from a single patient treated off-trial continues to show supra-physiological biochemical data and neurocognitive studies show an improved phenotype compared to the natural history of the disease.



Conclusions: These five children with MPSIIIA have safely received ex vivo autologous HSC-GT which was well tolerated, continues to deliver supra-physiological levels of enzyme and reduces substrate accumulation.

Clinical Trial Registry: NCT04201405.

Disclosure: BB—Orchard Therapeutics: current equity holder in publicly traded company, membership on an entity's Board of Directors or advisory committees, research funding. SJ–Orchard Therapeutics: current equity holder in publicly traded company, membership on an entity's Board of Directors or advisory committees. AT—Orchard Therapeutics: consultancy, membership on an entity's Board of Directors or advisory committees, other: equity ownership; Rocket Pharmaceuticals: consultancy, membership on an entity's Board of Directors or advisory committees; Generation bio: consultancy, membership on an entity's Board of Directors or advisory committees, other: equity ownership; 4Bio Capital: consultancy, membership on an entity's Board of Directors or advisory committees.

Infectious complications

O084

Listeria infection in hematopoietic cell transplant recipients: an international case–control study of the Infectious Diseases Working Party of the EBMT

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Background: *Listeria* infection (listeriosis) is a rare infection after hematopoietic cell transplantation (HCT). Current literature is limited to small case series, and risk factors in this population are poorly identified. The aim of this international retrospective study was to identify risk factors for listeriosis and to describe its presentation and outcome in HCT patients.

Methods: All EBMT centers were invited to report listeriosis cases diagnosed during 1 Januray 2000 to 31 March 2021. The objectives were to assess risk factors for listeriosis and to describe the disease's clinical, microbiological, and outcome characteristics. Two matched control subjects were requested per each case. For

risk factors identification, a multivariable analysis was performed using logistic regression.

Results: We identified 42 listeriosis episodes in 31 (74%) allo- and 11 (26%) auto-HCT recipients (20 centers, 11 countries); 5/42 (12%) were children. Listeriosis occurred at a median of 4.5 (interquartile range [IQR] 0.3–19) months post-HCT. The most common underlying diseases were plasma cell disorders (14; 33%) and acute myelogenous leukemia (12; 29%). The most common signs and symptoms were fever (39; 93%), headache (9; 21%); diarrhea, and impaired consciousness (8 each; 19%). Thirty-nine (92%) patients had *Listeria* bacteremia at presentation.

Central nervous system (CNS) infection was reported in 11 (26%) patients; all presented with fever, bacteremia, and neurological findings. Cerebrospinal fluid (CSF) analysis revealed high protein (median 1267; IQR 1168–1807 mg/L; $n = 10$); pleocytosis (median white blood cells count 172; IQR 91–623 cells/mm^3; $n = 8$; 2 missing data); variable lymphocyte/neutrophile ratio; low glucose (in 3/8; 38%); and yielded *Listeria* in 8 patients. Two patients with negative CSF culture presented with fever, limb paralysis, CSF pleocytosis, and high protein, and brain imaging demonstrating focal lesions. The eleventh patient presented with septic shock and impaired consciousness; abnormal electroencephalogram, MRI revealed leukoencephalopathy, CSF was not obtained; he died 17 days later.

Listeria species were *monocytogenous* ($n = 41$), or *innocua* ($n = 1$). *Listeria* were susceptible to all tested antibiotics, including amoxicillin ($n = 35$), trimethoprim–sulfamethoxazole ($n = 31$), gentamicin ($n = 17$), meropenem ($n = 16$), penicillin ($n = 9$) and linezolid ($n = 4$), except for 1/6 isolates resistant to fluoroquinolones. The most used antibiotics were of penicillin-group (38; 91%; mainly ampicillin; 27; 64%); 21 (50%) patients received combination (>3 days); mainly beta-lactam and aminoglycoside (17/42; 41%). Treatment duration was median 20 (IQR 15–25) days.

Thirty-seven (88%) patients fully recovered; one (2%) had residual neuropathy. Four patients (10%) died within 15–53 days after listeriosis diagnosis, among them 3/11 (27%) with and 1/31 (3%) without CNS listeriosis. Sixty-nine controls were reported. In the multivariate analysis, the following factors were significantly associated with listeriosis: ≥2 HCT (OR [95% CI] 5.9 [1.4–24.4], $p = 0.01$); lymphocytopenia<500 cells/mm^3 (2.7 [1.1–7.0], $p = 0.04$); not being in complete remission at the time of listeriosis (3.1 [1.1–9.0], $p = 0.03$). There were no significant differences in demographic, HCT characteristics, immunosuppression, and cotrimoxazole prophylaxis. At the last follow-up, 20 (48%) of listeriosis cases and 50 (72%) of controls were alive ($p = 0.009$).

Conclusions: CNS listeriosis in HCT patients is associated with high mortality. Patients following multiple HCT, having lymphocytopenia, and those not in complete remission are at increased risk for listeriosis. Listeriosis was associated with increased post-HCT mortality.

Disclosure: No conflicts of interest relevant for this study

O086

Posoleucel, multivirus-specific T-cell (VST) therapy, for prevention of clinically significant viral infections in allogeneic transplant recipients: persistence of VSTs in an open-label phase 2 trial

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Background: Approximately 70% of high-risk allogeneic hematopoietic stem cell transplant (allo-HCT) recipients experience clinically significant infections (CSI) and/or end-organ disease (EOD) from double-stranded DNA viruses; adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus- 6 (HHV-6) and JC virus (JCV). Posoleucel is an allogeneic, off-the-shelf, multivirus-specific T-cell therapy designed to target these six viruses. We completed target enrollment to the Phase 2 open-label trial for the prevention of viral CSI/EOD in high-risk post-allo HCT recipients and report updated clinical data and novel biomarker analyses from the trial.

Methods: Patients received posoleucel infusions every 2 weeks starting 15–42 days post allo-HCT for a total of seven infusions. The primary endpoint was number of new-onset CSI or EOD from any of the six viruses through week 14, and through week 26 as a key secondary endpoint. IFN-ɣ ELIspot analysis was performed on serial peripheral blood samples to assess immune reconstitution and determine the frequency of circulating virus-specific T cells (VSTs) over time. To evaluate the potential contribution of posoleucel to anti-viral immune reconstitution T-cell receptor beta (TCR-ß) immunosequencing using ImmunoSEQ(r) (Adaptive Biotechnologies) was performed at selected timepoints. TCR sequences unique to posoleucel were identified computationally and used to track in vivo persistence in serial patient samples.

Results: In the 25 high-risk allo-HCT recipients dosed to date, posoleucel has been generally well tolerated with no unanticipated safety signals identified. Patients receiving posoleucel have had low rates of CSI and no EOD due to the six target viruses. Preliminary assessment of infecting virus-specific T cell activity by IFN-γ ELIspot demonstrated that in six of seven patients with CSI or high viral loads there was a corresponding increase in VST activity to the infecting viruses. Of the six patients with TCR-ß immunosequencing data currently available, all had detectable posoleucel cells, with confirmed persistence for up to 14 weeks after the last infusion. Five of these six patients had transient viremia from at least one virus during the first 14 weeks with subsequent posoleucel expansion. Updated safety, efficacy, and biomarker data will be presented.

Conclusions: The high-risk allo-HCT recipients receiving posoleucel in this phase 2 open-label trial had low rates of CSI and no EOD. Repeat dosing of posoleucel was generally safe and well tolerated. ELIspot and Immunosequencing data shows in vivo activity of posoleucel in the presence of reactivating viruses. This biomarker data along with the clinical data generated from this Phase 2 trial support advancement into Phase III to determine efficacy and safety in a larger placebo-controlled population.

Clinical Trial Registry: Clinicaltrials.gov NCT04693637.

Disclosure: SSD has served on an advisory board for Merck, and has served as a speaker for Merck and Astellas, and has received research funding from AlloVir and Sire/Takeda. GDM has served on an advisory board and speakers bureau for Novartis, he has consulted for Eliana, and has received research funding from AlloVir. J-AY, RB, JY have nothing to declare. MM and KB are employees of and hold stock in AlloVir. SV and AL are consultants for AlloVir. JH has served as a consultant for Amplyx.

O087

Safety and immunogenicity of high-dose influenza vaccine in pediatric hematopoietic cell transplant recipients

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Bocchini[7], E. Moulton[7], M. Grimley[8], G. Paulsen[8], C. Harrison[1], J. Freedman[3], P. Carpenter[9], J. Englund[9], L. Danziger-Isakov[8], F. Munoz[7], A. Spieker[2], N. Halasa[2]

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Background: Pediatric hematopoietic stem cell transplant (SCT) recipients are at high risk for influenza-related morbidity and mortality and have suboptimal immune responses to influenza vaccination compared with age-matched healthy controls. Prior phase I studies demonstrated high-dose (HD) influenza vaccination to be safe and immunogenic in immunocompromised populations.

Methods: This phase II, randomized-controlled, double-blind, multi-center trial compared two doses of either HD trivalent (HD-TIV) or standard dose-quadrivalent (SD-QIV) influenza vaccine administered 1 month apart in children 3–17 years who were 3–35 months post-allogeneic SCT. Local and systemic adverse events were assessed for 7 days post-vaccination, and hemagglutinin antibody inhibition (HAI) titers were performed at baseline, approximately four weeks following each vaccine dose, and approximately 6 months post-second vaccination. We determined the geometric mean fold rise (GMFR) from baseline within each vaccine group at each time-point. Linear mixed-effects models were used to determine adjusted geometric mean ratios (aGMR) for each antigen included in HD-TIV (A/H1N1, A/H3N2, and B/Victoria), including age, sex, baseline titer, and CD4 count as covariates. We further stratified by post-SCT period, defined as early (3–5 months) and late (6–35 months).

Table 1. Description of cohort demographics by treatment arm.

	Control (SD-QIV) ($N = 86$)	Experimental (HD-TIV) ($N = 84$)
Median age at enrollment, years (IQR)	10.6 (6.7, 14.2)	11.9 (7.1, 14.3)
Male	49 (57.0)	45 (53.6)
White	62 (72.1)	55 (65.5)
Median time from HCT to enrollment, months (IQR)	9.3 (5.0, 15.9)	5.9 (4.1, 12.1)
Donor type (related)	40 (46.5)	39 (46.4)
Stem cell source, bone marrow	55 (64.0)	53 (63.1)
Myeloablative preparation regimen	65/85 (76.5)	58/83 (69.9)
T cell depletion	39 (45.3)	36/83 (43.4)

Results: We enrolled and randomized 170 children at nine sites (Table 1) from 2016 to 2019. Fold-rises in HAI titers and corresponding geometric means are depictedand further stratified by post-SCT period. The GMFR was significantly higher than 1 at all time points for each vaccine group. HD-TIV recipients ($n = 84$) had higher geometric mean titers compared to SD-QIV recipients ($n = 86$) (A/H1N1: aGMR = 1.7, 95% CI = [1.1–2.6]; A/H3N2: aGMR = 2.1, 95% CI = [1.3–3.4], B/Victoria: aGMR = 1.5, 95% CI = [1.0–2.4]). Further, the degree of vaccine immunogencity was greater for the late post-SCT group as compared to the early group. Participants reported more local reactions following two doses of HD-TIV vs. two doses of SD-QIV (aOR = 7.8, 95% CI = [2.1–29.4]).

Conclusions: Two doses of HD-TIV produced higher HAI antibody responses compared with SD-QIV, particularly when administered ≥6 months post-SCT. More local reactions occurred in the HD-TIV group, but they were mild and self-limited. These data provide further evidence that HD-TIV is safe and may benefit certain immunocompromised pediatric patients.

Clinical Trial Registry: NCT02860039.

Disclosure: LD-I serves as a consultant for Takeda and Merck and receives research support from Ansun BioPharma, Astellas, Merck, Pfizer, Takeda, Viracor. JE seves as a consultant for Sanofi Pasteur and AstraZeneca and received research support from AstraZeneca, GlaxoSmithKline, Merck, Pfizer. CK serves on an advisory board for Horizon Therapeutics. SC serves on a DSMB for Merck and received research support from Merck. JS received research support from Merck. NH received grant support from Sanofi and Quidel, educational grant support for speaker fees for Genentech. Sanofi Pasteur had donated vaccines and and HAI testing but had no role in the design or conduct of the trial. HD-TIV use was not consistent with product labelling.

O089

Real-world outcomes associated with letermovir use for cytomegalovirus (CMV) primary prophylaxis in allogeneic-hematopoietic cell transplant recipients: a systematic review and meta-analysis of observational studies

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Background: Letermovir use for CMV primary prophylaxis reduced the risk of clinically significant CMV infection (cs-CMVi) among adults undergoing allogeneic-hematopoietic cell transplant (allo-HCT) in randomized controlled trials and many real-world studies. However, these findings have not been systematically summarized. We conducted a systematic review (SR) and meta-analysis of real-world studies to summarize the impact of letermovir use for primary prophylaxis among adult allo-HCT recipients.

Methods: We performed systematic searches in MEDLINE/PubMed, Embase (from database inception to September 2021) and conferences for the past 3 years to identify the studies for inclusion. We included any single-arm or comparative observational studies assessing outcomes of letermovir primary prophylaxis among adults with allo-HCT. We utilized random-effect models to derive pooled estimates on the absolute and relative effectiveness of letermovir primary prophylaxis in comparison to the control arm.

Results: Of 576 retrieved citations, 48 unique retrospective studies ($N = 7069$ patients) met inclusion criteria. Most of the studies were comparative ($n = 40$), single center ($n = 43$), conducted in the United States ($n = 28$) and Italy ($n = 7$). The sample size in these studies ranged from 12 to 204 patients in the letermovir arm and 18 to 638 patients in the control arm. A total of 32 studies included any allo-HCT recipients and the remaining studies included cord-blood recipients only (4 studies), either cord-blood or unrelated donors cell recipients, or in the setting of post-transplant GvHD prophylaxis or after T-cell depletion therapy (12 studies). There was a trend towards a higher baseline proportion of cord-blood or unrelated donors in the letermovir arm in comparison to the control arm. Pooled absolute rates of CMV reactivation (CMVr), cs-CMVi, and CMV disease (CMVd) were 19% vs 61%, 10% vs 58%, 1% vs 5% at day +100 (d100), and 27%

vs 60%, 22% vs 64%, 2% vs 6% at D200 in the letermovir arm vs. the control arm, respectively. Moderate to high heterogeneity was seen given the differences in the studied population. Letermovir was associated with a reduction in the odds of CMVr, cs-CMVi, and CMVd at d100 (with moderate heterogeneity) and d200 (without heterogeneity). In addition, letermovir was associated with lower odds of all-cause mortality and non-relapse mortality at d200 post-HCT without any significant heterogeneity. Five studies reported recurrent and resistant/refractory CMV infection and five studies reported CMV-related hospitalization as an outcome with a trend toward lower rates of the event in the letermovir arm in comparison to the control arm.

Conclusions: Our systematic review of real-world studies supports that letermovir use for CMV primary prophylaxis was effective in reducing the risk of CMV manifestations (CMVr, cs-CMVi, CMVd) overall and all-cause and non-relapse mortality at d200 among adult HCT recipients.

Disclosure: This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. University of Rhode Island received funding from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. AR: employee and stockholder of Merck & Co., Inc. SK: nothing to declare. AV: received institutional/federal/state/foundation research grants from: Merck & Co., Inc,, Rhode Island, Pharmacy Quality Alliance, Advance-Clinical and Transplantation Research Pilot Projects. KL: received investigator-initiated research grant from Merck & Co., Inc., Pfizer, National Institute of Health, HSRD&Merits; consultant: Paratek, Ferring Pharmaceuticals. YT: employee and stockholder of Merck & Co., Inc., spouse: employee and stockholder of JnJ. RC: received institutional research grants: AiCuris, Ansun Biopharma, Genentech, Chimerix, Janssen, Karius, Merck, Oxford Immunotec, Takeda/Shire, Viracor, Janssen; honoraria: Ansun Biopharma, Genentech, Qiagen, Chimerix, Janssen, Merck, Oxford Immunotec, Partner Therapeutics, Pulmotect, Takeda, Shinogi, Adagio.

O090

Upper and/or lower respiratory tract infection caused by human metapneumovirus after allogeneic stem cell transplantation

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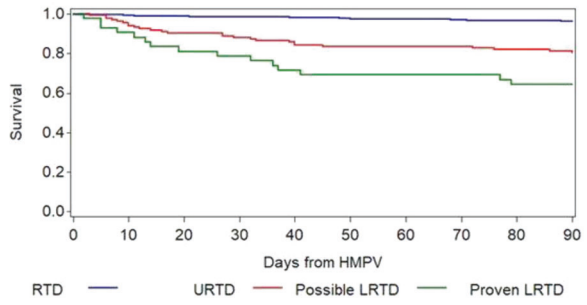
Background: Human metapneumovirus (hMPV) belongs to the paramyxoviridae family. HMPV infection occurs in approximately 5–12% of allogeneic hematopoietic cell transplantation (allo-HSCT) recipients, and can cause severe and even fatal lower respiratory tract disease (LRTD). However, the epidemiology, clinical characteristics and risk factors for poor outcome after allogeneic stem cell transplantation (allo-HSCT) remain little explored.

Methods: We describe here a retrospective multicentre cohort of the Spanish transplant and cell therapy group (GETH-TC) and the EBMT infectious disease working party (IDWP) multicentre study includingall consecutive allo-HSCT recipients (adults and children) who developed upper (URTD) and/or LRTD caused by HPMV diagnosed by multiplex PCR panels. Centres were asked to report consecutive patients with HMPV respiratory infections diagnosed from the start of conditioning until the last follow-up from January 2012 to January 2019. Specific information, regarding respiratory symptoms, clinical and laboratory variables for immunodeficiency scoring index (ISI) computation, as well as hospital admission, intensive care unit (ICU) admission, was obtained retrospectively.

Results: We included 431 allo-HSCT recipients who developed 441 U/LRTD HMPV episodes, reported from 40 EBMT transplant centres in 15 countries around the world (Europe, Asia and Australia). Clinical and transplant characteristics are detailed in Table 1. A total of 66% of the recipients were allografted from alternative donors [other than HLA identical family donors]. HMPV episodes were diagnosed at a median of 370 days after allo-HSCT (range, day −12 to + 13.3 years). Most of recipients had URTD ($n = 265$, 60%) whereas 176 (40%) had LRTD involvement [possible $n = 134$ (30%), proven $n = 42$, (10%)]. Compared to URTD, recipients who developed HMPV LRTD were older and earlier after allo-HSCT. Furthermore, patients had significantly higher proportion of lymphopenia ($<1 \times 10^9$/L), neutropenia ($<0.5 \times 10^9$/L), high-risk ISI score and more often were treated with steroids and ribavirin at the time of HMPV ($p \le 0.05$ for all comparisons). The HMPV LRTD episodes were more frequently associated with hospitalization (13% vs 56%) and ICU admission (1.5% vs 19%), ($p \le 0.01$ for all comparisons). Preliminary multivariate analysis for LRTD identified lymphopenia at the time of HMPV identification [≤ 0.2 vs $>0.5 \times 10^9$/L OR 6.60, 95% confidence interval (CI) 3.05–14.28; >0.2–0.49 vs $>0.5 \times 10^9$/L OR 2.97, 95% CI 1.53–5.76; $p < 0.0001$], corticosteroids >30 mg/d (OR 3.11, 95% CI (1.51–6.40), $p = 0.01$) as independent risk factors. Overall, 29 patients had died at day +30 (7%). Day +30 overall mortality after HMPV detection was 2% vs 12% vs 21% for URTD, possible and proven LRTD, respectively ($p < 0.0001$) (see Fig. 1). Multivariate analysis for day +30 LRTD overall

mortality identified lymphopenia (≤0.2 vs >0.5 × 10^9/L OR 5.41, 95% CI 2.16–13.57, $p = 0.0003$) as the only risk factor.

Figure 1. 90 days Overall survival from HMPV detection according to URTD and possible or proven LRTD.



Group	Episodes	Death	90-day OS (95% C.I.)	p
URTD	265	10	96.2 (93.1-97.9)	<0.0001
Possible LRTD	134	26	80.5 (72.6-86.2)	
Proven LRTD	42	15	64.3 (47.9-76.7)	

Conclusions: HMPV after allo-HSCT could progress to LRTD in many instances, leading to hospitalization and ICU admission in a significant proportion of cases. Our study suggests that LRTD was mainly driven by lymphopenia and corticosteroids therapy at the time of infection whereas lymphopenia was independently associated with higher mortality in recipients with LRTD.

Disclosure: no

O092

Antibody response to a third SARS-CoV-2 vaccine dose in recipients of an allogeneic hematopoietic cell transplantation

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Background: Allogeneic hematopoietic cell transplantation (allo-HCT) recipients are at increased risk of developing severe COVID-19. We and others have recently shown impaired antibody (AB) responses in these vulnerable patients after two priming SARS-CoV-2 vaccination doses. In July 2021 a third dose of the vaccine was approved by the Swiss authorities for immunocompromised individuals and those at high risk of developing severe COVID-19. Here, we report initial data on the AB response after the third vaccination in allo-HCT recipients at the University Hospital of Zurich.

Methods: AB titers were prospectively collected at 1 month after the third dose using an in-house developed multiplex AntiBody CORonavirus Assay (ABCORA) that measures SARS-CoV-2 IgG, IgA, and IgM reactivities against RBD (receptor binding domain), S1 (subunit 1 of the spike protein), S2 (subunit 2 of the spike protein) and N (nucleoprotein). A neutralizing threshold of 17 for the sum of S1 SOC value (sum S1) was previously established. Both, patients without response after initial priming with two doses, and patients with initial seroconversion but declining AB titers over time, were included in this analysis.

Results: As of December 2021, a total of 49 allo-HCT recipients (median age 59 years, 26.5% females and 73.5% males) received a third dose of BNT162b2 ($n = 42$) or mRNA-1273 ($n = 7$). Patients were grouped into those: (A) 6–12 months, (B) 12–24 months and (C) >24 months post HCT. Median time between the second and third dose was 211 days [interquartile range (IQR): 173–229 days)]. Median time from third dose to AB measurement was 35 days (IQR: 29–40 days) with AB data available in 34/49 patients at the time of analysis. After the third dose sufficient neutralization activity was documented in 22/34 patients (65%), whereas 12/34 patients (35%) showed no adequate humoral response. By comparing sum S1 at 1 month after the second and the third dose (data available in 27/34 patients for both time points) we observed seroconversion among 10/20 (50%) previous low responders, whereas in 10 patients sum S1 remained below the neutralization threshold. In the group of the low responders after the third dose, immunosuppressive treatment (IST) was still ongoing in 7/12 (58%) patients, whereas only 4/22 (18%) responders were under IST. Of note, in previous low responders, who achieved seroconversion after the third dose IST was discontinued in 5 and reduced in 1 patient prior the third dose. One patient, who remained a low responder after triple vaccination developed symptomatic COVID-19 infection, which was successfully treated with casirivimab/imdevimab and remdesivir.

Conclusions: A third dose of SARS-CoV-2 vaccines has been recently recommended for both immunocompromised and healthy individuals, and follow-up data on its effectiveness are eagerly awaited. Our results highlight the importance of a third dose in allo-HCT recipients and point toward improvement in AB responses even in patients identified as low responders to priming vaccination. For those who still fail to achieve seroconversion after triple vaccination novel treatment strategies to decrease the mortality of COVID-19 should be considered and behavioral measures including masks and social distancing remain of utmost importance.

Clinical Trial Registry: BASEC No 2021-00261.

Disclosure: The authors declare no competing financial interests.

O093

Reduced immunogenicity of a third COVID-19 vaccination in recipients of allogeneic stem cell transplantation

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Background: We examined the immunogenicity of a third dose of mRNA-based COVID-19 vaccine in allo-SCT recipients who fulfilled the Swedish criteria for a third dose prior to the general population, i.e., transplanted within three years and/or with ongoing immunosuppressive treatment for GvHD.

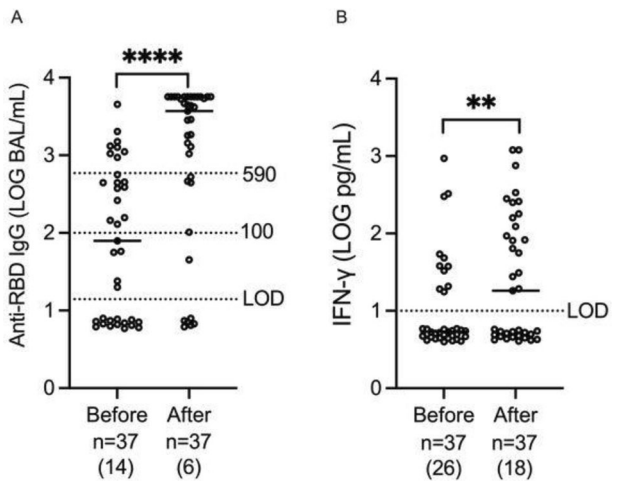
Methods: Allo-SCT recipients, $n = 37$, median age 61 (19–78) who had received two doses of COVID-19 mRNA vaccine ≥8 weeks ago were included in the study and sampled at Sahlgrenska University Hospital. Median time from transplant was 23 months (6–191). Twenty-one patients (57%) had cGvHD and 25 (68%) were on immunosuppressive treatment (IST) (prednisone ($n = 20$), photopheresis ($n = 5$), ibrutinib ($n = 4$), ruxolitinib ($n = 4$) and other ($n = 7$)). Patients received the same vaccine as in their two initial doses, i.e., BNT162b2 (Pfizer-BioNTech Comirnaty®; $n = 24$) or mRNA-1273 (Moderna Spikevax®; $n = 13$), at a median of 127 days (56–174) days after the second immunization. Blood samples were collected just before and 4 weeks (median 24 days, 19–30) after the third dose.

Serology: chemiluminescent microparticle immunoassays (CMIAs) using the automated Alinity system for analysis of IgG antibodies against the spike receptor binding domain (RBD) (SARS-CoV-2 IgG II Quant, Abbott, Illinois, USA) were performed with levels reported in binding antibody units (BAU)/mL (detection range of 14–5680 BAU/mL).

T cell reactivity: blood was stimulated with 1 µg/mL/peptide of 15-mer peptides with 11-amino acid overlap spanning the N-terminal S1 domain of the SARS-CoV-2 surface glycoprotein (S1; product number: 130-127-041, Miltenyi Biotec). After 2 days of incubation at 37 °C, plasma was recovered for analysis of IFN-γ by ELISA (DY285B, R and D systems). The S1-induced IFN-γ (S1-γ) production was presented with unstimulated samples subtracted. Limit of detection (LOD) was 10 pg/mL.

Results: The majority of allo-SCT recipients responded with increased levels of anti-RBD S1 IgG levels after the third vaccination (Fig. 1A) with a subgroup of patients (12/37, 32%) reaching very high levels (>5680 BAU/mL). However, 6 of the 14 patients (42%) seronegative before the third dose, remained negative also 4 weeks after the third vaccination (Fig. 1A). No significant differences in anti-RBD IgG responses were seen in patients with or without cGvHD or ongoing IST. Eighteen of 37 patients (49%) lacked a T-cell response after the third vaccination (Fig. 1B). T-cell responses were lower in patients with cGVHD and in patients on corticosteroids.

Figure 1. A Levels of IgG against the spike receptor-binding domain (RBD). **B** IFN-γ in supernatant plasma reflecting reactivity of SARS-CoV-2-specific T cells.



Adverse events were observed in 15 (41%) patients after the third vaccination, mainly mild local reactions. No exacerbations of GvHD were noted.

Conclusions: We report that a significant subset of allo-SCT recipients failed to respond with anti-RBD IgG (16%) and/or mount detectable SARS-CoV-specific T cells (49%) despite three doses of COVID-19 mRNA vaccine. Thus, we found SARS-CoV-2 specific T-cell responses to be more affected compared to serological responses among allo-SCT recipients.

Clinical Trial Registry: EudraCT 2021-000349-42.

Disclosure: Funding was received from a regional research fund (Stiftelsen för hematologisk forskning). PL: lecturing, Pfizer.

O094

Dynamics of antibody response to BNT162b2 mRNA COVID-19 vaccine in recipients of hematopoietic stem cell transplant compared to healthy controls: a longitudinal prospective study

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Background: SARS-CoV-2 mRNA vaccines have proven high efficacy in the general population, however limited data exists on immunogenicity and antibody persistence in recipients of hematopoietic stem cell transplant (HSCT).

Methods: In this prospective observational study, we evaluated immunogenicity and antibody persistence after the two-dose BNT162b2 (Pfizer–BioNTech) vaccine in recipients of allogeneic HSCT compared to healthy controls. Blood samples were taken before the fist vaccine dose (baseline), before the second dose (TP0), 2 weeks after the second dose (TP1), then at 3 months (TP2) and 6 months (TP3) after the second dose. Samples were analyzed for the IgG antibodies to SARS-CoV-2 Spike protein receptor-binding domain (anti-S), neutralizing antibodies and T-cell response by IFN-γ production. Baseline samples were further analyzed with multiparameter flow cytometry for immune reconstitution by complete lymphoid cell subsets evaluation.

Results: Fourthy-six adult (age >18 years) HSCT recipients from four italian centers were evaluable for the present analysis. Enrolled patients received two successive vaccine doses (at 3-week interval) at a median of 15 months (range 2–141) after HSCT. A total of 29 age-matched health care workers who were vaccinated with the same product were recruited as the control group. After the first dose 23% of patients developed anti-S IgG antibodies as compared to 97% of controls ($p < 0.01$). In univariate analysis, transplant-to-vaccination interval (>12 months, $p < 0.01$), baseline CD4+ T cell count (>200/mm^3, $p = 0.01$), and CD4+ CD45RA+ T naive cell count (>100/mm^3, $p < 0.01$) were significantly associated with antibody response after the first vaccine dose. After the second dose, 77% of the patients developed anti-S antibodies, as compared to 99% of healthy controls ($p < 0.01$). HSCT recipients showed lower antibody titers (median 380.7 BAU, range 0.5–2465.8) as compared to healthy controls (median 1960 BAU, range 390.1–5384.7, $p < 0.01$). When serum of patients positive for anti-S IgG was tested for neutralizing

antibodies, 18% of patients showed non-neutralizing sera. Further, 76% of responders had no T-cell response to S protein. Anti-S and neutralizing antibody persistence was re-evaluated at 3 and 6 months following vaccination in HSCT recipients and controls. At 3 months, median anti-S antibody titer decreased by 49% in HSCT and by 65% in controls ($p = 0.008$). At 6 months, median anti-S titer decreased by 73% in HSCT vs 88% in controls ($p = 0.004$). Neutralizing antibody titer decreased by 24% vs 14% at 3 months and by 25% vs 71% at 6 months in HSCT recipients vs controls (Fig. 1).

Conclusions: In conclusion, HSCT recipients showed an impaired response to mRNA COVID-19 vaccination as compared to healthy controls. Patients who were vaccinated beyond 1 year after HSCT were more likely to mount anti-S IgG antibodies, which could be due to a broader immune reconstitution, as we observed an enhanced response in patients with higher CD4+ T cell and particularly CD4+ CD45RA+ naïve T cell counts. Interestingly, anti-S neutralizing antibody titers decreased significantly over time, with a more pronounced decline in healhty subjects as compared to HSCT recipients.

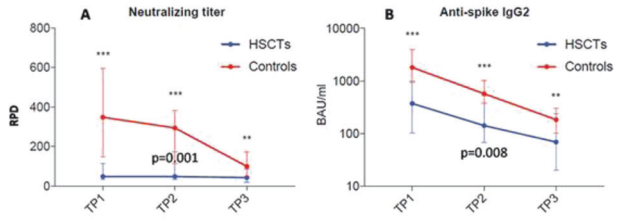

Figure 1. Decline of neutralizing (A) and anti-S antibodies (B) over time in HSCT and controls. TP1, 2 weeks after 2ª dose; TP2, 3 months after 2ª dose; TP3, 6 months after 2ª dose.

Disclosure: Nothing to declare

O095

Longitudinal study of the humoral and cellular response developed in allosct patients during a two-dose vaccination schedule against COVID-19

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Background: The current recommendation in patients who received a stem cell transplantation is to vaccinate against COVID-19 within the first 3–6 months after transplant. However, data that support recommendations are scarce and mainly based on humoral seroconversion.

The aim is to compare the humoral and cellular immune responses in a group of allogenic stem cell transplantations (AlloSCT) patients during the first two doses of one COVID-19 vaccine comparing to three groups of other oncohematological diseases (OHD) and healthy donors.

Methods: We recruited 40 patients in four groups: CLL ($n = 11$), CML ($n = 6$), MM ($n = 13$), and AlloSCT ($n = 10$) (Table 1); and a group of healthy donors ($n = 6$). Samples were collected prior to vaccination, 3 weeks and 1 month after receiving the first and second dose respectively of COMIRNATY (BioNTech-Pzifer), mRNA-1273 (Moderna), or AZD1222 (Astra-Zeneca). IgG titers against SARS-CoV-2 were quantified by Euroimmun-Anti-SARS-CoV-2 ELISA. Direct cellular cytotoxicity (DCC) was determined against Vero E6 cells infected with pseudotyped SARS-CoV-2, measuring caspase-3 activation after co-culture with PBMCs for cellular death quantification and renilla expression to measure viral replication.

	CLL ($n = 11$)	CML ($n = 6$)	MM ($n = 13$)	AlloSCT ($n = 10$)
Age, median (IQR)	65 (65–77)	62.5 (49.5–76-5)	73 (60–76)	62 (46.8–66.25)
Sex: male, *n* (%)	6 (54.5)	3 (50)	8 (61.54)	6 (60)
Collection days after second dose, median (IQR)	34 (27–39)	38 (32–46)	33 (25.5–42.5)	36.5 (26.25–43.7)
Treatment, *n* (%)	Active treatment 5 (45.5)	ITKs discontinuation 2 (33.33)	Maintenance treatment after ASCT 5 (38.46)	Immunosuppresive treatment 4 (40)
	Watch and wait 6 (54.5)	ITKs 4 (66.66)	Not-ASCT candidates 8 (61.54)	Non-immunosuppresive treatment 6 (60)
Months since transplantation, median (IQR)	N/A	N/A	30 (23–65)	40 (27.3–56.8)
cGvHd, *n* (%)	N/A	N/A	N/A	7 (70)
Vaccines, *n* (%)				
AZD12222	3 (27.27)	1 (16.67)	0	0
mRNA-1273	5 (45.45)	4 (66.67)	6 (46.15)	10 (100)
COMIRNATY	3 (27.27)	1 (16.67)	7 (53.85)	0

Results: (1) Humoral response characterization one month after receiving two-dose vaccination in AlloSCT showed similar titers of IgGs against SARS-CoV-2 than healthy donors. This response was also achieved in CML patients, whereas CLL and MM IgG titers were reduced 4.1- ($p < 0.0001$) and 1.6-fold ($p = 0.0465$).

(2) The DCC against SARS-CoV-2-infected Vero E6 cells in AlloSCT's PBMCs was increased, as well as in CLL and CML, in comparison with healthy donors, whereas MM showed a reduced cytotoxic activity ($p > 0.05$). OHD patient's PBMCs were also more efficient to eliminate SARS-CoV-2 than those from healthy donors; this cytotoxic activity was increased 4.7- ($p < 0.0001$), 3.7- ($p = 0.0003$), 2.6- ($p = 0.0228$), and 2.3-fold ($p = 0.0046$) in patients with CLL, CML, MM and AlloSCT, respectively.

Conclusions: We found adequate serological response in AlloSCT patients and also in the other OHD after one month of receiving a two-dose vaccine schedule, except in CLL, in which the IgGs titers remained low. Conversely, PBMCs from patients with AlloSCT and CLL showed increased cytotoxic activity against SARS-CoV-2 infected cells with a higher efficiency to eliminate the infected cells.

Seroconversion is not enough to evaluate the quality of the immune response after a complete regimen of vaccination. Instead, assays to evaluate the cytotoxicity activity are needed to determine the immune response after vaccination.

An update of the study with up to 150 OHD patients 1 month after receiving two-dose vaccine schedule, including more than 30 AlloHSCT patients and 20 patients after receiving autologous HCT, will be presented.

Disclosure: no disclosures to declare.

O096

Evaluation of T and B lymphocytes subsets after two doses of BNT162b2 anti-SARS-CoV-2 mRNA vaccination in hematopoietic stem cell transplantation patients

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Background: To assess vaccine efficacy among immunocompromised patients, excluded from initial trials evaluating SARS-CoV-2 mRNA vaccines, is a crucial need. We previously demonstrated (Attolico et al., BJH 2021) that two doses of BNT162b2 m-RNA vaccine can elicit an immune response (measured by the magnitude of binding antibodies to the SARS-CoV-2 spike protein) in 76% of allogeneic (ALLO) and 94% of autologous (AUTO) hematopoietic stem cell transplantation (HSCT) recipients. Time from transplant was the main clinical factor associated to response. Aim of the present study was to evaluate possible differences in T and B lymphocytes (Ly) subsets and their maturation profile, useful to explain the different antibody response.

Methods: We evaluated 111 transplanted patients and 88 age and sex matched healthy controls (HC), after two doses of BNT162b2 anti-SARS-Cov-2 mRNA vaccine. Samples were collected 1 month after the second dose. Eighteen out of 111 (16%) patients, 15 ALLO and 3 AUTO, did not respond to vaccination (NR; anti-spike IgG: <50 AU/ml). Responders (R; anti-spike IgG: ≥50 AU/ml) were 93 (84%). T, B and NK counts were performed with Multitest 6-color TBNK reagent, using FACSCanto Cytometer and Canto software (Becton Dickinson). B and T cell maturation was evaluated with DuraClone IM B and T cells kits, using Navios Cytometer and Kaluza software (Beckman Coulter). Comparison between groups was performed with Mann–Whitney test.

Results: No differences were observed in total Ly count between R and HC (Fig. 1a). CD4+ Ly count and CD4+/CD8+ ratio were higher in HC than in R (Fig. 1d, e). On the other hand, R had higher total CD8+, CD16+/CD56+ and CD19+ Ly than HC (Fig. 1e). When analyzing the T and B maturation subsets, HC showed higher CD4+ central memory ($p < 0.0001$), CD4+ naïve ($p < 0.0001$), CD4+ senescent ($p < 0.02$), CD19 marginal zone ($p < 0.0001$), CD19+ switched memory ($p < 0.002$), but lower CD4+ effector memory ($p < 0.0002$), CD8+ effector T ($p < 0.001$), CD8 senescent ($p < 0.0009$), CD19+ naïve ($p < 0.0001$), CD21 low ($p < 0.0003$) and CD19 transitional ($p < 0.0001$). We also observed a significantly higher Ly count in R than in NR (Fig. 1b). CD4+, CD19+ Ly count and CD4+/CD8+ ratio were lower in NR than in R (Fig. 1d, f). R patients also exhibited a significantly higher number of CD4+ central memory ($p < 0.0019$), CD4+ naïve ($p < 0.0001$), CD4+ effector memory ($p < 0.03$), CD4+ senescent CD27- ($p < 0.03$), CD19+ naïve ($p < 0.03$), CD21 low ($p < 0.007$) and switched ($p < 0.003$). When comparing ALLO and AUTO subgroups, ALLO recipients showed higher total Ly and CD3+ (Fig. 1c, g). Regarding T and B maturation subsets, ALLO recipients showed higher CD4+ effector memory ($p < 0.03$), CD4+ effector T ($p < 0.01$), CD4+ exhaust CD279+ ($p < 0.01$), CD4 senescent CD27- ($p < 0.03$), CD8 central memory ($p < 0.009$), B naïve ($p < 0.0001$), marginal-zone ($p < 0.002$), CD21low ($p < 0.0001$), unswitched memory ($p < 0.004$), switched ($p < 0.01$) and plasmoblasts ($p < 0.02$).

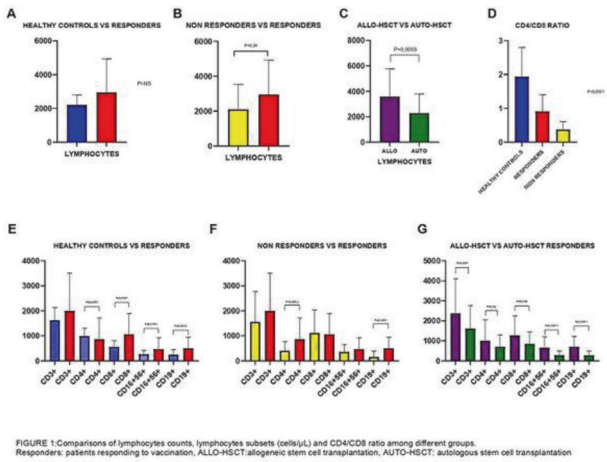

FIGURE 1:Comparisons of lymphocytes counts, lymphocytes subsets (cells/µL) and CD4/CD8 ratio among different groups.
Responders: patients responding to vaccination, ALLO-HSCT:allogeneic stem cell transplantation, AUTO-HSCT: autologous stem cell transplantation

Conclusions: Overall, our preliminary evaluation confirms the prognostic role of absolute Ly count and CD4+/CD8+ ratio in response to vaccination. Furthermore, differences in Ly count and T and B maturation subsets between ALLO and AUTO are in line with our previous observation of a better immunological response in ALLO recipients vaccinated more than 1 year after HSCT, though studies are ongoing to better clarify these aspects.

Disclosure: Nothing to declare

Lymphoma and chronic lymphocytic leukemia

O098

Cord blood transplantation for adult lymphoid neoplasms in Europe and Japan: a collaborative study between Eurocord/LWP-EBMT and JSTCT/JDCHCT

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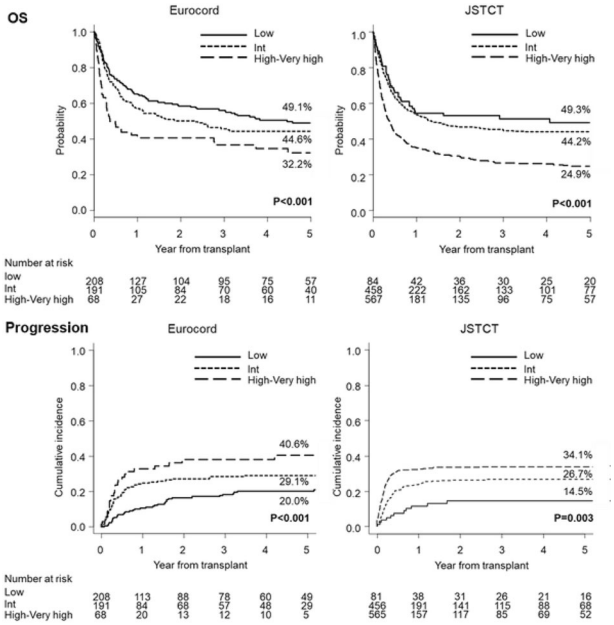
Background: In the aim of identifying the different characteristics and find universal prognostic factors of cord blood transplantation (CBT) in patients with lymphoid neoplasms between Europe and Japan, we conducted a collaborative study between Eurocord/LWP-EBMT and Japanese Society for Transplantation and Cellular Therapy (JSTCT)/Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT).

Methods: Patients aged 18-75 years with lymphoid neoplasms who received their first unrelated CBT between 2000 and 2018

were included. Overall survival (OS) and progression/relapse free survival (PFS) 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 were added in a stepwise manner ($P < 0.05$) in the multivariate models of each registry.



Results: A total of 496 patients (single CBT, $n = 192$; double CBT, $n = 304$) from European registry and 1150 patients (single CBT only) from Japanese registry were included. The distributions of lymphoma subtypes were different between Europe [mature B-cell neoplasms, $n = 247$ (49.8%); mature T/NK-cell neoplasms, $n = 98$ (19.8%); Hodgkin's lymphoma (HL), $n = 131$ (26.4%)] and Japan [mature B-cell neoplasms, $n = 658$ (57.2%); mature T/NK-cell neoplasms, $n = 401$ (34.9%); HL, $n = 58$ (5.0%)]. Median total nucleated cell (TNC) counts were 3.76×10^7/kg for single and 4.93×10^7/kg for double CBT in Europe, and it was 2.66×10^7/kg in Japan (only single CBT). Median CD34+ cell counts were 1.51×10^5/kg for single CBT, 1.88×10^5/kg for double CBT in Europe and 0.88×10^5/kg in Japan. The Japanese cohort comprised more elderly patients over 50 years old (59% vs 39%) with higher revised DRI (high-very high: 49% vs 13%) and lower rate of autologous stem cell transplantation (27% vs 94%) than the European cohort. High-very high revised DRI (vs. low DRI) was a significant factor for poor OS (Europe: HR 1.78 $p = 0.002$; Japan: HR 2.24, $p < 0.001$), poor PFS (Europe: HR 1.74, $p = 0.002$; Japan: HR 2.25, $p < 0.001$) and higher risk of progression/relapse (Europe: HR 2.04, $p = 0.007$; Japan: HR 2.93, $p < 0.001$) in both registry cohorts (Fig. 1). TBI-containing conditioning regimen contributed to superior OS in both populations (Europe: HR 0.53, $p < 0.001$; Japan: HR 0.63, $p < 0.001$), regardless of revised DRI. The impact of ≥2 HLA mismatches on OS was significant in European cohort (HR 1.55, $p = 0.006$) but not in Japanese cohort (HR 1.16, $p = 0.149$). Neither TNC nor CD34+ cell counts had an impact on survival.

Conclusions: Lymphoma subtypes and their disease risks for which CBTs had been performed largely differed between the two registries. Patients with high-very high refined DRI had poor survival (5-year OS; Europe: 32%; Japan: 25%). High incidences of PFS and TRM were observed in both cohorts, suggesting a need for improving treatment strategies. Interestingly, different impact of HLA-mismatches was found between the two registries, which calls attention to the differences among the populations and the importance of analyzing risk factors separately. On the other hand, TBI was associated with improved outcomes in both cohorts, and should be considered in conditioning regimen protocols for patients with lymphoma.

Disclosure: Nothing to declare.

O099

Allogeneic hematopoietic stem cell transplantation (allo-HSCTs) for non-Hodgkin lymphoma (NHL): outcomes at the National Cancer Center Hospital (NCCH) of Japan

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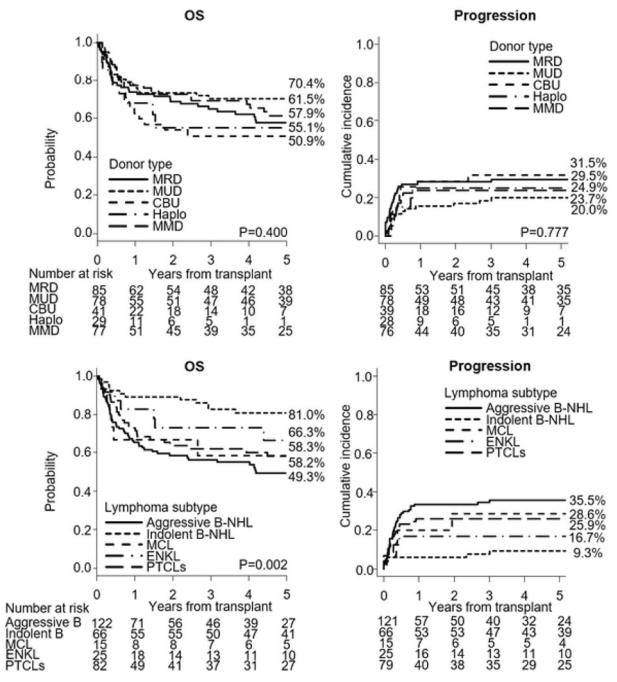
Background: The transplantation strategies for patients with relapsed/refractory lymphomas have not yet been clarified in the current landscape of broadened donor availability, due to the small number of patients scattered at the various institutions performing multifarious allo-HSCTs. We analyzed a relatively large data set on allo-HSCT for patients with NHLs performed at a single institution, the NCCH of Japan.

Methods: A total of 311 patients who had received allo-HSCT for B-NHLs (aggressive NHL, $n = 122$; indolent NHL, $n = 66$, mantle cell lymphoma (MCL), $n = 15$) and mature T/NK-NHLs (extranodal NK/T-cell lymphoma nasal type (ENKL), $n = 25$; peripheral T-cell lymphomas (PTCL), $n = 83$) at the NCCH between 2000 and 2021 were examined. Patients with Adult T-cell leukemia/lymphoma were excluded. Median age at transplantation was 52 years (range, 19–70). Eighty-five patients received bone marrow transplantation (BMT)/peripheral blood stem cell transplantation (PBSCT) from HLA-matched related donors, 78 received HLA-matched unrelated BMT/PBSCT, 41 received unrelated single cord blood transplantation (CBT), 29 received haplo-identical related PBSCT, and 78 received BMT/PBSCT from HLA-mismatched related/unrelated donors other than haplo-identical. Lymphoma status at transplantation was complete response (CR) in 112 patients, partial response (PR) in 53 patients, and stable disease (SD)/progressive disease (PD)/relapse (REL) in 145 patients. Median follow-up time for survivors was 5.0 years.



Results: Overall survival (OS) and progression-free survival (PFS) rates at 5 years after transplantation were 60.7% (aggressive NHL, 49.3%; indolent NHL, 81.0%; MCL, 58.3%; ENKL, 66.3%; PTCL, 58.2%) and 53.1% (aggressive NHL, 39.3%; indolent NHL, 74.7%; MCL, 42.9%; ENKL, 63.2%; PTCL, 54.1%), respectively (Figure). Cumulative incidences of progression/REL and transplant related mortality at 5 years were 24.9% (aggressive NHL, 35.5%; indolent NHL, 9.3%; MCL, 28.6%; ENKL, 16.7%; PTCL, 25.9%) and 22.3% (aggressive NHL, 25.2%; indolent NHL, 16.0%; MCL, 28.6%; ENKL, 20.1%; PTCL, 21.0%), respectively (Figure). In multivariable analysis, performance status over 1 (vs 0–1: OS, HR 2.97, $P = 0.007$; PFS, HR 2.59, $P = 0.011$) and being male (OS, vs female, HR 1.58, $P = 0.020$; PFS, HR 1.43, $P = 0.043$) negatively affected survival. Lymphoma status of SD/PD/REL at transplantation was significantly associated with poor OS (vs CR, HR 2.72, $P < 0.001$), PFS (HR 2.20, $P < 0.001$) and progression/REL after transplantation (HR 0.84, $P = 0.006$), whereas patients in PR showed comparable PFS (vs CR, HR 1.36, $P = 0.242$) and progression/REL (HR 1.36, $P = 0.663$) as those in CR. TBI-containing conditioning was associated with reduced progression/REL risk (HR 0.42, $P = 0.005$). Neither intensity of conditioning regimen nor donor source affected transplant outcomes.

Conclusions: Allo-HSCT for NHLs could be favorable, if performed for patients with good disease control of PR (5-year OS, 56.5%) or better (5-year OS, 74.9%). Allo-HSCT for mature T/NK-NHL s showed acceptable outcomes, suggesting that these patients are as good candidates for allo-HSCT as are patients with indolent NHLs. Since donor source showed comparable impact on transplant outcomes regardless of lymphoma subtypes, high emphasis should be placed on lymphoma control when deciding the timing of allo-HSCT, and the use of alternative donors should be considered for those who have limited opportunity for sustained disease control.

Disclosure: Nothing to declare

O100

Outcomes of autologous hematopoietic cell transplantation (AHCT) in elderly patients with diffuse large B cell lymphoma (DLBCL)

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Background: Consolidation with high-dose therapy and AHCT remains the standard treatment for relapsed DLBCL sensitive to salvage chemotherapy. However, elderly patients ≥70 years may be denied this treatment due to age per se. Data for outcomes after AHCT in DLBCL in this age group are limited.

Methods: Using CIBMTR database, we compared outcomes of AHCT in 466 DLBCL patients aged 60-69 years ($n = 363$) and ≥70 years ($n = 103$) receiving an AHCT between 2008 and 2019 in the US. Non-relapse mortality (NRM), Disease relapse/progression (REL), progression-free survival (PFS), and overall survival (OS) were modeled using Cox proportional hazards models. Hazard ratio (HR) with 95% confidence intervals (CI) are reported.

Results: Table 1 shows some baseline characteristics. All patients received BEAM with or without rituximab as the conditioning regimen. On univariate analysis, 100-day NRM was 3% (95% CI, 2–6%) in the 60–69 years and 4% (95% CI, 1–9%) in ≥70 years groups, respectively, with 5-year REL 47% (95% CI, 41–52%) in 60–69 years and 45% (95% CI, 35–55%) in ≥70 years, 5-year PFS 40% (95% CI, 35–46%) in 60–69 years and 38% (95% CI, 28–49%) in ≥70 years, and 5-year OS 55% (95% CI, 50–60%) in 60–69 years and 41% (95% CI, 31–52%) in ≥70 years ($p = 0.02$). OS at 3 years (65% vs. 52%, $p = 0.02$) and 5 years (55% vs. 41%, $p = 0.02$) was better in 60–69-year age group. On multivariate analysis, adjusted for other covariates, compared to age group 60–69 years, patients ≥70 had no statistically significant difference in NRM (HR 1.43, 95% CI 0.85–2.39, $p = 0.18$), REL (HR 1.11, 95% CI 0.79–1.56, $p = 0.56$), PFS (HR 1.23, 95% CI 0.92–1.63, $p = 0.16$). Patients ≥70 years had higher mortality (HR 1.39, 95% CI 1.05–1.85, $p = 0.02$), reflected by inferior post relapse OS in this cohort (HR 1.82, 95% CI 1.27–2.61, $p = 0.001$). DLBCL was the major cause of death in both age groups (62% vs. 59%).

Conclusions: From this largest contemporary data set, where all elderly DLBCL patients received standard conditioning regimen BEAM, our results confirm that fit patients ≥70 years can undergo AHCT safely and achieve similar benefits as 60–69 years old patients. OS in the elderly is expected to be lower due to several factors unrelated to the AHCT efficacy as REL was comparable between the groups. Elderly patients should be assessed for overall physiological function with comprehensive geriatric assessments of which data remains deficient.

Disclosure: Nothing to declare

O101

Outcomes of allogeneic hematopoietic cell transplantation (alloHCT) in anaplastic large cell lymphoma (ALCL)

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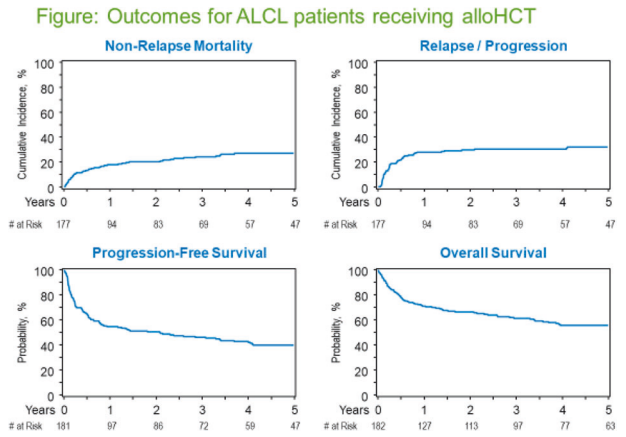
Background: Despite the remarkable activity of brentuximab vedotin, prognosis of relapse/refractory (r/r) ALCL with remains poor (Chihara et al. Hematol Oncol. 2019). Large registry studies evaluating outcomes alloHCT in systemic r/r ALCL are not available.

Methods: Using CIBMTR database, we evaluated outcomes of 182 adults (≥18years) with r/r ALCL undergoing alloHCT between 2008 and 2019. Non-relapse mortality (NRM), disease relapse/progression (REL), progression-free survival (PFS), and overall survival (OS) were modeled using Cox proportional hazards models. Hazard ratio (HR) with 95% confidence intervals (CI) are reported.

Results: Table shows baseline characteristics. Median time from ALCL diagnosis to alloHCT was 19 months (range: 2–208). Median follow-up of survivors was 62 months (range: 3–148). Day +180 cumulative incidence of grade 2–4 acute GVHD was 33%, while 1-year cumulative incidence of cGVHD was 48%. On univariate analysis, 1-year NRM was 18%. The 5-year REL, PFS and OS were 32%, 41% and 56%, respectively (Figure).

Table	$N = 182$ (%)
Age, median (range)	47 (18–76)
White race vs. African American vs. Others	128 (70) vs. 25 (15) vs. 25 (15)
CR vs. PR vs. refracotry disease before alloHCT	113 (62) vs. 53 (30) vs. 15 (8)
ALK+ ALCL	42 (23)
Myeloablative vs. reduced-intensity conditioning	65 (36) vs.117 (65)

Table	N = 182 (%)
HCT-CI ≥3	61 (34)
Median of lines of prior therapy	3 (2-5)
Matched related vs. matched unrelated vs. haploidentical donor	95 (52) vs. 55 (30) vs. 32 (18)
Prior autologous HCT	66 (36)



On multivariate analysis African American race (HR = 2.7, 95% CI = 1.6–4.8, $p < 0.001$) and refractory disease (HR = 3.2, 95% CI = 1.6–6.2, $p < 0.001$) were predictive of inferior OS. Similarly, African American race (HR = 2.1, 95% CI = 1.3–3.4, $p = 0.003$), other minority race (HR = 2.5, 95% CI = 1.2–5.3, $p = 0.02$) and refractory disease (HR = 2.2, 95% CI = 1.2–4.3, $p = 0.01$) were predictive of inferior PFS. Finally, African American race (HR = 3.7, $p < 0.001$) and refractory disease (HR = 3.1, $p = 0.01$) were predictive of higher NRM. ALK status (positive vs. negative) was not predictive of survival outcomes. Relapsed ALCL was the major cause of death (42%).

Conclusions: These data, the largest study to date, confirm that alloHCT can result in durable disease control in a sizable proportion of patients with r/r ALCL. Refractory disease and ethnic minority status predict inferior alloHCT outcomes. Whether the inferior outcomes of racial minorities with r/r ALCL post alloHCT are driven by differences in disease biology or disparities in post alloHCT care (or both) require further investigation.

Disclosure: Nothing to declare

Minimal residual disease, tolerance, chimerism and immune reconstitution

O104

The immunological synapsis of acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: pleiotropy of immune escape

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Background: Allogeneic hematopoietic cell transplantation (allo-HCT) is considered a form of immunotherapy able to direct the donor-derived immune system against malignant cells, successfully curing many hematological disorders. However, the escape from graft versus leukemia (GvL) effect represents one of the major challenges hampering the success of this procedure. Lessons learned from solid cancer immunobiology illustrate that an immune suppressive phenotype may derive from many patterns of immune evasions.

Methods: Herein we sought to characterize the transcriptomic signatures associated with escape from alloreactivity in acute myeloid leukemia (AML) relapsing after allo-HCT and to delineate their association with leukemia mutational burden.

To that end we molecularly characterized the dysfunction of the immunological synapsis of a composite cohort of patients with AML at diagnosis ($N = 311$) and at relapse after allo-HCT ($N = 26$) from our institutional cohort and from two previously published studies (10.0.4.32/NEJMoa1808777 [1] and 10.0.4.14/s41586-018-0623-z [2]). We used whole-exome and whole-transcriptome sequencing, focusing on a signature of nearly 500 genes involved in antigen presentation/processing and in T and Nk cell activation.

Results: First, we performed an unbiased differential analysis between the two groups and identified in post-transplant relapses, as downregulated, genes involved in interferon-gamma (FDR = $2.15e^{-6}$) and interferon-alpha responses (FDR = $6.9e^{-6}$), as well as genes required for IL6/JAK/STAT3 signaling (FDR = $3.66e^{-3}$). Interestingly, when focusing on the granular differences in the immune gene sets we found an increased expression of most of the inhibitory killer-cell immunoglobulin-like receptors (KIR), KIR2DL1, KIR2DL2 and KIR2DL3 (LogFC >1) as well as of some negative regulators of the immune checkpoint, namely LGALS9C, PDCD2L, CD270, VISTA, CTLA4 (LogFC >0.5), together with downregulation of some class II human leukocyte antigen molecules (HLA, including HLA-DRB1, DRA, DQA1 and DQB1 [LogFC <–1], as also previously reported) and HLA transcriptional regulators (CIITA, SP1, ATF1, RFX5, LogFC <–0.5). After performing a hierarchical clustering of the expression values of the pre-selected immune genes and assigning a binary phenotype to all the cases in study (based on the presence/absence of an immune escape signature), we observed an increased mutational burden in patients characterized by more evident immune escape features. Despite this characteristic, post-transplant escaping diseases did not correlate with the presence of driver mutations (i.e., TP53, NPM1, FLT3).

Conclusions: These findings, in continuum with previous work, highlight the pleiotropy of immune escape in alloreactive setting and pinpoint the complexity of leukemia evolution in the context of evasion from the GvL effect. While driver hits can easily gain a fitness advantage regardless of the acquisition of immune escape signatures, immune-aberrant clones (especially when lacking stronger leukemogenic hits) would accrue subclonal alterations since characterized by lower immunogenicity. In analogy with solid cancers, our results show that, also in leukemia relapsing after transplant, the biology underpinning immune escape mechanisms is intimately related to initial processes of immunoediting and may shape malignant clonal progression.

Disclosure: Nothing to disclose

O105

Mechanisms of T cell tolerance after PT-Cy haplotransplantation

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Background: The mechanisms of T cell-dependent tolerance after haploidentical hematopoietic stem cell transplantation (haplo-

HSCT) are incompletely understood. Both central and peripheral regulation mechanisms are suspected. We interrogated eight patients with leukemia (five) or MDS (three) (age 35–73 years, median: 51 years) following IRB-approved consenting. All received Flu+TBI (±Cy) pre-conditioning and haplo-HSCT with post-transplant Cytoxan (PT-Cy) and FK506 as GvHD prophylaxis. Chimerism at tolerance studies was donor dominant (97–100%, mean: 99% for both CD33+ myeloid cells and CD3+ T cells). Immunosuppression drug (ISD) was withdrawn ~6 months before setting up in vitro tolerance studies.

Methods: To test the involvement of regulatory T cells (Tregs), we depleted them from purified T cells with Denileukin Diftitox (IL2R immunotoxin, Seragen Inc™) pre-incubation. The contribution of Tr1 cells or possible anergy was examined by either blocking IL10R or supplementing cultures with low-dose IL2, respectively. T-cell exhaustion was tested by blocking the PD1 pathway with anti-PD1 MoAb (OPDIVO, Bristol Myers Squibb™). Purified T cell responses to recipient dendritic cells (DC) were measured in mixed lymphocyte reaction (MLR) assay and further tested by quantifying cytokine secretion in MLR culture supernatants using Bio-Plex immunoassays (Bio-Rad Lab™). To test for clonal deletion, alloreactive T-cell clones with frequency >0.1% identified in vitro from the graft pre-infusion were serially tracked by monitoring their T-cell receptor CDR3 sequence using ImmunoSEQ assay (Adaptive Biotech™).

Results: Circulating T cells were hyporeactive to recipient DCs in patients at 1 year (or 2 years 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 third-party APC. Meanwhile, host DC triggered a robust third-party T-cell response. Neither depletion of Tregs, nor blockade of IL10R or PD1 could reverse T-cell hypo-reactivity. Low-dose IL2 triggered mild anti-host proliferation responses. Similar scenarios were detected in graft T cells against self-DC, while vigorous responses were shown in the graft T cells against host-DC pre-haplo-HSCT. Cytokine profiling corroborated the proliferative MLR responses. ImmunoSEQ revealed the gradual disappearance of alloreactive T-cell clones from peripheral blood with time. Low dose IL2 had minimal impact to reverse hypo-reactivity.

Conclusions: In summary, 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 to be insignificant as their removal or blocking antibodies did not lead to 'flare' in 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. Anergy may play a minor supportive role.

Disclosure: Nothing to declare.

Source of funding: UPMC ITTC fund.

Myelodysplastic syndromes

O108

Allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome unclassifiable – a retrospective study on behalf of the Chronic Malignancies Working Party of the EBMT

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Background: Myelodysplastic syndrome unclassifiable (MDS-U) is a rare subtype of myelodysplastic syndromes (MDS). According to the WHO classification, the diagnosis can be made in the following settings: (1) MDS-U with 1% blood blasts (MDS-U-BL), (2) MDS-U with single lineage dysplasia and pancytopenia (MDS-U-SLD-Pan), and (3) persistent cytopenia, <1% circulating blood blasts, <5% bone marrow blasts, no significant (<10%) unequivocal dysplasia in any myeloid lineage and the presence of MDS-defining cytogenetic abnormalities (MDS-U-CG). There is very limited data on the prognosis and treatment outcomes for this entity. According to published data, median overall survival (OS) is 43 months [1], being shorter for patients with MDS-U-BL [2]. Here we present characteristics and outcome data for allogeneic hematopoietic stem cell transplantation (allo-HSCT) performed for patients with MDS-U.

Methods: Patients with MDS-U who received allo-HSCT between 2012 and 2019 were selected from the EBMT database. Additional data to verify the diagnosis was requested from the participating centres. Reported percentages are calculated for the patients for whom data was available. OS and relapse-free survival (RFS) were analysed using Kaplan–Meier methods.

Results: Additional data was received for 75 patients, of whom only 14 were enrolled. The other patients were excluded either because of missing data ($n = 19$, 25%) or because they did not meet the diagnostic criteria for MDS-U ($n = 42$, 56%). 50% were male, and the median age at allo-HSCT was 54 years (IQR, 33–61). The prevalence of the MDS-U subtypes was as follows: MDS-U-BL 21%, MDS-U-SLD-Pan 36%, and MDS-U-CG 43%. IPSS-R at diagnosis was high in 30%, intermediate in 50% and low or very low in 20%.

The median interval between diagnosis and allo-HSCT was 4.6 months (IQR, 3.6–6.9). 79% of patients had Karnofsky scores of 90–100%. A total of 54% of patients did not receive treatment for MDS-U prior to transplant. A total of 21% had identical sibling donors, and 64% had unrelated donors. Peripheral blood was the source of stem cells in 92%. The intensity of conditioning was reduced in 61.5% patients, and 23% received TBI. 92% received fludarabine-based conditioning. The most frequently used immunosuppression protocols were cyclosporine A (CsA) with mycophenolate mofetil (36%) and CsA with methotrexate (29%).

The 100-day cumulative incidence of acute graft versus host disease (GvHD) was 62% (95% CI, 35–88%), while the cumulative incidence of chronic GvHD was 43% (95% CI, 17–69%) at 1 year. At a median follow-up of 36.8 months (95% CI, 27.1–48.0) the median OS and RFS had not been reached, while 2-year OS was 64% (95% CI, 25–100%) (Fig. 1). No patient relapsed during the follow-up period.

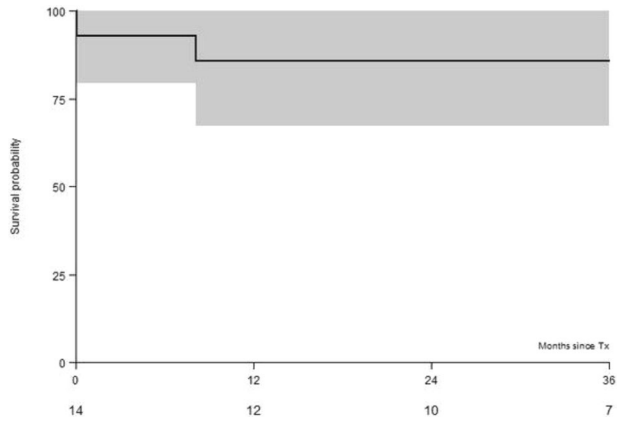

Figure 1. Overall survival of patients with MDS-U after allo-HSCT

Conclusions: Allogeneic hematopoietic stem cell transplantation is an option for patients with MDS-U. However, the accuracy of diagnosis remains an issue of concern.

References:

1. Baidoun F, et al. Clinical outcome of patients diagnosed with myelodysplastic syndrome-unclassifiable (MDS-U): single center experience. Leuk Lymphoma. 2019;60:2483–7.

2. Margolskee E, et al. Myelodysplastic syndrome, unclassifiable (MDS-U) with 1% blasts is a distinct subgroup of MDS-U with a poor prognosis. Am J Clin Pathol. 2017;148:49–57.

Disclosure: The authors declare no competing interests.

Myeloproliferative neoplasm

O109

Allogeneic hematopoietic cell transplant for blast phase of philadelphia-chromosome negative myeloproliferative neoplasms: a retrospective study from the Chronic Malignancies Working Party of the EBMT

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Background: Blast phase transformation of BCR-ABL1 negative myeloproliferative neoplasms (MPN-BP) associates with a dismal prognosis. Allo-HCT provides the only potential of long-term survival but is only applicable to a minority of patients. We hereby report on a large, retrospective EBMT-registry based study of MPN-BP patients undergoing allo-HCT.

Methods: Retrospective, multicentre, registry-based analysis using EBMT-registry data. Inclusion criteria: ≥18 years, MPN-BP diagnosis and first allo-HCT between 2005 and 2019. The Kaplan–Meier estimator and log-rank test were used for OS, PFS and GRFS. RI and NRM were modelled in a competing risk setting using the CI estimator and Gray's test. Prognostic variables were studied in Cox regression multivariable analyses (MVA). Cause specific hazards were modelled for competing risk endpoints.

Results: A total of 663 patients were included. Acute leukemia (AL) had evolved from PMF in 269 patients (42%), ET in 221 (33%) and PV in 169 (25%). Median age at allo-HCT was 60 years (IQR, 54–64) and the median time from diagnosis to AL was 63 months (IQR, 16.9–152). RIC was used in 65% of the patients, T-cell depletion was used in 69% and PB in 89%. MSD were used in 28% of the allo-HCT and 65% of allo-HCT were fully HLA matched. KPS at allo-HCT was ≥90 in 60% and disease stage at allo-HCT was CR in 45% of the patients. Median follow-up was 62 months (IQR, 30–95). The 3-year overall survival (OS) was 36% (95% CI, 32–36). The 3-year OS for those transplanted between 2015 and 2019, 2010 and 2014 and before 2010 was 39%, 36% and 28% ($p = 0.030$), respectively. The 1-year GRFS was 29% (95%, 25–33). The 3-year PFS, 3-year RI and 3-year NRM were 28% (95% CI, 24–32), 48% (95% CI, 44–52) and 24% (95% CI, 20–27), respectively. In univariate analyses, a more recent allo-HCT (after 2010) ($p = 0.030$), KPS ≥ 90 ($p < 0.001$), MSD ($p < 0.001$) and CR at allo-HCT ($p < 0.001$) associated with longer OS. Transplantation before 2010 ($p = 0.030$), KPS < 90 ($p = 0.010$) and not in CR at allo-HCT ($p < 0.001$) were associated with lower PFS. MSD ($p < 0.001$), KPS ≥90 ($p < 0.001$), PB ($p = 0.040$) and CR at allo-HCT ($p < 0.001$) were associated with lower NRM. TBI was associated with higher grade II-IV acute GvHD ($p = 0.020$) and PB associated with higher chronic (cGvHD) ($p = 0.030$).

OS MVA included 585 patients. KPS ≥90 ($p < 0.001$), CR at allo-HCT ($p < 0.001$) and more recent allo-HCT ($p = 0.023$) associated with better OS. These factors were also independently associated with better PFS, whereas only CR at allo-HCT ($p < 0.001$) and more recent allo-HCT ($p = 0.02$) were associated with longer time without relapse. KPS ≥90, CR at allo-HCT ($p = 0.003$) were associated with lower NRM and mismatched donors with higher NRM (HR (95% CI) MMRD and MMUD vs. MSD 2.66 (1.56–5.01) and 1.76 (1.04–2.98), respectively).

Conclusions: This study represents the largest cohort of MPN-BP patients undergoing allo-HCT reported to date. Results demonstrate that MPN-BP allo-HCT patients have poor outcomes overall; however, improvements in survival in patients undergoing allo-HCT in more recent years is evident. Patients with a KPS ≥90, in CR at allo-HCT and undergoing allo-HCT more recently were all associated with a better prognosis.

Disclosure: GO: BMS, Incyte, Novartis, Pfizer.

O111

Impact of high risk molecular mutations after allogenic transplantation in myelofibrosis: long term results of a prospective GITMO clinical trial

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Background: Allogeneic hematopoietic stem cells transplantation (allo-HSCT) is the only available curative option for myelofibrosis (MF), but the non-relapse mortality (NRM) limits its indication only to high-risk patients. The definition of risk has changed over time and the most recent MIPSS70 and MIPSS70+ scoring systems also incorporated the prognostic role of high-molecular risk mutation/s (HMR) (i.e., ASXL1, EZH2, SRSF2, IDH1/2). Here we present the retrospective evaluation of post transplant outcome according to the MIPSS70 scores of patients enrolled in a GITMO perspective clinical trial (Patriarca et al., BBMT 2019).

Methods: We retrospectively characterized the pre-transplant DNA obtained from 43 MF patients (intermediate or high risk according to DIPSS). Samples from all these patients were sequenced by Illumina MiniSeq platform. We selected for sequencing a subset of 30 genes involved in myeloid leukemogenesis by applying SOPHiA GENETICS™ Myeloid Solution to assess molecular risk classification. We considered as mutations the variants detected with a Variant Allele Fraction (VAF) major than 2.5% and classified as "pathogenic" or "likely pathogenic" by different biologic public databases.

Results: By NGS analysis, we identified a total of 114 mutations in the 30 analyzed genes, including non-synonymous point mutations ($n = 91$, of which 11 were nonsense), small insertions or deletions ($n = 22$) and splicing sites mutations ($n = 1$). At least one HMR mutation was detected in 44% of patients while two or more HMR mutations in 7%. Based on these molecular data, we redefined the clinical risk of our patients according to MIPSS70 and MIPSS70+ scoring systems which allowed to show that the great part of them were high or very high risk patients (73% and 78%, respectively). With a median follow-up of 4.2 years (range 0.02–9), the 5-year overall survival (OS) and progression free survival (PFS) were 6.5 years (95%, CI 1.6–NA) and 1.6 years (95%, CI 0.7–NA), respectively. The NRM at 2 years was 26% (95%, CI 13.6–39.4). According to the MIPSS70s scores, a higher risk of death ($HR_{high} = 4.07$, $HR_{very\ high} = 4.72$) and progression ($HR_{high} = 4.05$, $HR_{very\ high} = 3.24$) was observed when compared to low/intermediate risk group patients. However, the presence of HMR mutations did not significantly affect OS and PFS (Fig 1). Univariate analysis of the impact of each individual molecular alteration did not show any statistically significant association with post-transplant outcomes, even though, in JAK2-V617F mutated patients, a lower NRM was found in those with a VAF ≥50% ($HR = 0.25$, $p = 0.044$).

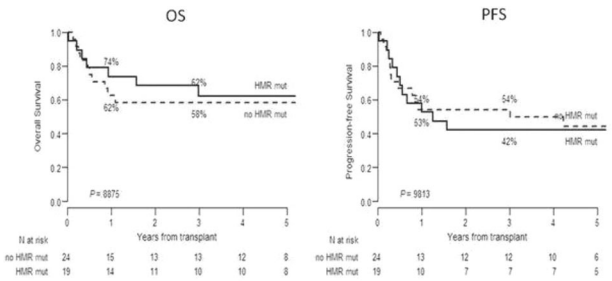

Figure 1

Conclusions: The use of molecular based scoring systems is crucial for an appropriate indication to transplant of MF patients. Allo-HSCT can lead to a significant cure rate of MF patients no matter the presence of HMR mutations.

Clinical Trial Registry: Clinical Trial.gov Identifier:NTC01814475.

Disclosure: Nothing to declare

O112

Outcome of allogeneic haematopoietic cell transplantation in eosinophilic disorders: a retrospective study by the Chronic Malignancies Working Party of the EBMT

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Background: Hypereosinophilic Syndrome (HES) and Chronic Eosinophilic Leukaemia (CEL) are rare and heterogeneous disorders. Allo-HCT has been reported in small case series of CEL or refractory HES, outcomes remaining ill-defined. We report on a retrospective, EBMT-registry based study of adult HES or CEL patients undergoing allo-HCT.

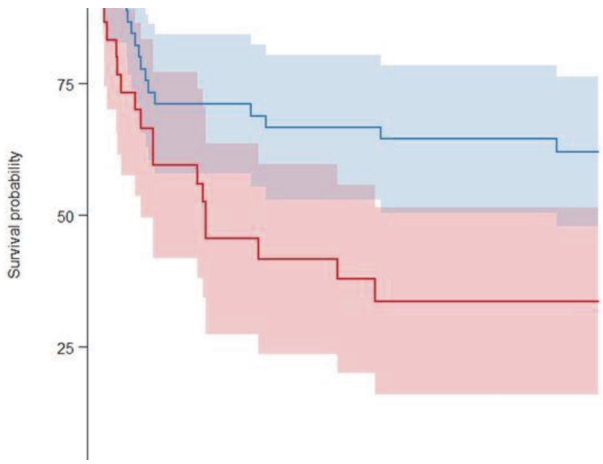
Methods: Patient selection included patients undergoing first allo-HCT for HES or CEL between 2000 and 2018, using either RIC or MAC defined by standard criteria. Overall survival (OS) was

calculated from date of transplant until death/last observation alive and progression free survival (PFS) until death, progression or last observation alive, whichever occurred first. The Kaplan–Meier estimator and log-rank test were used to estimate OS and PFS. The crude cumulative incidence estimator and Gray's test were used to estimate non-relapse mortality (NRM) and relapse incidence (RI) within competing risk settings, as well as acute graft vs. host disease (aGvHD)/death before aGvHD and chronic graft vs. host disease (cGvHD)/death before cGvHD.

Results: A total of 77 patients, diagnosed as HES ($n = 47$) or CEL ($n = 30$) were analysed, from 51 transplant centres. Median age of HES and CEL cohorts was 37.7 years (range (r), 30.1–44.0) and 46 years (r, 39.6–55.4), respectively. Majority of patients were male; HES ($n = 38$; 80.9%) and CEL ($n = 23$; 76.7%). Median interval from diagnosis to allo-HCT was 22.2 months (r, 11.5–55.8) for HES and 15.1 months (r, 9.8–27.9) for CEL ($p = 0.01$). Complete response at time of transplant reported for 23% (HES) and 47% (CEL) of patients, respectively. MAC regimens utilised in 56% of cohort, (HES (52%) and CEL (61%)). For HES, 20 (43%) patients had a matched sibling donor (MSD), 25 (53%) an unrelated donor (URD) with 2 (4%) utilising a mismatched related donor (MMRD). For CEL, 9 (30%) had a MSD, 20 (67%) an URD with 1 (3%) utilising a MMRD. T cell depletion reported in HES (57.2%) and CEL (54.2%), respectively. Regarding stem cell source: HES peripheral blood (PB; $n = 37$ (78.7%)); bone marrow (BM; $n = 9$ (19.1%)) and cord blood (CB; $n = 1$ (2.1%)) and for CEL; PB ($n = 20$ (66.7%)), BM ($n = 8$ (26.7%)) and CB ($n = 2$ (6.7%)), respectively. Median time to neutrophil engraftment in both cohorts was 18 days. Acute GVHD grades II-IV incidence at 100 days after allo-HCT was 45% in HES and 19% in CEL ($p = 0.03$). Median follow-up (IQR) was 102.3 months for HES (54.5–147.4) and 29.9 (23.8–88) for CEL. NRM estimates at 1 and 3 years were 25% and 27% (HES) and 38% and 45% (CEL); $p = 0.22$. Main causes of NRM were GVHD and infections. The 1, 3 and 5-year median OS estimates were 69%, 62% and 57% (HES), and 46%, 34% and 34% (CEL), respectively ($p = 0.017$ censored at 36 months; Fig. 1). Relapse Free Survival (RFS) estimates at 1 and 3 years were 58% and 55% (HES) and 42% and 35% (CEL), respectively ($p = 0.22$).

Conclusions: This represents the largest reported evaluation of allo-HCT outcomes for eosinophilic disorders. Albeit a heterogeneous cohort, long term survival can be achieved although strategies to address considerable NRM and relapse rates are required, particularly for CEL.

Figure 1



Clinical Trial Registry: Not applicable.

Disclosure: No relevant disclosures or conflicts of interest. No relevant funding.

New drugs- and cell-based immune therapies

O114

Combining blinatumomab and donor lymphocyte infusion in B-ALL patients relapsing after allogeneic hematopoietic cell transplantation: a study of the SFGM-TC

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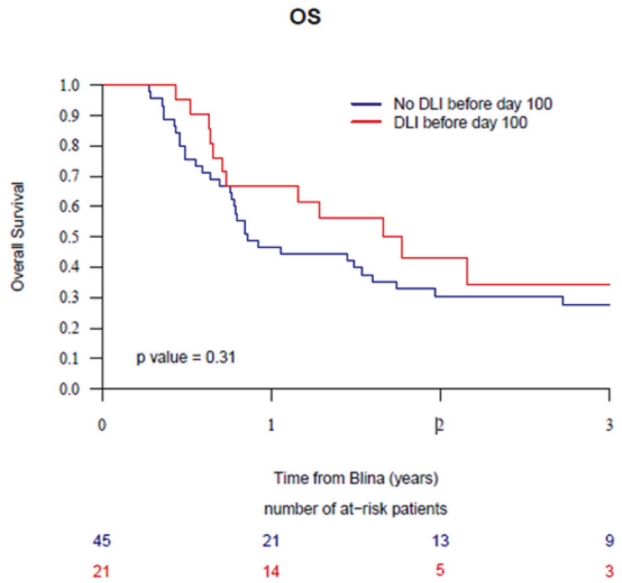
Background: Post-transplant relapse of B-cell acute lymphoblastic leukemia (B-ALL) still represents a major concern nowadays with poor outcome. Donor lymphocyte infusion (DLI) has been used as a salvage therapy with a proven anti-leukemic effect. More recently, Blinatumomab (Blina) has been approved for relapse/refractory B-ALL with CR rate of 45% in the post-transplant setting. Considering Blina is a bispecific antibody T cell-engager, administration of Blina in combination with DLI could be of interest. The aim of this study was to compare the efficacy and safety of Blina +DLI versus Blina alone for R/R B-ALL patients after allogeneic stem cell transplantation (allo-HCT).

Methods: This is a multicenter retrospective study from centers of SFGM-TC . All B-ALL patients who received blina as a salvage therapy after post-transplant relapse were included. For descriptive analysis, patients who received a DLI from 1 month before to 100 days after start of Blina were included in the Blina-DLI group. The others were considered having received Blina alone (Blina group). For studying the potential impact of DLI on the outcome, DLI was analyzed as a time dependent variable in multivariate analysis and a landmark analysis was performed at day 100.

Results: Seventy-two patients were included; 50 in the Blina group and 22 in the Blina+DLI group. Patient's age, sex, cytogenetic characteristics, disease status at transplant, conditioning regimen and type of donor were comparable in the two groups. The median number of cycle of Blina in the Blina group was 2 (min–max: 1–19) and 3 (min–max: 1–7), in the Blina+DLI group ($p = 0.01$). Sixty-one percent of the patients obtained a complete remission (CR) after the first cycle of Blina. Overall survival (OS) of the whole cohort was 49.3% and 32% at 1 and 2 years. One-year and 2-year progression free survival (PFS) were 37.5% and 23%. A landmark analysis was conducted on patients alive at day 100 post Blina (Blina group, $n = 45$; Blina-DLI group, $n = 21$). Two-year OS rates were 30.5% in the Blina group and 43% in the Blina-DLI group ($p = 0.31$). In multivariate analysis, DLI was not significantly associated with outcome (CR rates, HR = 0.54 (95% CI 0.23–1.27) $p = 0.15$; PFS, HR = 0.73 (95% CI 0.35–1.51) $p = 0.39$; OS, HR = 0.64 (95CI 0.32–1.27) $p = 0.2$) Adverse events were mostly hematological, neurological, and immunological (including cytokine release syndrome). Six percent of the patients developed newly acute graft-versus-host disease (GVHD) after treatment in the Blina group and 9% in the Blina+DLI group ($p = 0.64$). Chronic GVHD rates were similar in the two groups and accounted for 24% of patients in the Blina group and 22.7% of patients in the Blina-DLI group ($p = 0.91$).

Figure 1. Overall survival based on Landmark analysis on patients alive at day 100 DLI donor lymphocyte infusion, OS overall survival.



Conclusions: In our study, adding DLI between 1 month before and 100 days after start of Blina does not seem to improve outcomes in B-ALL patients who relapsed after allo-HCT.

Disclosure: PC has received honoraria from Amgen. The others authors declare no conflict of interest relative to this work.

O116

A phase 2 study of itacitinib for the prevention of cytokine release syndrome (CRS) induced by immune effector cell (IEC) therapy: preliminary results

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Background: CRS and IEC-associated neurotoxicity syndrome (ICANS) are common adverse events following IEC therapy. Janus kinase (JAK) pathways are important for cytokine signaling involved in CRS pathogenesis. Itacitinib is a potent, selective oral JAK1 inhibitor with broad anti-inflammatory activity. We describe preliminary results from a single-arm portion of a phase 2 study evaluating itacitinib for CRS prevention (NCT04071366).

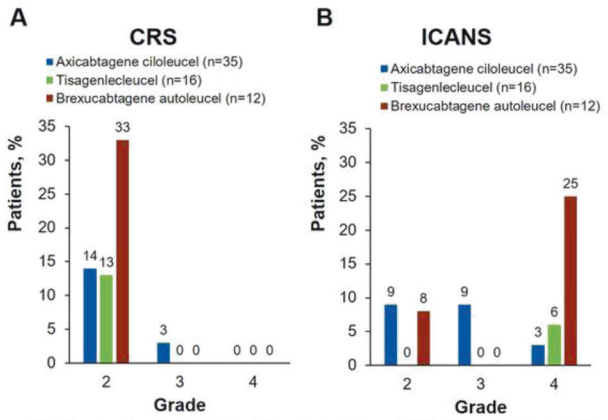
Methods: Patients ≥12 years old receiving commercial IEC therapy for approved hematologic indications are enrolled. Patients receive once-daily (QD) oral itacitinib 200 mg (3 days before IEC infusion through day 26). The primary endpoint is day +14 grade ≥2 CRS incidence per American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading. Secondary endpoints include overall response rate, day +28 ICANS incidence per ASTCT grading, CRS/ICANS duration, and safety.

Results: As of November 1, 2021, 63 patients (median age, 67 [range: 18–80] years; male, 73%) with relapsed/refractory B-cell malignancies were enrolled (diffuse large B-cell lymphoma [DLBCL], $n = 48$; mantle cell lymphoma, $n = 12$; follicular lymphoma, $n = 2$; B-cell acute lymphoblastic leukemia, $n = 1$). Median number of prior regimens was 3 (range: 1–6). Fourteen patients had prior autologous hematopoietic cell transplantation. Thirty-five (56%), 16 (25%), and 12 (19%) patients received axicabtagene ciloleucel, tisagenlecleucel, and brexucabtagene autoleucel, respectively.

A total of 54 (85.7%) patients developed CRS [grade 1, $n = 42$ [66.7%], 7 treated with tocilizumab). The intent-to-treat analysis showed CRS grade ≥2 in 12 (19.0%) patients (grade 3, $n = 1$; grade 4, $n = 0$; Fig. 1a). Median time to CRS onset was 4 (range: 2–8) days; median duration was 3 (range: 1–5) days. ICANS occurred in 26 (41.3%) patients. Grade 2, 3, and 4 ICANS were reported in 4 (6.5%), 3 (4.8%), and 5 (8%) patients, respectively (Fig. 1b). Median time to ICANS onset was 5 (range: 1–12) days; median duration was 2 (range: 1–17) days. Persistent grade 3/4 thrombocytopenia and neutropenia at Day 28 occurred in 16 (31%) and 11 (21.6%) patients, respectively. Grade 3/4 systemic infections (all unrelated) included Fusarium and BK virus ($n = 1$), klebsiella ($n = 1$), and staphylococcal ($n = 1$). Four patients experienced fatal AEs (multi-organ failure [$n = 1$], sepsis [$n = 2$], atrial fibrillation and hypotension due to lymphoma progression [$n = 1$]), all unrelated to itacitinib.

Among patients with DLBCL, all 48 were evaluable for IEC therapy efficacy, including 33 and 15 patients treated with axicabtagene ciloleucel and tisagenlecleucel, respectively. Best overall response was 74.5% (95% CI, 58–85; complete response [CR], 49%). Overall response rate at 3 and 6 months was 48% (95% CI, 33–63; 35% CR) and 30% (95% CI, 17–45; 25% CR), respectively.

Figure 1. Incidence of **a** CRS and **b** ICANS grade ≥2 by CAR-T therapy.



CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, IEC-associated neurotoxicity syndrome; IEC, immune effector cell.

Conclusions: Preliminary results demonstrate itacitinib 200 mg QD as prophylaxis is generally well tolerated, with promising activity for preventing grade ≥2 CRS/severe ICANS. The study was expanded with a randomized, double-blind, placebo-controlled portion of itacitinib 200 mg twice a day with plans to enroll 46 patients with DLBCL receiving axicabtagene ciloleucel.

Clinical Trial Registry: ClinicalTrials.gov: NCT04071366.

Disclosure: MJF: consultant for Arcellx, BMS, Editas, Iovance, Kite, and Novartis. RTM: advisor or consultant for Artiva, CRISPR Therapeutics, Incyte Corporation, and Novartis; has received research support from BMS and Novartis; has participated in a data and safety monitoring board for Novartis. AL: consultant for Avrobio, CareDX, Humanigen, and Kadmon; and has received honoraria from Avrobio and Humanigen. NVF: consultant and has participated in advisory boards for Kite Pharma and Sana Biotechnology; and has received research funding from Novartis. AA: research funding from Incyte Corporation. NNS: honoraria, travel support, and research funding from Miltenyi Biotec; honoraria from Celgene and Incyte Corporation; has served on scientific advisory boards for Celgene, Kite, Lilly, and TG therapeutics; and has received institutional research support for clinical trials from BMS and Miltenyi Biotec. LJL: no conflicts of interest. JHP: consultant for Affyimmune, Intellia, Kite Pharma, Amgen, Autolus, Allogene, Curocel, BMS, Minerva, Pfizer, Artiva, Kura Oncology, and Servier. CLP: advisory board participation for Incyte Corporation and Novartis. LB, ML, and RMZ: employees and shareholders of Incyte Corporation. JFD: equity or ownership of Magenta Therapeutics and WUGEN; consultant for Rivervest, and has received research support from Bioline, Incyte Corporation, and Macrogenics.

Non-infectious early complications

O118

Incidence, severity, management and outcome of sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) in allogeneic HSCT in adult patients: a retrospective EBMT Transplant Complications Working Party study

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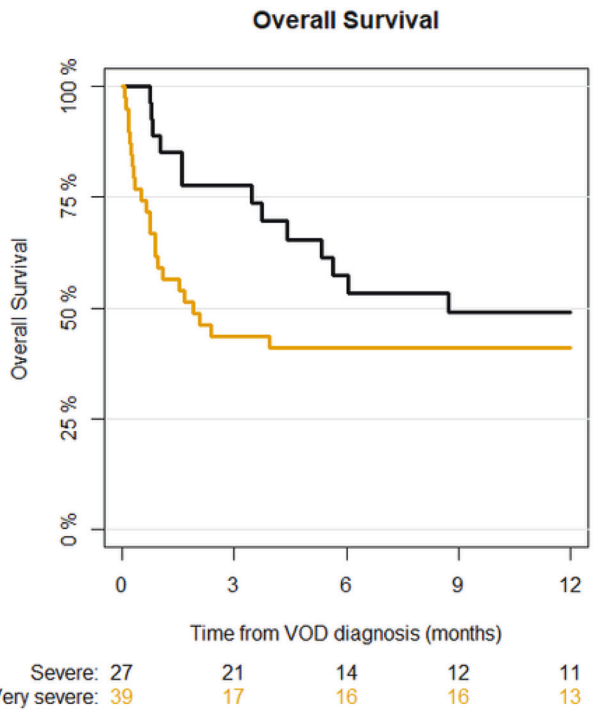
Background: As the diagnostic approach and treatment options of SOS/VOD have developed in the recent years, the EBMT Transplant Complications Working Party performed a study to evaluate the current incidence as well as the diagnostic policy, management, and outcome of this complication at EBMT centers.

Methods: All EBMT centers that had carried out allogeneic HSCTs to adult patients in the year 2018 were invited to participate. They were asked to report the total number of allogeneic transplantations in that year, the number of SOS/VOD cases among these transplantations, and, in addition to routine reporting, to report additional SOS/VOD-specific data. The data was collected to permit assessment according to the revised EBMT diagnostic and severity criteria (Mohty et al., BMT 2016). The primary endpoint of the study was the incidence of SOS/VOD.

Results: A total of 106 centers (36%) from 20 countries participated. The total number of allogeneic transplantations to adult patients at these centers in 2018 was 2886, and among these 93 cases of SOS/VOD were diagnosed. SOS/VOD cases were diagnosed at 45/106 centers. The cumulative incidence of SOS/VOD at day 21 was 1.8% and at day 100 2.4%. Additional SOS/VOD-related data was received of 70 patients from 37 centers; these cases were analyzed in detail. According to the EBMT criteria, 54 of the SOS/VOD cases were classical, 16 (23%) late onset (>21 days). All except two patients had at least two SOS/VOD risk factors. According to the EBMT criteria the severity grades were: mild 0, moderate 3, severe 28, and very severe 39. SOS/VOD prophylaxis had been given to 40 of the 70 patients, most often ursodeoxycholic acid (23) or heparin (17). A total of 60 patients received SOS/VOD-targeted treatment, 56 of them defibrotide. The severity grade did not significantly affect the choice of treatment. SOS/VOD resolved in 3/3 patients with moderate, 21/27 with severe, and 15/36 with very severe grade; the data were lacking for 4 patients. Very severe grade was significantly associated with less SOS/VOD resolution than severe grade (42% vs. 78%, Fisher test $p = 0.008$). By day +100 post-transplantation 40 patients (57%) were alive; 3/3 with moderate, 21/28 (75%) with severe and 16/38 (42%) with very severe SOS/VOD. At 1 year from the SOS/VOD diagnosis the survival of all patients with this complication was 46%, in the severe grade 49% and in the very severe grade 41% (Figure). SOS/VOD or MOF was listed as a cause of death in 17 cases.



Conclusions: The incidence of SOS/VOD was low, the cumulative incidence at 100 days was 2.4%. Close to one quarter were late onset cases. The overall survival at 1 year from the diagnosis was 46%. According to the EBMT criteria severe and very severe grades dominated, there were no patients with mild and only very few with moderate grade. The data support the prognostic value of very severe vs. severe grade. Low numbers of the mild and moderate grades did not permit an evaluation of their prognostic impact.

Disclosure: No author has any conflict of interest related to this study. OP has received honoraria or travel support from Astellas, Gilead, Jazz, MSD, Neovii Biotech, Novartis, Pfizer and Therakos. He has received research support from Gilead, Incyte, Jazz, Neovii Biotech and Takeda. He is member of advisory boards to Jazz, Gilead, MSD, Omeros, Priothera, Shionogi and SOBI. HS reports having received personal fees from Incyte, Janssen, Novartis, Jazz Parmaceuticals, Takeda and from the Belgian Hematological Society (BHS), as well as research grants from Novartis and the BHS. She has also received non-financial support from Incyte, Novartis, Gilead, the EBMT (European Society for Blood and Marrow transplantation) and the CIBMTR (Center for International Bone Marrow Transplantation Research). All of these interactions are unrelated to the submitted work.

O119

Liver stiffness assessed before hematopoietic stem cell transplantation predicts graft-versus-host disease and non-relapse mortality

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Background: Graft-versus-host disease (GvHD) and sinusoidal obstruction syndrome (SOS) are allogeneic hematopoietic stem cell transplantation (allo-HSCT) complications associated with significant morbidity and mortality. Predicting these complications might improve survival. Prior studies suggest that liver stiffness measurement (LSM) prior transplant could help to assess the risk and early detection of complications, although LSM data in allo-HSCT remains scarce. We present a prospective study to evaluate the utility of LSM to predict SOS and GvHD in the allo-HSCT setting.

Methods: Allo-HSCT patients with a baseline fibroscan prior transplantation were consecutively included from May 2014 to April 2021 at University Hospital Vall d'Hebron. Primary endpoint was the development of SOS and GvHD. Secondary endpoints were NRM and OS. We considered abnormal a LSM ≥6 kPa, upper limit of normal (ULN) at our institution.

Results: Sixty-eight allo-HSCT patients were included. Median follow-up for survivors was 23.85 months (95% CI 19.94–32.56). Patients were categorized in normal (<6 kPa) or abnormal (≥6 kPa; 36.7% patients exhibit an abnormal LSM. Both groups exhibit similar baseline characteristics, except for liver enzymes and BMI (related to LSM), age, and the use of TBI based-conditioning regimens or CNI-based GvHD prophylaxis (Table 1). Overall cumulative incidence (CI) of acute GvHD (aGvHD) at 100 days was 41.6%, being of 56.8% in the higher LSM cohort (H-LSM) and of 32.8% in the lower LSM cohort (L-LSM) (Fig. 1a). Univariate analysis (UVA) showed that aGvHD was associated with H-LSM (OR 3.25, $p = 0.026$), active disease at allo-HSCT (OR 4.64, $p = 0.016$), GGT >50 UI/L (OR 4.58, $p = 0.011$), female gender (OR 0.29, $p = 0.016$), ATG or alemtuzumab-based conditioning (OR 0.28, $p = 0.016$) and CD34(+)-selected allo-HSCT (OR 0.15, $p = 0.008$). Hepatic aGvHD (HaGvD) ocurred in 28% of H-LSM patients and in 6.9% L-LSM patients. H-LSM was associated with HaGvHD in UVA (OR 5.19, $p = 0.03$).

CI of chronic GvHD (cGvHD) at 1 year was 23.3%, 42% in H-LSM cohort and 17.4% in L-LSM cohort (Fig. 1c) (HR 3.77 $p = 0.01$). In contrast, cGvHD was diagnosed in 32% H-LSM patients and 23.2% L-LSM patients ($p = 0.43$). Hepatic cGvHD (HcGvHD) ocurred in 24% H-LSM patients and 4.6% L-LSM patients. H-LSM was the only significant variable predicting HcGvHD (OR 6.47 $p = 0.03$). SOS was diagnosed in 4% H-LSM patients and 4.6% in the L-LSM cohort. We found no differences of SOS according to LSM.

According to NRM UVA, CI of NRM at 2 years in H-LSM was 33.2% and in L-LSM was 16.1% (HR 4.02, $p = 0.01$) (Fig. 1e). The 2-year OS was 72.7% [95% CI: 61.6–85.8], 69.3% [95% CI: 52.5–91.5] in the H-LSM cohort and 75.4% [95% CI: 62–91.6] in the L-LSM cohort (HR 2.16, $p = 0.10$).

Table 1	LSM ≥6 kPa *n* = 25 *n* (%) or median (IQR)	LSM <6 kPa *n* = 43 *n* (%) or median (IQR)	*p*
Baseline characteristics			
Female	8 (32)	22 (51.1)	0.130
Age	55.8 (47.5–60.6)	45.7 (31–56)	0.020
LSM	7.6 (6.7–9)	4.3 (3.4–5.1)	<0.001
BMI	28.4 (25.5–31.8)	23.4 (21.4–27.4)	<0.001
HCT-CI ≥3	9 (36)	13 (30.2)	0.788
Hepatic HCT-CI			0.654
Lower	10 (40)	15 (34.8)	
Severe	3 (12)	3 (6.9)	
GGT > 50 UI/L	12 (48)	8 (18.6)	0.014
AST > 35 UI/L	11 (44)	4 (9.3)	0.001

Table 1	LSM ≥6 kPa	LSM <6 kPa	
	n = 25	*n* = 43	
	n (%) or median (IQR)	*n* (%) or median (IQR)	*p*
ALT > 35 UI/L	14 (56)	11 (25.5)	0.018
Bilirrubin >1.3 mg/dL	2 (8)	6 (13.9)	0.700
INR < 1.3	25 (100)	43 (100)	–
Hematological disease			0.517
AML	10 (40)	13 (30.2)	
ALL	2 (8)	10 (23.2)	
MDS	2 (8)	3 (6.9)	
NHL	4 (16)	8 (18.6)	
MPN	3 (12)	1 (2.3)	
MM	2 (8)	5 (11.6)	
Others	2 (8)	3 (6.9)	
Allo-HSCT			
Source			0.101
PB	24 (96)	34 (79)	
BM	1 (4)	3 (6.9)	
HUCB	0 (0)	6 (13.9)	
Donor			0.175
MRD	5 (20)	6 (13.9)	
MMRD	1 (4)	9 (20.9)	
MURD	12 (48)	13 (30.2)	
MMURD	7 (28)	15 (34.8)	
Conditioning regimen			0.596
MAC	7 (28)	16 (37.2)	
RIC	18 (72)	27 (62.7)	
Based-regimen			
Busulphan	19 (76)	25 (58.14)	0.189
TBI	2 (8)	15 (34.88)	0.019
ATG/alemtuzumab	11 (44)	17 (39.53)	0.800
GvHD prophylaxis			0.003
CNI	19 (76)	17 (39.5)	
PTCy	1 (4)	15 (34.8)	
None (CD34(+)-selected)	5 (20)	11 (25.5)	

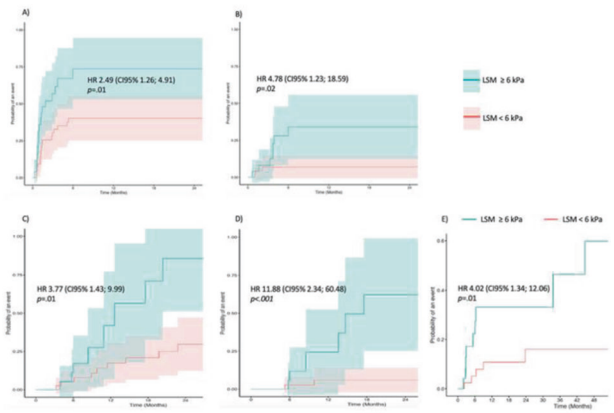

Figure 1. 1A) CI aGvHD according to H-LSM and L-LSM. 1B) CI HaGvHD according to H-LSM and L-LSM. 1C) CI cGvHD according to H-LSM and L-LSM. 1D) CI HcGvHD according to H-LSM and L-LSM. 1E) CI NRM according to H-LSM and L-LSM.

Conclusions: In our cohort, a H-LSM assessed prior transplant resulted associated with an increased risk of aGvHD, HaGvHD, HcGvHD and NRM, and a trend towards worse OS. In contrast, LSM was not predictive of SOS and cGvHD. Therefore, performance of LSM to candidates to allo-HSCT could be a useful and easy tool for identification patients at risk of complications.

Disclosure: GO: BMS, Incyte, Novartis, Pfizer. PB: Amgen, BMS/Celgene, Gilead, Novartis, Pfizer, Abbvie, Roche, Incyte Jazz Pharmaceuticals, MSD. FB: Roche, Celgene/BMS, Karyospharm, Takeda, AstraZeneca, Novartis, Abbvie, Janssen, Gilead, Mundipharma, Lilly, BeiGene. DV: Amgen, Novartis, Celgene, Pfizer, JAZZ, Astellas, MSD.

O120

Toward improving diagnostic criteria for TA-TMA: interim analysis of a multi-center retrospective review by the TA-TMA Working Group

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Background: Current diagnostic criteria for transplant-associated thrombotic microangiopathy (TA-TMA) were developed by expert panel or single-institution chart review and have not been rigorously validated or updated in several years. Several complications after hematopoietic cell transplantation (HCT) may share elements of these criteria, in part leading to considerable variability in the reported incidence of TA-TMA.

The TA-TMA Working Group is conducting a multi-national, multi-center retrospective chart review to better estimate the occurrence of patients meeting defined criteria for TA-TMA, with the aim of using these data to inform consensus diagnostic criteria. The first stage of this study involved identifying appropriate screening criteria for TA-TMA.

Methods: A total of 12 centers retrospectively screened patients who received allogeneic HCT (alloHCT) between 2015 and 2017. The following five criteria were used to screen for TA-TMA: schistocytosis (>2 per high-power field); LDH level above ULN; doubling of baseline creatinine; platelet refractoriness (50% decrease in platelet count and/or platelet count less than individual center's transfusion threshold × 4 days despite transfusions); and decreased haptoglobin. Patients were considered to have possible TA-TMA if they met ≥3 criteria within a 10-day period during the first 12 months post-HCT. Patients who had a positive biopsy, were diagnosed with TA-TMA or aHUS, or had received eculizumab following alloHCT were considered to have definite TA-TMA. Patients whose underlying hematologic disease relapsed before or within 1 month of screening positive for TA-TMA were excluded.

Results: This interim analysis evaluated 2992 patients (total 2997 adult and pediatric cases) from 8 US and EU centers who underwent alloHCT during the study period. Patient characteristics are summarized in Table 1. There were no notable differences in HCT characteristics across study sites. Among all cases, 21.7% (range, 4.9–56.4%) met ≥3 criteria for TA-TMA; 5.6% were categorized as "unknown" due to missing data for TA-TMA criteria.

There was wide variability among the centers for number of patients screened for TA-TMA.

	Overall study population (N = 2992)		Overall study population (N = 2992)		Overall study population (N = 2992)
Median age at HCT, years (range)	55.0 (0–79)	CMV antibody status, n (%)		Underlying disease or diagnosis[a], n (%)	
Gender, n (%)		Positive	1789 (59.8)	Acute leukemia	1525 (51.0)
Male	1784 (59.6)	Negative	1147 (38.3)	Lymphoma	313 (10.5)
Female	1208 (40.4)	Unknown	51 (1.7)	Myeloma	181 (6.1)
Race, n (%)		Prior HCT, n (%)		Myelodysplastic syndrome	759 (25.4)
White	2499 (83.5)	Yes	216 (7.2)	Sickle cell disease	7 (0.2)
Black or African American	154 (5.2)	No	1595 (53.3)	Thalassemia	2 (0.1)
Asian	111 (3.7)	Missing	1172 (39.2)	Other (includes marrow failure, non-cancer disease, severe combined immunodeficiency, and congenital enzyme deficiency)	611 (20.4)
Other	228 (7.6)				

[a]Patients could have multiple diagnoses.

Conclusions: Variability in identified potential cases across centers demonstrates the challenges associated with diagnosing TA-TMA. These preliminary results of patients meeting ≥3 criteria for TA-TMA provide data toward better defining diagnostic criteria; the next step is to adjudicate these cases and develop criteria for TA-TMA. The TA-TMA Working Group will ultimately develop guidelines and recommendations for the screening and diagnosis of TA-TMA.

Disclosure: GR and SM: Advisor (Omeros); SG: research funding (Amgen, Celgene, CSL Behring, Janssen, Pfizer, Quintiles, Sanofi); J-JB: consultant (Advanced Clinical, Avrobio, BlueRock, Omeros, Race Oncology, Sanofi); MSC: consultant (Jazz, Novartis, Omeros); speaker (Amgen, Jazz, Sanofi, Servier, Sobi); research funding (Miltenyi Biotec, Jazz, Omeros); RC, MH, CH, JHJ, SV, and SH: consultant (Omeros); RFD: consultant (Cidara, Omeros, Sobi, Takeda); advisor (Astellas); speaker (Amgen, BMS, Gilead, Jazz, Merck Sharp & Dohme, Miltenyi Biotec); VTH: consultant (Alexion, Janssen, Jazz, Omeros); speaker (Omeros); JL: advisor (Omeros); speaker (Omeros); research funding (Alexion, Jazz); RN: consultant (Bluebird, Omeros, Sanofi, Viracor); advisor (Kadmon, Magenta); research funding (Miyarisan); OP: advisor (Jazz, Gilead, MSD, Omeros, Priothera, Shionogi, SOBI); research funding (Gilead, Incyte, Jazz, Neovii Biotech, Takeda); honoraria (Astellas, Gilead, Jazz, MSD, Neovii Biotech, Novartis, Pfizer, Therakos); M-AP: consultant (Merck, Omeros); advisor (Abbvie, Astellas, Celgene, Bristol-Myers Squibb, Incyte, Karyopharm, Kite/Gilead, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, NexImmune, Novartis, OrcaBio, Takeda, VectivBio, Vor Biopharma); research funding (Incyte, Kite/Gilead, Miltenyi Biotec, Novartis); equity (NexImmune, Omeros); MS: consultant (Angiocrine Bioscience, McKinsey & Company, Omeros); advisor (Kite/Gilead); research funding (Angiocrine Bioscience, Omeros); honoraria (I3Health, Medscape).

O121

EASIX and mortality after allogeneic stem cell transplantation – a prospective study by the EBMT Transplant Complications Working Party

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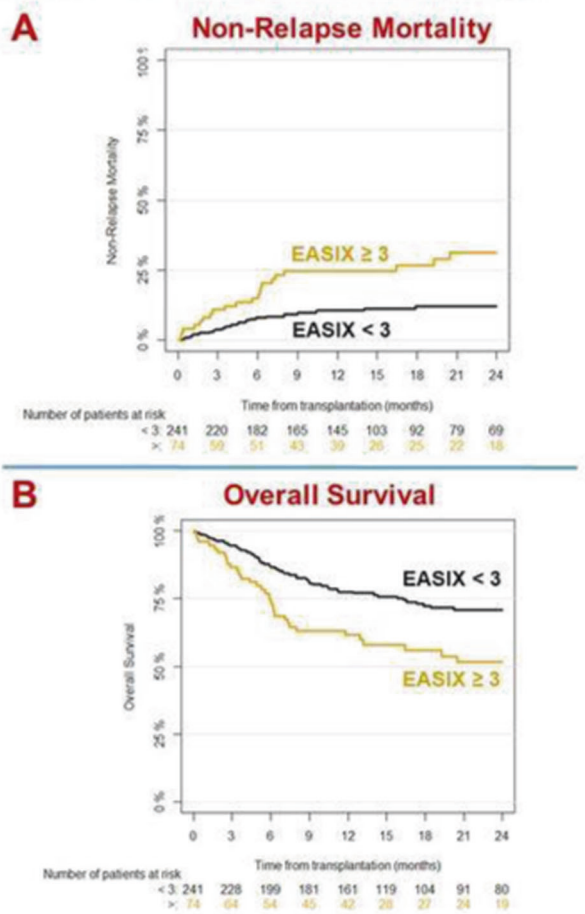
Background: The 'Endothelial Activation and Stress Index' (EASIX; [(creatinine × LDH) ÷ thrombocytes]) measured before start of conditioning predicts mortality after alloSCT independently from established clinical criteria (BMT. 2020;55:553–61). For broad clinical implementation, a prospectively validated EASIX cut-off is needed that defines a high risk cohort.

Methods: To define a cut-off for predicting non-relapse mortality (NRM), we performed a retrospective cohort analysis (LogRank) of four independent alloSCT cohorts (Heidelberg, Seattle, Berlin, Essen). For cut-off validation, we conducted a multicenter prospective study with inclusion of first alloSCTs from PBSC in patients with acute leukemia, lymphoma or MDS/MPN from 2017 to 2020 in the EBMT network. Patients with EASIX higher than the cut-off were compared to patients with EASIX lower than the cut-off using cause-specific Cox model. Primary outcome was NRM, secondary outcomes were overall survival (OS), relapse incidence (RI) and progression-free survival (PFS). Adjusting variables for multivariate analysis were: donor type (related vs. unrelated), Disease Risk Index (DRI – divided in two categories: low and intermediate vs. high and very high), patient age, sex (female to male vs. other combination) and intensity of conditioning (RIC vs. MAC).

Results: In the retrospective cohort of $n = 2012$ alloSCT recipients, we found that the optimal cut-off EASIX to predict NRM is 3. In the prospective analysis we included $n = 317$ patients from centers in seven countries. *Patient characteristics*: patients were transplanted for acute leukemia (62.1%), MDS/MPN (22.7%) or lymphoma (15.1%), mainly from an unrelated donor (55.1%). Complete remission was achieved at transplant for 58.8%, leading to a higher proportion of low/intermediate DRI (74.1%). Patient median age was 54.6 years, with a majority of male recipients (57.7%) and donors (72.8%). MAC was more frequently performed (59.3%) than RIC, with TBI in 28.4%. ATG for GvHD prevention was given for 34.1%.

Outcome: A total of 23% ($n = 74$) of alloSCT recipients had EASIX ≥3 taken before conditioning. NRM at 2 years was 31.1% in the high EASIX group (12% only in the low EASIX group). Patients with high EASIX also had worse 2-year OS (51.6% vs. 70.9%) and 2-year PFS (49.0% vs. 62.3%). No statistically significant difference could be observed for RI. We were able to validate the cut-off and found that EASIX ≥3 was associated with more than twofold increased risk for NRM (HR = 2.1, 95% CI = [1.16–3.78]; $p = 0.01$) in multivariate analysis. Figure 1 shows the univariate outcome graphs for NRM (**A**) and OS (**B**) in cohorts with EASIX <3 vs. ≥3.

Figure 1. Univariate outcome graphs in patients with EASIX <3 vs. EASIX ≥3 before alloSCT.



Conclusions: The results of this study provide a prospectively validated standard laboratory biomarker index as a predictor of transplant-related mortality after alloSCT independently from established clinical criteria. EASIX ≥3 taken before conditioning identifies a population of alloSCT recipients who have a more than two fold increased risk of treatment-related mortality.

Disclosure: HS reports having received personal fees from Incyte, Janssen, Novartis, Jazz Parmaceuticals, Takeda and from the Belgian Hematological Society (BHS), as well as research grants from Novartis and the BHS. She has also received non-financial support from Incyte, Novartis, Gilead, the EBMT (European Society for Blood and Marrow transplantation) and the CIBMTR (Center for International Bone Marrow Transplantation Research). All of these interactions are unrelated to the submitted work.

OP has no COIs directly related to this manuscript. OP has received honoraria or travel support from Astellas, Gilead, Jazz, MSD, Neovii Biotech, Novartis, Pfizer and Therakos. He has received research support from Gilead, Incyte, Jazz, Neovii Biotech and Takeda. He is member of advisory boards to Jazz, Gilead, MSD, Omeros, Priothera, Shionogi and SOBI. The remaining authors declare no COIs

O122

Second transplantation for graft failure after haploidentical HSCT: a survey by the Transplant Complications Working Party of the EBMT

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Background: Even though novel approaches have significantly reduced the incidence of graft failure (GF) in haploidentical stem cell transplantation (haplo-HSCT), its frequency with 8–13% is still higher than HLA-matched transplantation.

All current knowledge on further treatment options post GF in haplo-HSCT is based on data from the HLA matched setting, suggesting second transplantation as an option. The aim of this study is to examine what are the current practices among EBMT centres for GF after haplo-HSCT.

Methods: To address this questions Transplant Complications Working Party of the EBMT performed a survey between June and December 2021 among 177 centres reporting to the EBMT preforming haplo-HSCT. The questionnaire consisted of 33 questions focusing on current practice and the use of second transplant in patients with GF after haplo-HSCT performed in the period between January 2018 and December 2019. Results were analysed and reported as frequencies of the centres answering the question.

Results: A total of 64 transplant centres from 16 countries participated in this study. Within the study period a median of performed transplants among participating centres was 89 (range 10–1000), with a median of 20 (range 3–700) haplo-HSCT. Majority of centres ($n = 51$, 89.5%) used post-transplantation cyclophosphamide for GVHD prophylaxis. The median prevalence of primary GF was 3.6% while most centres (60.7%) did not report any secondary GF (prevalence Q3 5.3%). Preferred donor for second transplant was haploidentical in 25 (45.5%) centres, 25 (45.5%) centres stated no preference. Whenever possible, an alternative donor was recruited ($n = 30$, 62.5%), while 14 (29.2%) use the same donor and 4 (8.3%) centres never use the same donor. Predominant cause for using another donor in 25 (78.1%) centres was concerns of repeated engraftment issues. Change in donor-specific antibodies (DSA) status was never noted in 29 (64.4%) centres, 7 (15.6%) noticed it once, while 9 (20%) notice this frequently. The conditioning regimen was usually changed: in 33 (70.2%) centres conditioning was de-escalated while in 9 (19.1%) centres the intensity was escalated. Peripheral blood stem cells were the preferred stem cell source in 35 (74.5%) centres in second transplant. Most centres ($n = 34$, 72.3%) did not change GVHD prophylaxis.

Engraftment after second transplant occurred in 24 (55.8%) centres. Most severe side-effects reported by the centres were severe GVHD and VOD (3 centres, 8.1%).

Conclusions: Currently there are no prospective studies examining treatment options for patients with GF after haplo-HSCT resulting in the lack of guidelines. Therefore, centres use individual strategies, based on their experience. When second transplant is an option, the majority of centres use PBSC as source, de-escalate the conditioning, and do not change the GVHD prophylaxis. There is an interest among centres participating in this study for conducting a prospective trial to examine current strategies for GF after haplo-HSCT.

Disclosure: Nothing to declare

O123

Cytokine release syndrome after peripheral blood haploidentical stem cell transplantation with post-transplant cyclophosphamide: time of onset matters

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Background: The use of post-transplant cyclophosphamide (PT-Cy) has favored haploidentical hematopoietic stem cell transplantation (haplo-HSCT) when an HLA-matched donor is not available or when transplantion is urgent.

Although a high percentage of patients receiving PT-Cy haplo-HSCT develop CRS after infusion, it only seems to affect prognosis in the reduced proportion of patients that develop severe CRS. Literature regarding clinical impact of this complication is scarce.

The aim of our study is to analyze new CRS characteristics and their prognostic implication on both transplant-related mortality (TRM) and overall survival (OS).

Methods: From the cohort of 637 patients who underwent allo-HSCT at our centre between January 2012 and December 2020, 150 patients who received PT-Cy haplo-TPH were selected for this retrospective analysis. Regarding CRS analysis, 16 patients were excluded due to the impossibility to distinguish between infectious and CRS fever.

Results: Median follow-up was 18 months (37 months for alive patients). Most patients (86%) developed CRS. The cohort was divided into two groups: patients who developed early-onset CRS (≤24 h after infusion, 50%) and those with late-onset CRS or no CRS. The main characteristics of the patients are summarized in Table 1.

Patients who developed early-onset CRS had a significant increase in first-year TRM (Fig. 1A) as well as lower first-year overall survival (Fig. 1B).

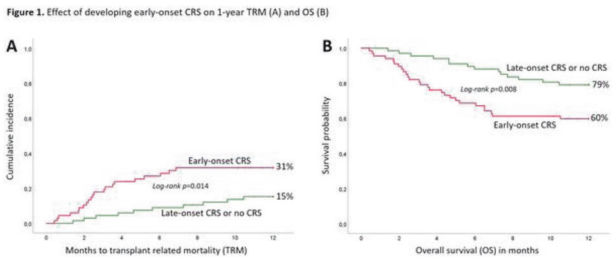
Multivariate analysis of first-year TRM identified the following independent prognostic factors: SOS (HR 9.24, $p < 0.001$), aGvHD grade ≥3 (HR 6.89, $p < 0.001$), early-onset CRS (HR 3.09, $p = 0.007$) and patient age at transplantation (HR 1.05 per year increment, $p = 0.002$).

Several risk factors were associated to developing early-onset CRS in a multivariate analysis: modified Baltimore haplo-HSCT platform (HR 7.54, $p < 0.001$), active disease at transplantation (HR 2.94, $p = 0.015$) and increased infused CD3+ cells (HR 1.05 per 10^7/kg increment, $p = 0.002$). Graft-cryopreservation would be a protective factor (HR 0.14, $p = 0.005$).

Table 1. Baseline patient characteristics.

Variable	Study population ($n = 150$)	Early-onset CRS ($n = 67$)	Late-onset CRS or no CRS ($n = 67$)	p value
	n (%)[a]	n (%)[a]	n (%)[a]	
Age in years, median (range)	56 (16–73)	59 (16–73)	53 (17–70)	0.196
Active disease at transplantation	53 (35)	32 (48)	15 (22)	0.002
Non-myeloablative conditioning	109 (75)	55 (82)	42 (63)	0.003
Haplo-HSCT platform[b]				
Modified Baltimore	110 (73)	57 (85)	40 (60)	<0.001
Modified Bacigalupo	34 (23)	7 (10)	25 (37)	<0.001
CD3+ dose per 10^7/kg, median (range)	21.4 (1.8–110.9)	25.2 (4.6–112.7)	18.2 (5.3–81.8)	0.005
Graft-cryopreservation	19 (13)	3 (4)	16 (24)	0.001
Severe aGvHD (grade ≥3)	18 (12)	5 (8)	12 (18)	0.069
SOS	10 (7)	7 (10)	2 (3)	0.082

aGvHD acute graft-versus-host-disease, *SOS* sinusoidal obstruction syndrome.
[a]Unless otherwise specified. Early-onset CRS: cytokine release syndrome developed within 24 h after haplo-HSCT infusion.
[b]Modified Baltimore (PT-Cy on +3 and +4, tacrolimus and mycophenolate from +5); modified Bacigalupo (PT-Cy on +3 and +5, tacrolimus from 0 and mycophenolate from +1).



Conclusions: We propose the definition of early-onset CRS as the one that is developed within 24 h after haplo-HSCT infusion. Patients who develop early-onset CRS have a higher TRM and lower OS. However, this is a single-centre retrospective study and further studies will be required in order to confirm these findings.

Disclosure: Nothing to declare

O124

Safety and efficacy of defibrotide in late-onset veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) after haematopoietic cell transplantation (HCT) from the Defifrance Registry Study

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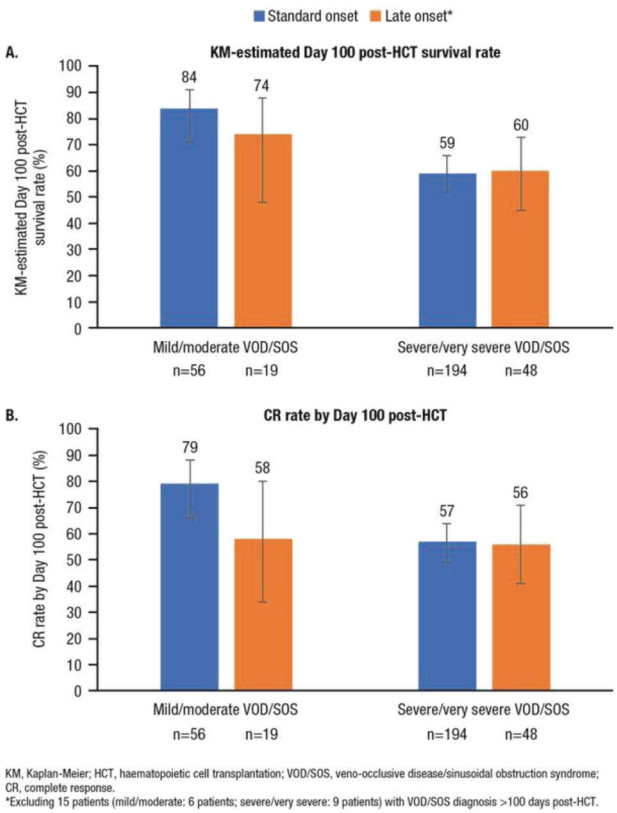
Background: VOD/SOS is a life-threatening complication of HCT conditioning. VOD/SOS was classically diagnosed ≤21 days post-HCT; however, in a large, prospective study, late-onset VOD/SOS occurred in 26% of patients, necessitating vigilance for VOD/SOS beyond day 21. The DEFIFrance study collected real-world data on defibrotide-treated patients from HCT centres across France. This analysis presents efficacy and safety of defibrotide according to timing of VOD/SOS diagnosis (standard or late).

Methods: DEFIFrance collected retrospective and prospective data on defibrotide-treated patients from 53 French HCT centres. VOD/SOS diagnosis was per investigator's typical practice. Disease severity was categorised using adult EBMT criteria in adults; paediatric patients (<18 years) were retrospectively/prospectively categorised using paediatric EBMT criteria. VOD/SOS onset was defined as standard (≤21 days post-HCT) or late (>21 days post-HCT). Survival and complete response (CR; total serum bilirubin <2 mg/dL and multiorgan failure [MOF] resolution per investigators' assessment) rates by day 100 post-HCT were calculated. Treatment-emergent serious adverse events (SAEs) of interest, irrespective of relationship to treatment, were haemorrhage, coagulopathy, injection-site reactions, infections, and thromboembolic events.

Figure



KM, Kaplan-Meier; HCT, haematopoietic cell transplantation; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; CR, complete response.
*Excluding 15 patients (mild/moderate: 6 patients; severe/very severe: 9 patients) with VOD/SOS diagnosis >100 days post-HCT.

Results: Of the 336 defibrotide-treated patients in this analysis, 83 (25%) were diagnosed with late-onset VOD/SOS (mild/moderate: $n = 25$ [31% of cases]; severe/very severe: $n = 57$ [23% of cases]; severity data missing: $n = 1$). Late-onset VOD/SOS was more common in adults than paediatric patients (mild/moderate: 39% vs 17%; severe/very severe: 25% vs 16%). Conditioning regimen did not impact timing of diagnosis except for reduced intensity conditioning (RIC)-treated patients diagnosed with mild/moderate VOD/SOS, where 9/20 (45%) of cases were late-onset. Patients receiving prior ozogamicin-containing therapy were more likely to have standard-onset VOD/SOS than patients without prior ozogamicin-containing therapy (85% vs 74%). Anicteric VOD/SOS was more likely to be diagnosed as late-onset; however, ~2/3 of anicteric cases were standard-onset, regardless of severity. Excluding 15 patients with VOD/SOS diagnosed >100 days post-HCT, the Kaplan–Meier (KM)–estimated day 100 post-HCT survival rate and day 100 CR rate was numerically higher in patients with standard- versus late-onset VOD/SOS in patients with mild/moderate VOD/SOS (Figure). Among patients with severe/very severe VOD/SOS, the KM-estimated day 100 post-HCT survival rate and day 100 CR rate was similar between patients with standard- versus late-onset VOD/SOS (Figure).

Treatment-emergent SAEs of interest occurred in 21% and 44% of mild/moderate VOD/SOS patients with standard- and late-onset VOD/SOS, respectively; among patients with severe/very severe VOD/SOS, corresponding values were 26% and 37%. The most common (>10%) treatment-emergent SAE categories of interest were haemorrhage (mild/moderate VOD/SOS: 11% [standard onset]; 36% [late onset]; severe/very severe: 13% [standard onset]; 25% [late onset]) and infection (mild/moderate VOD/SOS: 7% [standard onset]; 8% [late onset]; severe/very severe: 16% [standard onset]; 19% [late onset]).

Conclusions: In DEFIFrance, 25% of patients developed late-onset VOD/SOS post-HCT, highlighting the need for continued vigilance for VOD/SOS beyond 21 days post-HCT. Anicteric VOD/SOS was identified in both standard- and late-onset cases. Patients with late-onset VOD/SOS are likely to begin treatment later post-HCT versus with standard onset, so caution should be used when comparing Day 100 post-HCT outcomes. The safety profile of defibrotide was consistent with data from previous real-world studies.

Disclosure: AH, DB, J-HD, ML, RPL, and IY-A have received honoraria from Jazz Pharmaceuticals. KA and HY are employees of and hold stock and/or stock options in Jazz Pharmaceuticals. SN serves as an investigator for Jazz Pharmaceuticals. MM has received honoraria and research funding from Jazz Pharmaceuticals. AB, LL, and GM have no conflicts to disclose.

Non-infectious late effects, quality of life and fertility

O125

HCT Frailty Scale for adults undergoing allogeneic hematopoietic cell transplantation

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Background: Hematopoietic cell transplantation (HCT) Frailty Scale for overall survival (OS) prediction has been designed by our Institution to identify fit, pre-frail, and frail candidates for allogeneic (allo) HCT at the time of the first consultation. This scale consists of measurement of eight variables: Clinical Frailty Score, Instrumental Activities of Daily Living scale, Grip strength score, Timed Up and Go Test, Self-Rated Health questionnaire, a single

question on Falls, Albumin level and C-reactive protein level, in a median time of 5–6 min.

This study reports the results of this scale applied to a cohort of 298 patients undergoing alloHCT between 2018 and 2020 and compares its predictive ability with HCT-CI and KPS.

Methods: Frailty was evaluated prospectively at first consultation in all adult patients referred for transplantation after providing informed consent.

HCT Frailty Scale application: A normal result obtained from each of the eight variables is scored as 0. For any abnormal result, a proportional weight score is given to each respective index variable. This value was defined based on the HR coefficient from the multivariate Cox model for OS estimated including the eight variables of interest. The total score value is calculated as the weighted sum of values of the eight indices evaluated and ranges from 0 to 10.5. Based on the score obtained from the application of the scale, patients are classified in one of the following three groups: Fit: scale score ≤1/Pre-Frail: 1 < scale score < 5.5/Frail: scale score 5.5. After dividing the study cohort into the following groups: frail vs pre-frail and fit patients, KPS 70–80% vs 90–100%, and HCT-CI score >3 vs 0–3; the predictive ability of the HCT Frailty Scale was calculated using Harrell's Concordance Statistics and ROC curves, and compared with the predictive ability of HCT-CI and KPS.

Results: Overall, the median age was 58 years (range: 19–76), 53 (17.8%) patients had a KPS between 70 and 80%, and 54 (19.2%) and HCT-CI >3. The HCT Frailty Scale classified patients as-fit: 103 (34.5%), pre-frail: 148 (49.6%), and frail: 47 (15.7%) patients. The estimated 1-year OS of each group was 86.2% (95% CI 76.8–91.9), 73.8% (95% CI 65–80.7), and 50.9% (35.4–64.4) respectively ($P < 0.001$). The estimated 1-year NRM of each group was 5.4% (95% CI 2–11.5), 15.3% (95% CI 9.7–22.1) and 37.7% (23.6–51.7), respectively ($P < 0.001$). The predictive ability for OS of the HCT Frailty Scale was found to be higher than the predictive ability of HCT-CI score and KPS (Harrel's Concordance Index: 60.0% vs 54.5% and 52.8%, respectively).

Conclusions: The HCT Frailty Scale has been specifically designed to be applied in routine clinical practice to assess adult candidates for alloHCT across all ages. This innovative frailty scale is calculated as the weighted sum of values of eight domains and is a valuable predictive tool when evaluated at the first consultation. The use of this scale can identify frail and pre-frail patients prior to alloHCT.

Clinical Trial Registry: No applicable.

Disclosure: Nothing to declare

O126

Randomised trial on the impact of virtual-based multimodal training programme on physical fitness and quality of life in patients late post-haematopoietic stem cell transplant (HCT)

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Background: Reduced health-related quality of life (QOL) is well documented in post-HCT survivors. Supervised physical training (PT) or psychotherapy interventions have been shown to improve the well-being of transplant patients mainly within the first 3 months post-transplant. In-person trials of combined modal programmes produced promising results. Delivery of supervised interventions is more challenging in outpatient setting. Training via audio-visual platform alleviates many challenges of in-person trainings including infection risks. This study reports the 3-month outcomes following a multicentre, randomised controlled trial of a virtually supervised combined modal training.

Methods: Eligibility included aged ≥18, >6 months post-HCT and possessed basic computer kills. Exclusion criteria included severe graft-versus-host disease, exercise-limiting cardiovascular disease and severe anxiety or depression. Patients attending our four clinics were invited. Consented participants attended an in-person introductory session. Intervention group (InG) received training instructions followed by weekly PT and mindfulness-based stress management (MBSM) training for 6 weeks via videoconferencing. Assessments were done virtually pre-training, at 6 weeks and 3 months. For control group (CnG), participants were instructed to maintain usual activities and received same instructions on assessments as InG. An initial pilot study (SVH HREC approval 12/175) was used to design this multi-centre RCT (SVHS HREC 15/072, ANZCTR: ACTRN12615000570583).

Primary endpoint was the 6-min walk test (6-MWT) which is a validated measure of aerobic fitness reflecting capacity of daily living activities. Secondary endpoints included three other physical, eight QoL and psychological wellbeing measures.

χ^2 tests were used for categorical variables, *t*-test or Mann–Whitney *U* test for continuous variables, and mixed effect repeated measures model analysis for outcome differences over-time between CnG and InG.

Results: One hundred and thirty-nine of 219 responders participated (randomisation 1:1, median 21months post-HCT, median age 58, 25% lived >50 km from HCT centre). There were no significant differences between InG and CnG concerning age, gender, disease, HCT type or, time from HCT. 130 and 128 completed 6-week and 3-month assessments, respectively. Practice Logs showed mean weekly PT and MBSM practices increased in InG and remained low and static in CnG.

At 3 months, mean 6MWT increased to 549 from 463 m in InG and 501 from 464 m in CnG. The mean between-group difference (MD) was 51.4 ± 9.8 m SE, an effect size (ES) of 0.52 ($p < 0.0001$) favouring InG. There were significant differences between InG and CnG in 30'Sit to Stand (STS) at 3-month (MD 3.2 ± 0.8, ES 0.51, $p = 0.0002$), DASS depression score at 6 weeks (MD: −1.3, ES = 0.41, $P = 0.0007$) and in HADS anxiety score at 3 months (MD: −0.9, ES 0.27, $p = 0.03$).

Conclusions: This RCT demonstrated that a 6-week virtually supervised combined modal intervention could improve physical fitness and strength (6MWT and STS) and mental health (anxiety and depression) of transplant survivors. Improvements in 6MWT and STS correlate with increase functional capacity of patients. Over 50m increase in 6-MWT has been shown to correlate with significant improvement in functional capacity and health outcome in various diseases including cardiopulmonary diseases, diabetes, obesity and cancer. This trial demonstrates the potential benefits of a virtual-based supervised combined multimodal training programme to transplant survivors in their home.

Clinical Trial Registry: ANZCTR: ACTRN12615000570583

Disclosure: Nothing to declare

O127

Evaluation of secondary malignant neoplasms after hematopoietic stem cell transplantation (HSCT): a retrospective multicentric GETH (Grupo Español de Trasplante Hematopoyético) study

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Background: Secondary malignant neoplasms (SMN) are a long-term complication in HSCT recipients. Several host and clinical variables have been identified as risk factors for SMN. The main objective of this study was to describe the population with SMN and to assess outcome and risk factors for different SMNs types.

Methods: A retrospective multicentre study was performed in HSCT recipients who develop a SMN from June 2000 to October 2019 in ten centres belonging to the GETH group. Baseline patients' characteristics, HSCT and SMN data were analysed. Univariable and multivariable analysis were performed in patients with solid neoplasms, in order to identify risk factors for developing a specific SMN subtype.

Results: Three hundred and forty-four patients were included in the study. Patients' characteristics are summarized in Table 1. Haematological malignancies appeared at 3.4 (0.1–17.9) years from HSCT, earlier than solid neoplasms (5.6 (0.1–18.7) years) ($p < 0.001$). Post-transplant lymphoproliferative disease (PTLD) was the neoplasm with an earliest onset [0.5 (0.1–14.7 years)]. 179/210 (85%) patients were treated with curative intention. At univariable analysis, patients younger than 40 years, allografted recipients, patients with T-cell depleted graft or chronic GvHD (cGvHD) presented a significantly higher risk for skin/mucosal cancer, than for other SMNs. Age <40 years, masculine gender and smoking habit were associated with higher risk for lung cancer. Age >50 years, prior radiotherapy and allo-HSCT were associated with gastrointestinal tract (GIT) cancer. At multivariable analysis, the variables which maintained a statistically significant impact were: T-cell depletion and cGvHD for skin/mucosal cancer, smoking habit for lung cancer and allo-HSCT for GIT cancer. With a median (range) follow-up of 11 (0.8–21.1) years, median (95% CI) overall survival (OS) was 2.24 (1.02–3.46) years and in 151/189 (80%) of the patients the cause of death was the SMN. Patients with skin/mucosal cancer and breast cancer had significantly longer survival whereas patients with PTLD and lung cancer have the poorest prognosis.

Table 1. Patients' characteristics.

	Whole series ($n = 344$)	Auto-HSCT ($n = 188$)	Allo-HSCT ($n = 156$)	p value
Age at HSCT, median (range)	52 (19–72)	55.5 (19–72)	48 (19–69)	<0.001
Diagnosis				
No-Hodgkin lymphoma	105 (31%)	84 (45%)	21 (13%)	<0.001
Acute leukaemia	92 (27%)	24 (13%)	68 (44%)	
MM	49 (14%)	40 (21%)	9 (6%)	
Hodgkin disease	31 (9%)	25 (13%)	6 (4%)	
Myeloproliferative neoplasms	15 (6%)	2 (1%)	18 (11%)	
Myelodysplastic syndrome	15 (4%)	0	15 (10%)	
Others	32 (9%)	13 (7%)	19 (12%)	
Radiotherapy prior to HSCT				
No	194/218 (89%)	99/119 (83%)	95/99 (96%)	0.003
Yes	24/218 (11%)	20/119 (17%)	4/99 (4%)	
Total body irradiation (TBI)				
No	265/314 (84%)	183/187 (98%)	116/150 (77%)	0.001
Yes	49/314 (16%)	15/164 (9%)	34/150 (23%)	
T depletion				
No	37/95 (39%)	–	37/95 (39%)	–
Yes	58/95 (61%)	–	58/95 (61%)	
GvHD				
Acute GvHD	52/104 (50%)	–	52/104 (50%)	–
Chronic GvHD	59/101 (58%)	–	59/101 (58%)	
Immunosuppressive treatment duration				
<6 months	6/56 (18%)	–	6/56 (18%)	–
6–12 months	9/56 (16%)	–	9/56 (16%)	
12–24 months	5/56 (9%)	–	5/56 (9%)	
>24 months	36/56 (64%)	–	36/56 (64%)	
Secondary Malignant Neoplasm Group				
Haematological malignancies	101 (29%)	70 (37%)	31 (20%)	<0.001
PTLD	27 (9%)	5 (3%)	22 (14%)	
Other haematological malignancies	74 (21%)	65 (34%)	9 (6%)	
Solid neoplasms	243 (71%)	118 (63%)	125 (80%)	<0.001
Skin and mucose	52 (15%)	9 (5%)	43 (27%)	
Lung	44 (13%)	24 (13%)	20 (13%)	
GIT	41 (12%)	26 (14%)	15 (10%)	
Breast	22 (6%)	15 (8%)	7 (4%)	
Head and neck	21 (6%)	6 (3%)	15 (10%)	
Gynaecological	11 (3%)	3 (2%)	8 (5%)	
Kidney and urothelial	10 (3%)	7 (3%)	3 (2%)	
Thyroid	9 (2%)	8 (4%)	1 (1%)	
Others	33 (10%)	20 (11%)	13 (8%)	

Conclusions: SMNs represent a significant cause of late mortality in HSCT recipients. Patients with PTLD and lung cancer present especially poor prognosis. Time from HSCT to SMN is shorter in haematological neoplasms, especially for PTLD. T depletion and cGvHD are associated with a higher risk for skin/mucosal cancer. Smoking habit is associated with lung cancer and allo-HSCT is associated with GIT cancer.

Disclosure: Nothing to declare.

O128

HLA-HAPLO-identical donor HSCT achieved better QoL without compromise of survival compared to HLA-matched-sibling donor HSCT

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Background: Hematopoietic stem cell transplantation (HSCT) offers long-term survival options for most patients with hematological diseases. Recently, increasing numbers of patients achieved

comparable survival from receiving HLA-haplo-identical donor (HID) HSCT, but it is still unclear whether their long-term quality of life (QoL) is comparable to HLA-matched-sibling donor (MSD) HSCT. We aimed to establish a sound system for QoL evaluation and investigate the differences in long-term QoL between MSD and HID HSCT.

Methods: We prospectively enrolled consecutive patients who had received allo-HSCT from January 2018 to December 2019 at the HSCT Center, Blood Disease Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS & PUMC). Patients who survived more than one year after all-HSCT were informed about the objective of the study and asked to fill out the QoL questionnaires, including the Mos 36-Item Short-Form Health Survey (SF-36) and The Functional Assessment of Cancer Therapy Bone Marrow Transplant (FACT-BMT, version 3). SF-36 Form assesses multi-item subscales: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality, social functioning (SF), role-emotional (RE), and mental health (ME). The FACT-BMT used the subscales including Physical well-being (PWB), Functional well-being (FWB), Social well-being (SWB), Emotional well-being (EWB), BMT scale (BMTS), and Total with BMT module (FACT-BMT). Patients completed the questionnaires using the online applets named HSCT-QoL-CLOUD, which was designed by our department, and the database could be stored and exported from the cloud.

Results: This study included 425 patients who underwent allo-HSCT and 279 survivors (mean age: 36.10 ± 11.76, 49.10% female) who accepted the QoL assessment. Among the enrolled patients, there were 97 patients received HID and 182 patients received MSD donors. In this study, our endpoint includes the differences of both survival and QoL between HID and MDS groups. During the follow-up (median 8 months, interquartile range: 4–19 months), the estimated survival time of HID and MSD patients was 35.2 and 35.3 months, respectively. In the multi-adjusted COX model, compared to the MSD group, the HR (95% CI) of mortality was 0.77 (0.37–1.61) for the HID. In the QoL analysis, HID patients had higher global FACT ($\beta = 4.46$, 95% confidence interval [CI]: 1.08–7.83), as well as higher PWB ($\beta = 1.32$, 95% CI: 0.04–2.59), SWB ($\beta = 1.57$, 95% CI: 0.54–2.61), FWB ($\beta = 1.51$, 95% CI: 0.22–2.80), and TOI ($\beta = 2.43$, 95% CI: 0.17–4.68). Using SF-36 form, the HID patients showed significantly greater GH ($\beta = 5.50$, 95% CI: 0.25–10.75) and VT ($\beta = 4.22$, 95% CI: 0.15–8.30) compared to MSD patients. There was no significant difference in QoL change over time between HID and MSD (all $P > 0.05$).

Conclusions: In conclusion, our study demonstrated that HID HSCT achieved better QoL in some sub-scales without compromise of survival compared to MSD HSCT. In addition, both QoL questionnaires focus on different aspects of QoL and neither could be replaced. The FACT-BMT questionnaire maintains its psychometric properties, and it was administered to long-survivor patients together with the SF-36.

Disclosure: The authors declare no competing interests.

O129

Predictors and significance of renal dysfunction in patients with chronic graft-versus-host disease

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Background: Renal complications have been studied in hematopoietic stem cell transplant patients but are not extensively described among cGVHD patients. The purpose of this study is to explore the prevalence of and identify correlates of kidney dysfunction, with assessment of overall survival in this patient population.

Methods: Patients were enrolled on the cross-sectional NIH cGVHD natural history study featuring comprehensive multidisciplinary evaluation. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI 2021 equation using age, sex, and serum creatinine with eGFR ≤60 mL/min/1.73 m^2 defining any kidney dysfunction and eGFR ≤45 mL/min/1.73 m^2 defining severe kidney dysfunction. Transplant- and cGVHD-related factors, medication use, and biomarkers were assessed for association with any kidney dysfunction in univariable and multivariable analysis. Survival was estimated among eGFR groups using the Kaplan–Meier method and compared using the log-rank test.

Results: Among 365 patients with a median age of 49 years (range, 18–74), enrolled a median of 24 months (0–374) after cGVHD diagnosis and of 36 months post-transplant (4–378), most patients had severe ($n = 266$; 73%) or moderate ($n = 9$; 25%) cGVHD per NIH criteria. Median eGFR was 96.4 mL/min/1.73 m^2, 64 (18%) patients had any kidney dysfunction, and 29 (8%) patients had severe kidney dysfunction. Patients with any kidney dysfunction were more likely to be receiving antihypertensives ($p = 0.0043$) including angiotensin II receptor blockers (ARBs; $p = 0.030$) and to have proteinuria as measured by positive dipstick test ($p = 0.049$) at evaluation. Patients with any kidney dysfunction were also more frequently treated with cyclosporine at evaluation ($p = 0.0014$), for GVHD prophylaxis ($p = 0.011$), and at any time ($p = 0.0065$). Use of prophylaxis with tacrolimus was found to be associated patients without kidney dysfunction ($p < 0.011$), tacrolimus use at evaluation and at any time was not associated with renal dysfunction. Patients with kidney dysfunction were less severely affected by cGVHD of skin ($p = 0.03$), mouth ($p = 0.037$), and joints/fascia ($p = 0.009$); and had lower average NIH organ score ($p = 0.0048$) and inflammatory biomarkers (C3, $p = 0.0001$; CRP, $p = 0.0011$). Conditioning chemotherapy agents, or total body irradiation were not associated with kidney dysfunction. In Multivariable modeling, history of cyclosporine use (OR = 2.19, 95% CI 1.13–4.25) and ARB use (OR = 5.56, 95% CI 1.49–20.84), proteinuria (OR = 2.39, 95% CI 1.19–4.79), CRP (OR = 0.95, 95% CI 0.91–0.99), C3 (OR = 0.98, 95% CI 0.97–0.99), and hemoglobin (OR = 0.70, 95% CI 0.58–0.84) at evaluation were jointly associated with any kidney dysfunction. There was no association between any kidney dysfunction and overall survival ($p = 0.22$), but overall survival was significantly lower in those with severe kidney dysfunction ($p = 0.013$).

Conclusions: Kidney dysfunction was found in 18% of patients with cGVHD. The associations of less severe cGVHD and lower levels of inflammatory biomarkers with kidney dysfunction suggest an etiology unrelated to cGVHD but potentially a consequence of transplant-related toxicities. Interestingly, use of cyclosporine but not tacrolimus was associated with kidney dysfunction. Patients with severe kidney dysfunction were found to have lower overall survival defining a high-risk subset not ordinarily appreciated in cGVHD. Additional prospective studies are needed to advance the understanding of renal pathophysiology in cGVHD.

Clinical Trial Registry: ClinicalTrials.gov identifier NCT00092235.

Disclosure: The authors declare no competing interests.

O130

Cardiotoxicity in pediatric patients who underwent stem cell transplantation: retrospective analysis on 289 children

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Background: Cardioncology deals with the management of side effects of antineoplastic drugs. Published guidelines mainly address the adult population, whereas limited data are still available in the pediatric population.

Methods: We retrospectively collected data on 289 pediatric patients who received hematopoietic HSCT at the Pediatric Hematology/Oncology of the Policlinico San Matteo, Pavia, between January 2010 and November 2020. Cardiotoxicity criteria based on the ESMO Guidelines were used to define pediatric adverse cardiovascular events as reduction in ejection fraction LVEF >10% or a LVEF <53% using the biplane Simpson method and M-mode technique. We also added inverted E/A and E/E' <8 as index of cardiotoxicity. QTc prolongations >460 msec and ST depression and inversion were interpreted as pathologic electrocardiographic abnormalities. Moreover, we tried to define the role of the cardiac biomarkers Bnp and TnI in cardiotoxicity.

Results: In our cohort, 56% subjects were male with a median age of 7.4 years at HSCT. A total of 10% of patients underwent an autologous HSCT, 22% from an HLA-matched family donor, 46% from a HLA matched unrelated donor and 22% from a haploidentical donor.

Among children receiving a HSCT, 30% were affected by hemoglobinopathy, 30% by acute leukemia, 9% by myelodysplastic syndrome, 9% had solid tumors, 9% bone marrow aplasia, 7% immunodeficiencies and 6% Hodgkin or non Hodgkin Lymphoma.

We observed a 24% cumulative incidence (CI) of cardiovascular events, which was higher in those patients who underwent HSCT for malignant disease compared to those with non-malignant disease (32% vs 11%, $p < 0.05$). The median age of children developing cardiotoxicity was 12.1 years. A higher incidence of cardiotoxicity was observed in patients treated with anthracyclines before HSCT (33% vs. 19%, $p < 0.05$).

There was no gender difference when comparing the incidence of cardiovascular events, (males 18% vs females 24%, $p = 0.1$); nor were there significant differences in patients who did or did not receive mediastinal irradiation (29 vs 25%, $p = 0.44$), nor patients who did or did not receive total body irradiation (TBI) (29 vs 22%, $p = 0.2$). Biomarkers showed a highly predictive value in identifying children at risk of cardiotoxicity: the CI of cardiovascular events was significantly higher in children with pathological Bnp (31% vs. 12%) and TnI (65% vs. 24%). Furthermore, we found a progressively higher risk of cardiotoxicity with increasing Bnp levels.

Conclusions: HSCT represents an important risk factor for cardiotoxicity. In particular, previous antracycline exposure in malignant disease is the main risk factors associated with cardiovascular events. No significant difference was found in the comparison of patients who received TBI and mediastinal irradiation, but this observation could be biased by a limited follow-up: their cardiovascular toxicity seems to occur later and a longer follow-up is needed to confirm this hypothesis. Biomarkers like TnI and Bnp showed good predictive value to detect cardiotoxicity. According to this retrospective analysis we could underline the importance to create a standardized program of cardiosurveillance for all patients given HSCT.

Disclosure: Nothing to declare

O131

Sexual function of adult long-term survivors and their partners after allogeneic hematopoietic cell transplantation (S-FAST): a study by the EBMT TCWP and EBMT Nurses Group

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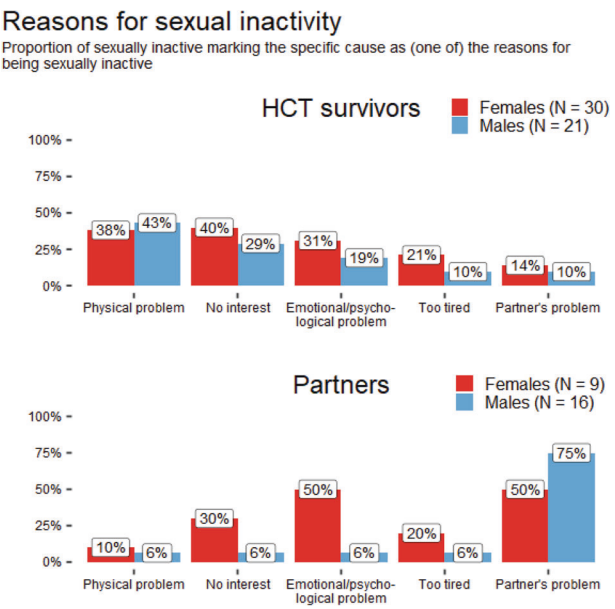
Background: Sexual dysfunction after allogeneic hematopoietic cell transplantation (HCT) can be a major cause of reduced quality of life for survivors and their partners, but studies about the prevalence and causes of sexual dysfunction after HCT in European countries are scarce.

Methods: We conducted a European multicenter study of HCT survivors and their partners to investigate sexual functioning after HCT. Adults who had survived more than two years post-HCT and their partners were invited to answer a self-administered questionnaire regarding sexual functioning, the EuroQoL-5D (EQ5D) questionnaire and the Female Sexual Function Index (FSFI) or the International Index of Erectile Function (IIEF) questionnaire. The FSFI comprises an overall score, ranging from 2 (worst) to 36 (best), with a previously reported cutoff of 26.6 for sexual dysfunction, and the IIEF comprises an overall satisfaction score, ranging from 2 (worst) to 10 (best).

Results: From 2015 to 2020, 132 HCT survivors (74 males, 58 females) and 77 partners (33 males, 44 females) from centers in the Netherlands (44% of participants), France (26%), United Kingdom (16%), Italy (11%), Croatia (2%), and Belgium (1%) participated in the study. Median (IQR) age of male survivors was 57 (48–66) years and 55 (45–61) years in female survivors. A total of 130 (98%) survivors underwent HCT for a malignant disease and 59 (45%) had received total-body irradiation. At participation, 33 (26%) of the survivors reported having at least one chronic illness. 32 (47%, 6 missing answers) male and 33 (62%, 5 missing answers) female survivors reported sexual problems some, most or all of the time since HCT. 21 (30%, 3 missing

answers) male and 30 (54%, 2 missing answers) female survivors reported being sexually inactive, many of whom since before HCT (53% and 78% of sexually inactive male and female survivors, respectively). The most common reasons for sexual inactivity (Figure) reported by survivors were 'physical problems' (43% of males, 38% of females) and 'no interest' (29% of males, 40% of females), whereas partners reported mostly 'emotional or psychological problems' (6% of males, 50% of females) and 'partner's problems' (75% of males, 50% of females). The median (IQR) FSFI overall score was 18 (7–23) in female survivors and 26 (21–31) in female partners; for males, the median (IQR) IIEF overall satisfaction score was 8 (4–10) in survivors and 6 (2–8) in partners. Standardized FSFI/IIEF scores were positively correlated with self-reported EQ5D health status (Spearman's $\rho = 0.26$, $p = 0.005$). Although 73 survivors (61%; 13 missing answers) and 57 partners (79%, 5 missing answers) reported that sexual health had not been discussed with them during transplant, no association was found with their level of sexual functioning (Wilcoxon test of difference in standardized FSFI/IIEF scores: $p = 0.21$).



Conclusions: Over one third of European long-term HCT survivors reported being sexually inactive. HCT survivors and their partners reported different concerns and a general lack of discussion regarding sexuality. Sexual function should be addressed upfront in the transplantation process, with differentiated information and support for patients and their partners.

Disclosure: Nothing to declare

Paediatric issues

O132

Individualized alemtuzumab dosing for induction of disease remission prior to HSCT in children with HLH

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Background: Primary hemophagocytic lymphohistiocytosis (pHLH) is a congenital immune disease characterized by life-threatening hyperinflammation mostly occurring within the first weeks of life. Allogeneic hematopoietic stem cell transplantation (HSCT) can cure pHLH, but an efficient bridging therapy to control hyperinflammation prior to HSCT is pivotal to improve clinical outcome. In a prospective study on the use of alemtuzumab as first-line treatment in children with pHLH, alemtuzumab was shown to successfully inhibit hyperinflammation with minimal toxicity (Moshous et al. Blood. 2019). However, highly variable alemtuzumab pharmacokinetics may influence response to treatment. Individualized alemtuzumab dosing based on pharmacokinetic monitoring may improve the efficacy of this therapy and prevent over-dosing.

Methods: Six children (two girls and four boys) with molecularly confirmed pHLH [biallelic mutations in UNC13D ($n = 4$) and PRF1 ($n = 2$)] from birth to 14 months old were treated with an individualized alemtuzumab dosing regimen at the Leiden University Medical Center, The Netherlands, between 2018 and 2021. Reasons for this approach were insufficient response to first-line treatment with etoposide, cyclosporine and steroids ($n = 2$); prevention of chemotherapy-related toxicity in a newborn with mild disease ($n = 1$), or critical organ failure ($n = 2$ with liver failure, $n = 1$ with combined liver/kidney failure) which precluded the administration of conventional treatment. Initial alemtuzumab dosing ranged from 1 to 2.5 mg/kg (mean dose = 2 mg/kg) depending on clinical disease activity and laboratory inflammatory signs. According to the individual response to treatment, further alemtuzumab (mean cumulative dose = 4.1 mg/kg) was given until optimal clinical disease control was reached. In parallel, alemtuzumab levels were determined in patient serum by a validated ELISA assay (manuscript in preparation), in order to extensively monitor individual alemtuzumab elimination and to estimate the time when alemtuzumab concentration would be below the lympholytic level of 0.1 mcg/ml. After conditioning with treosulfan/fludarabine/thiotepa ($n = 4$) or treosulfan/fludarabine ($n = 2$), HSCT was scheduled when plasma alemtuzumab levels were estimated to be around 0.1 mcg/ml.

Results: All children tolerated alemtuzumab well and experienced an optimal overall survival and event free survival with high quality of life of 100% at a median follow-up time post-transplant of 12 months (range 5–39). Main transplant complication was acute graft-versus-host disease (GvHD) which occurred in all but one patient (83%). However, only one child developed severe (grade III) acute GvHD. All patients responded to immunosuppressive therapy, allowing progressive tapering of immunosuppressants. Despite profound alemtuzumab induced lymphodepletion, there were no severe virus complications post-transplant in this patient cohort.

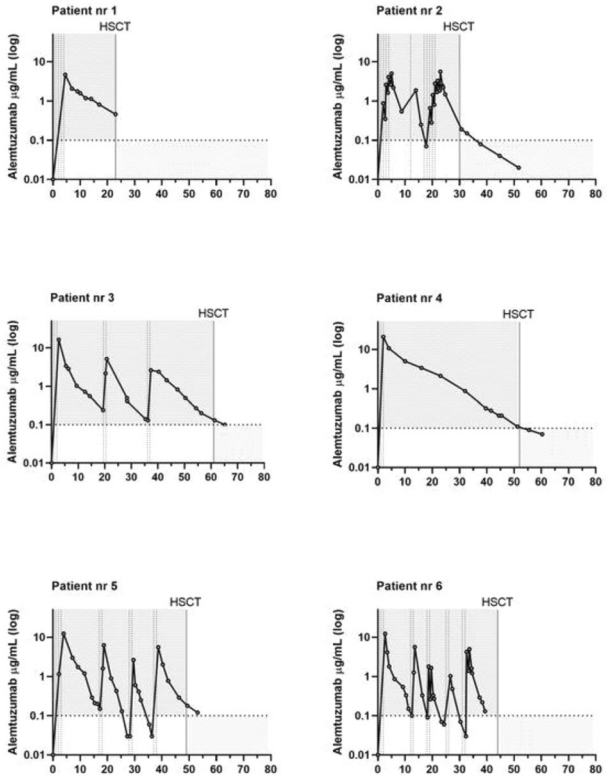

Figure 1. Serum alemtuzumab concentrations and dosage in relation to timeline. Vertical dotted lines represent alemtuzumab infusion days. Solid black lines connect measured alemtuzumab levels (black open circles) disregarding of sampling time and errors. A vertical grey line shows the HSCT day. Horizontal dotted lines indicate the lympholytic drug level.

Conclusions: Our experience shows excellent clinical outcome of individualized alemtuzumab dosing in critically ill children with hyperinflammatory pHLH refractory to conventional therapy or treatment naïve prior to HSCT. Prospective collaborative trials including larger numbers of patients are urgently needed to confirm these encouraging preliminary results. Alemtuzumab level monitoring and individualized dosing may further improve clinical outcome including control of GvHD.

Disclosure: Nothing to declare

Off Label Disclosure: Alemtuzumab has been used in this prospective trial to evaluate its efficacy as first line treatment in primary hemophagocytic lymphohistiocytosis based on current knowledge.

O133

Excellent outcomes after haploidentical bone marrow transplantation using post-transplant cyclophosphamide in 25 patients with Wiskott–Aldrich syndrome

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Background: Wiskott–Aldrich syndrome (WAS) is a rare X-linked disease characterized by microthrombocytopenia, immunodeficiency, eczema, and an increased incidence of autoimmune complications and/or malignancies. Hematopoietic cell transplantation (HCT) remains the only curative treatment, and haploidentical cell transplantation using post-transplantation cyclophosphamide (Haplo-PTCy) is an alternative for those without matched donors.

Methods: Retrospective study including all patients with WAS who underwent a Haplo-PTCY in three pediatric HCT centers. Statistics were performed using the EZR program.

Results: Twenty-five boys received 26 Haplo-PTCy transplants between July 2012 and August 2021. The median age was 33 months (range: 9.8–157), 80% had severe disease (WAS score: 4–5), and 92% were CMV positive. All received bone marrow from their haploidentical parents (father: 76%) and PTCy, cyclosporine, and MMF as GvHD prophylaxis.

Upfront transplants ($n = 20$): The median time for neutrophil and platelet recovery was 14 and 24 days, respectively. The cumulative incidence (CI) of rejection at 1 year was 10%. At 100 days, CI of acute GVHD grade II–III was 40% and, at 2 years, CI of chronic GVHD was 5.3%. The 100-day CI of CMV reactivation was 70% and occurred at a median of 26 days (range: 9–54) after transplant. Six patients had hemorrhagic cystitis at a median of 56 days after transplant. The first three patients received a RIC regimen using Fludarabine 150 mg/m^2 + Cyclophosphamide 29 mg/kg + TBI 200 cGy (FLU+Cy+TBI), two of those patients died (one from fungal infection at D41 with 100% donor cells and the other at D96 due to CMV infection and bacterial sepsis after a secondary graft failure (SGF)). The last patient also had a SGF and is alive 6.8 years after a second haplo-PTCy with full donor chimerism but refractory immune thrombocytopenia (ITP). The next 17 patients received a MAC regimen (Busulfan+Fludarabine +ATG), and are all alive and well. No primary graft failure (PGF) was observed, however, mixed chimerism occurred in approximately 30% of patients. One patient with mixed chimerism and refractory ITP received a second transplant (mismatched unrelated donor) and is alive 11 months post-transplant with normal platelet counts and full donor chimerism. With a median follow-up of 23 months (range 4–85), the 1-, 3- and 5-year OS is 90%.

Salvage Haplo-PTCy transplants ($n = 5$): These patients were rescued after PGF following unrelated cord blood transplants ($n = 3$) or SGF after unrelated HCT ($n = 2$). All received bone marrow as the stem cell source and a FLU+Cy+TBI RIC regimen. All are alive with a median follow-up of 6.5 years (range: 2.7–9.3). Four patients have full donor chimerism with normal platelets counts, while one has mixed chimerism with 50,000/ul platelets.

Conclusions: Haplo-PTCy leads to excellent survival for WAS patients who lack matched donors. Engraftment was better for patients receiving an upfront haplo-PTCY after a MAC regimen. Although results are excellent, mixed chimerism was observed in 30% of patients, and a longer follow-up is needed to determine graft outcome. Salvage transplants after previous graft failures using a RIC regimen were also very successful.

Disclosure: Nothing to declare

O134

Excellent outcomes after T-replete unrelated donor cord blood transplant to cure high risk and refractory paediatric AML and MDS

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Background: Outcomes of alternate donor stem cell transplant in high-risk and relapsed or refractory paediatric Acute Myeloid Leukaemia (AML) and Myelodysplasia (MDS) have historically been poor. Cord Blood (CB) allows T-cell replete transplant, potentially enabling enhanced graft-versus-leukaemia (GVL) in patients with myeloid malignancies. We report a large, multi-centre experience of T-replete unrelated CB transplant in high-risk paediatric AML/MDS.

Methods: Data was collected from nine UK paediatric transplant centres, including all children up to aged 18 who had undergone a T-replete (ie without serotherapy) single or double CB transplant between January 2014 and November 2021 for high-risk AML/MDS. Data was collected about patients including their disease, treatment and disease status at transplant, the CB unit, mismatch between donor and recipient, transplant morbidity and short- and long-term outcomes.

Results: Outcomes for 101 patients were analysed (AML $n = 93$, MDS $n = 8$). A total of 34 in high risk CR1 (Myechild01 study classification), 21 in CR2 and 46 patients had refractory disease at transplant (29 primary, 17 relapsed refractory). A total of 27 patients received a fully matched (8/8) cord, 40 patients a 7/8, 30 patients a 6/8 and 4 patients ≤5/8. A total of 79% patients had myeloablative vs 21% reduced intensity conditioning. Primary engraftment occurred in 93% and graft rejection in 4%. Transplant-related mortality was 11%. The incidence of significant and severe acute GVHD was 71% and 55%, respectively, but chronic GVHD rates were very low (<5%). Relapse risk was 26.3% at 1 year and 26.7% at 2 years. One- and two-year overall survival (OS) was 70.3% and 64.4% (details in Table 1). Disease-free survival (DFS) was 62.6% and 59.4% at 1 and 2 years, respectively. MRD negativity at transplant correlated with improved DFS at 2 years (73.5% vs 46%%, $p = 0.004$) (Fig. 1). There was no significant association between the number of mismatched HLA alleles and OS ($p = 0.55$) or relapse risk ($p = 0.126$) in patients with positive MRD going into transplant.

Disease status at transplant	Number of patients	Deaths	OS (%)	Number of relapse or deaths	DFS (%)
Primary refractory	28	12	57.1	13	53.6
Relapsed refractory	18	10	44.4	11	38.9
CR2	21	4	81	6	71.4
High risk CR1	34	10	70.6	11	67.6
Overall	101	36	64.4	41	59.4

Table 1. Survival by disease status at time of transplant.

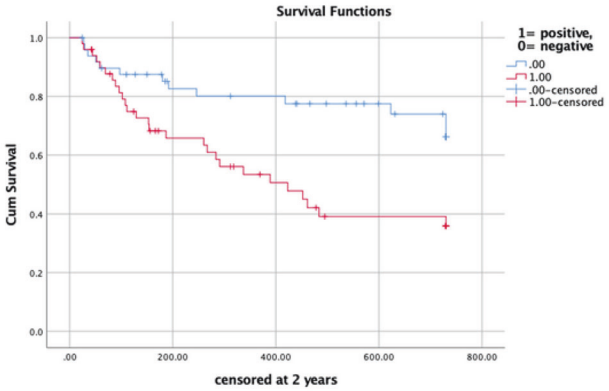

Figure 1. DFS at 2 years by MRD at time of transplant.

Conclusions: This is the largest yet reported series of T-replete CB transplant outcomes in very high-risk paediatric myeloid malignancy. Our data show significantly improved outcomes for children with such disease compared to registry data using other donors, including haplo-identical or unrelated. This is likely to reflect enhanced GVL effects with T-replete cords compared to alternate donor sources requiring T-cell depletion. OS and DFS were higher in patients with high risk CR1, CR2 and primary refractory disease than those with relapsed, refractory disease but even in the latter group many patients were salvaged. Our data indicate that CB transplant without serotherapy may be the optimal transplant option for children with high-risk AML/MDS.

Disclosure: Nothing to declare

O135

Exposure-response analysis of ATLG Grafalon® in paediatric all patients: towards individualized dosing to prevent acute GVHD after HSCT

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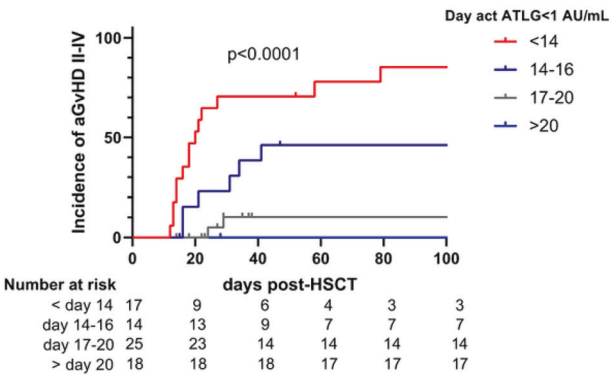
Background: ATG serotherapy in the HSCT setting is used for in vivo T-cell depletion to reduce the risk of graft failure and acute (aGvHD) and chronic GvHD (cGvHD). ATG Thymoglobulin pharmacokinetics (PK) and -dynamics (PD) have been investigated in a heterogeneous cohort of children, leading to a successful individualized dosing regimen based on patient weight, baseline lymphocyte counts and stem cell source. So far, very few studies investigating PK and PD of anti T-lymphocyte globulin (ATLG) Grafalon® have been published and no population PK models are yet available. This study describes the first population PK model

for Grafalon® and the relationship between Grafalon® exposure and the incidence of aGvHD in a homogeneous cohort of paediatric ALL patients.

Methods: Grafalon® treated patients transplanted between September 2014 and July 2020, who participated in the international FORUM study, were included in this study. Median cumulative dose of ATLG Grafalon® was 45 mg/kg (range 15–45), administered before transplantation at days −3, −2 and −1. Serum samples (pre-ATLG; 15 min after last ATLG dose; +1; +2; +3; +4 weeks post-HSCT) were collected and analysed by quantitative flowcytometry on HUT78 cells to determine the active ATLG concentration. In 16 patients, additional serum samples before and after each ATLG dose were obtained and measured. Population pharmacokinetic analysis was performed using NONMEM®. The relation between active ATLG exposure and clinical outcome was analysed using logistic regression and Kaplan–Meier estimates with the logrank test for curve comparison.

Results: For the population pharmacokinetic analysis a total of 813 samples from 121 paediatric ALL patients were available. Clinical outcome parameters were obtained for a representative cohort of 74 patients. The median age at transplantation was 9.7 years (range 0.6–18.6) and mean cumulative dosage of Grafalon® was 42.5 mg/kg (range 15–45). Donors were mainly matched unrelated (96%) and 76% of the patients received a bone marrow graft and 24% PBSC. A two-compartmental model with parallel linear and saturable clearance best described the ATLG Grafalon® concentration-time data. Body weight significantly and clinically relevant influenced active ATLG pharmacokinetics. ATLG exposure, more specifically, the day active ATLG concentration fell <1 AU/mL (median day 17 post-HSCT, range 1–41), was significantly associated with aGvHD grade II–IV occurring within 100 days post-HSCT ($p < 0.0001$). The incidence of aGvHD grade II-IV was significantly higher in patients who reached the active ATLG threshold level within 16 days after transplantation ($p < 0.0001$; <day 14 85% and 14–16 days 46% vs. 17–20 days 10% and >20 days 0%, see image). The overall incidence of severe aGvHD grade III–IV was low (5% only) and was exclusively seen in patients that cleared their ATLG within 21 days after HSCT. No association could be detected between ATLG exposure and overall survival.



Conclusions: This study describes the first ATLG Grafalon® population PK model in a large and homogenous paediatric ALL cohort. We demonstrated a clear relationship between Grafalon® exposure and aGvHD incidence. These data constitute a first step to further optimize 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 by Neovii Pharmaceuticals AG.

O137

Impact of acute GVHD on survival and disease relapse in paediatric patients undergoing allogeneic stem cell transplantation for acute lymphoblastic leukaemia: an EBMT registry-based analysis

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Background: The role of graft versus leukemia (GVL)/graft versus host disease (GVHD) in acute lymphoblastic leukemia (ALL) has previously been reported. The recent prospective randomized FORUM trial suggests that only a moderate aGVHD (grade II) achieves the goal of reducing relapse risk while maintaining survival advantage. We present a retrospective registry study which explores the role of acute GVHD in the largest reported paediatric cohort of patients undergoing allogeneic stem cell transplantation (SCT) for ALL.

Methods: Children with ALL in first/second complete remission (CR), receiving a myeloablative conditioning (MAC) and SCT from a sibling (MSD), an unrelated 10/10 matched (MUD) or 9/10 mismatched (MMUD) donor between 2007 and 2020 were enrolled. Recipients of mismatched related donors, cord blood or ex vivo T cell depleted grafts were excluded. To evaluate the impact of aGVHD on outcomes, a landmark analysis was applied, where patients with death, relapse or follow-up below 100 days were excluded.

Results: A total of 3328 children were included. Median age at transplant was 9.6 years (range 0.4–18). A total of 50% of patients were in CR1 and 50% in CR2 at SCT. A total of 68% received bone marrow (BM) and 32% peripheral blood stem cells (PBSC). A total of 49% of children received a graft from MSD, 37% from MUD and 15% from MMUD. A total of 68% received a TBI-based conditioning. A total of 51% had no in vivo T-cell depletion. CSA alone or in combination with methotrexate/MMF was administered as GVHD prophylaxis in 93% of the cases. Incidence of aGVHD grade II–IV was 35% (95% CI 34–37), grade III–IV 11% (95% CI: 10–12) at day +100. Incidence of chronic GVHD (cGVHD) at 2 years was 17% (95% CI: 15–18)/extensive cGVHD 8% (95% CI: 7–9). Non-relapse mortality (NRM) in the whole cohort was 10% (95% CI: 9–11) and relapse incidence (RI) 25% (95% CI 23–27) at 2 years. With a median follow-up of 3.1 years the overall survival (OS), leukemia free survival (LFS) and GVHD free/relapse free survival (GRFS) was

74% (95% CI 71–76), 65% (95% CI 64–67) and 51% (95% CI 49–53), respectively. In a multivariate analysis age at SCT, MMUD, female donor into male recipient increased the risk of aGVHD III/IV. Donor type (MUD and MMUD vs MSD), total body irradiation (TBI), female to male and no in vivo T cell depletion increased the incidence of aGVHD grade II–IV. After landmark analysis, patients with grade III/IV aGVHD had reduced RI (HR and 95% CI: 0.66 (0.48–0.89), $p = 0.008$) but increased incidence of NRM (HR: 5 (3.35–7.44), $p < 0.001$), thus abrogating a favourable LFS (HR: 1.25 (1.00–1.56), $p = 0.06$) and OS (HR: 1.75 (1.36–2.26), $p < 0.001$). Patients with grade II aGVHD had lower RI (HR: 0.71 (0.58–0.87, $p < 0.001$), non-significant higher NRM (HR: 1.26 (0.82–1.94), $p = 0.3$) significant higher LFS (HR = 0.78 (0.64–0.94), $p = 0.008$).

Conclusions: In a conventional MAC setting for paediatric ALL, the impact of aGVHD on RI is documented, specifically for patients who develop moderate (grade II) aGVHD, as supported by previous data. These data support approaches targeting moderate aGVHD in patients at higher risk of RI thus avoiding unnecessary TRM.

Disclosure: PB declares research grants from Neovii, Riemser, Medac (to Institution); advisory board for Novartis, Cellgene, Amgen, Medac, Servier (personal and to Institution); speakers bureau von Miltenyi, Jazz, Riemser, Novartis, Amgen (to Institution) and patent and royalties from Medac.

O138

Role of acute GVHD in paediatric patients undergoing allogeneic stem cell transplantation for acute myeloid leukaemia: an imperfect balance

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Background: The major cause of treatment failure in paediatric allogeneic stem cell transplantation (SCT) for malignant disorders is disease recurrence. In adults graft-versus-leukemia (GVL) has been shown to reduce disease recurrence in acute myeloid leukemia (AML), but not univocally in pediatric AML patients undergoing myeloablative (MAC) SCT. The present registry-based study of the Pediatric Diseases Working Party of the EBMT specifically addresses the role of GVL/acute graft versus host disease (aGVHD) in a large pediatric population with AML.

Methods: This retrospective registry study evaluated the role of aGVHD on transplant outcome for children with AML in first or second complete remission (CR), receiving MAC from a sibling (MSD), an unrelated 10/10 matched (MUD) or 9/10 mismatched (MMUD) donor between 2007 and 2020. Recipients of mismatched related donors, cord blood stem cells or ex vivo T cell depleted grafts were excluded. To focus on the impact of aGVHD on outcome, a landmark analysis was applied, meaning that all patients with death, relapse or follow-up below 100 days were excluded.

Results: A total of 2048 children were included in the study. Median age at transplant was 10.4 years (range 0.3–18). At SCT, 73% of the patients were in CR1 and 27% in CR2. 65% received bone marrow (BM) and 35% peripheral blood stem cells (PBSC). A total of 52% had a MSD, 35% a MUD, 13% a MMUD donor. The majority (71%) of children received a Busulfan/Cyclophosphamide (±Melphalan) based conditioning. A total of 55% received no in vivo T cell depletion. CSA alone or in combination with methotrexate/MMF was administered as GVHD prophylaxis in 92% of the cases. Day +100 incidence of aGVHD grade II–IV was 28% (95% CI: 27–30), grade III–IV 10% (95% CI: 9–11%). Incidence of chronic GVHD (cGVHD) at 2 years was 18% (95% CI: 17–21) and was extensive in 9% (95% CI: 7–10). Non-relapse mortality (NRM) was 8% (95% CI: 7–9) and relapse incidence (RI) was 25% (95% CI: 36–37) at 2 years. With a median follow-up of 3.4 years the overall survival (OS), progression free survival (PFS) and GVHD free/relapse free survival (GRFS) were 74% (95% CI: 72–76), 67% (95% CI: 65–69) and 53% (95% CI: 51–55), respectively. In a multivariate analysis higher age at SCT, higher degree of donor mismatch, no in vivo T-cell depletion significantly increased the incidence of aGVHD of any grade. Patient in CR1 had a significantly reduced RI and better LFS/OS.After landmark analysis at day 100, patients with grade III/IV versus no aGVHD had reduced risk of RI (HR and 95% CI: 0.66 (0.44–0.99), $p = 0.046$) but increased NRM (HR 95% CI: 4.34 (2.48–7.60), $p < 0.001$), thus abrogating a favourable prognostic impact on LSF (HR: 1.10 (0.81–1.50), $p = 0.54$) and OS (HR: 1.34 (0.95–1.87), $p = 0.09$). Any grade of aGVHD was associated with higher incidence of cGVHD.

Conclusions: This study reports on the largest cohort of pediatric patients with AML in CR1/CR2 undergoing SCT. In a MAC setting, disease status is the single most relevant predictor of outcome. The impact of aGVHD on RI is demonstrated, but novel strategies are warranted to avoid NRM following aGVHD and to further improve OS.

Disclosure: PB declares research grants from Neovii, Riemser, Medac (to Institution); advisory board for Novartis, Cellgene, Amgen, Medac, Servier (personal and to Institution); speakers bureau von Miltenyi, Jazz, Riemser, Novartis, Amgen (to Institution) and patent and royalties from Medac.

O139

Second hematopoietic stem cell transplant in children with relapsed JMML: a therapeutic option with limited toxicity

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Background: Juvenile myelomonocytic leukemia (JMML) is a rare and aggressive pediatric disease for which the only curative approach is hematopoietic stem cell transplantation (HSCT). Relapse after HSCT occurs in more than one third of patients and there are limited data on the efficacy of post HSCT salvage strategies.

Methods: We retrospectively collected data on children with JMML who underwent a second HSCT for disease relapse/

evolution to acute myeloid leukemia (AML) between January 2000 and December 2020 in the United Kingdom (UK).

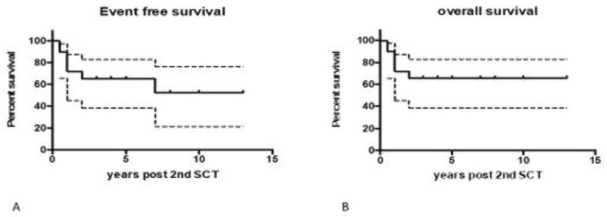

Figure 1

Results: Event free survival (**a**) and overall survival (**b**) for children with relapsed JMML who underwent a second HSCT.

Twenty children from four UK centers were included in the analysis, 14 male and 6 female. Genetics at diagnosis was positive for a germline mutation in three cases (one PTPN11 and two NF1 mutations). Somatic mutations were found on PTPN11 in seven patients (in one case associated with KRAS mutation), NRAS in three, NF1 in two, KRAS in one. Genetic analysis was unavailable in four patients. Cytogenetics at diagnosis showed monosomy 7 in two patients and complex karyotype in one. Median age at first HSCT was 3.5 years (range 0.5–8.1). Most patients (13/20, 65%) received a busulfan-based conditioning for the first HSCT, 7/20 had a matched sibling donor (MSD), 6/20 a matched unrelated donor (MUD), 7 had a mismatched unrelated donor (MMUD). All cases engrafted and achieved complete remission (CR) post HSCT. Median time from first HSCT to disease relapse was 173 days (range 73–522), 4/20 cases evolved to AML. Chemotherapy ± immunotherapy was administered to 13/20 (65%) patients between first and second HSCT. Median time between first and second HSCT was 290 days (96–2229 days). The second transplant was performed from a different donor than the first in 16/20 patients: in half of cases was a MMUD, no MSD was used for second transplant. Conditioning regimen for the second HSCT was treosulfan-based in 11/20. All patients engrafted, 18/20 experienced acute GVHD, in four cases this was grade III/IV. Two patients developed chronic GVHD (one extensive). One patient (5%) died of transplant related mortality (TRM) 19 months post HSCT in CR. Six patients (30%) relapsed after second HSCT at a median time of 228 days, one of them is still alive following third HSCT. Overall survival following second transplant was 65% (95% CI 81–38), with leukemia free survival of 52% (95% CI 75–21) at a median follow-up of 2.8 years (Fig. 1).

Older age at diagnosis predicted a poorer outcome with an increased risk of disease relapse ($p = 0.01$). Given the limited number of patients no other significant prognostic factor was identified in this cohort.

Conclusions: Second HSCT in JMML achieved high rates of remission and survival, similar to those described after first HSCT, with very low TRM. Despite the limitation of a small sample size and retrospective analysis, our data indicate that second HSCT should be considered in children with JMML who relapse after first HSCT, due to the high curative potential, low toxicity and lack of alternative therapeutic approaches.

Disclosure: Nothing to declare.

O140

Effect of KIR mismatch and NK cell dose on the incidence of leukemia relapse after alfa/beta T cell-depleted haplo HSCT

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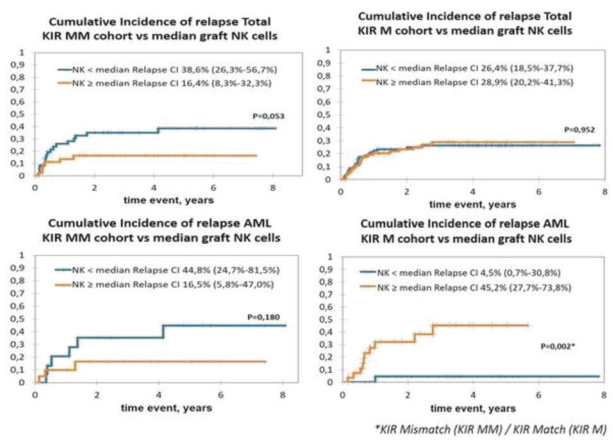
Background: TCRαβ+/CD19+ cells depletion allows to reduce the risks of developing severe complications after the Haplo HSCT, and also keeps NK cells in the graft. The effect of NK-related factors on the incidence of leukemia relapse was not analyzed in full. In this retrospective analysis we attempt to focus on the relationship between simple NK-related factors, namely KIR mismatch and NK graft content and the incidence of relapse in a cohort of children with acute leukemia, transplanted in complete remission.

Methods: The study cohort includes 296 patients: 190 ALL (acute lymphoblastic leukemia), 94 AML (acute myeloblastic leukemia), 12 ABL (acute biphenotypic leukemia). All patients received their first Haplo HSCT with αβ T cell depletion from January 2012 to April 2021, median of the age at HSCT was 9 (0.4–23) years. A total of 29.1% of patients received ATG. The HSCT, graft preparation, laboratory control of the graft composition, KIR genes HLA-typing was performed at one medical research center. KIR match or mismatch was predicted based on ligand-ligand model for all patients. Patients' cohorts were divided by median dose of graft NK cells subpopulation (30.9×10^6 cells/kg) and the relapse risk was calculated for each group by cumulative risk method, groups (graft NK ≥ median vs graft NK < median) were compared by gray test.

Results: The cumulative incidence of relapse was 28.6% (23.5%–34.9%) among the total cohort, 28.6% (22.6%–36.3%) among patients with ALL (28.2% for B-ALL, 29.2% for T-ALL), 26.8% (18.3%–39.4%) among patients with AML, 42.7% (19.6%–93.2%) in the small ABL cohort. KIR mismatch according to the ligand-ligand model was predicted among 32.7% donor-recipient pairs. No correlation was detected between the dose of NK cells in the graft and leukemia relapse in the whole cohort, while there was a trend for lower relapse incidence in the higher NK dose group among patients with ALL. We also failed to detect a correlation of KIR mismatch and relapse incidence neither in the total cohort nor in sub cohorts of ALL and AML. The higher dose of NK cells in the graft correlate with lower leukemia relapse risk in the group with donor-recipient KIR mismatch ($p = 0.05$) and there was no correlation in the KIR match patients' cohort. Among patients with AML without KIR mismatch, surprisingly, higher relapse incidence was seen among patients with higher dose of NK cells in the graft ($p = 0.002$). To investigate this fact, we looked into additional factors in the AML group and found a trend towards lower incidence of relapse with ATG use among patients without KIR mismatch. Results are summarized on the Graph.



Conclusions: A higher dose of NK cells in the graft was associated with a lower relapse risk for KIR mismatch patients with acute leukemia, both for ALL and AML cohorts. Paradoxically, higher dose of graft NK cells was associated with higher relapse risks for AML with KIR Match Haplo HSCT. ATG may play a role in reducing of the relapse risk for AML patients' cohort without KIR mismatch.

Disclosure: MM received speakers fee from Miltenyi Biotec.

O141

Matched unrelated donor transplantation with ATG versus haploidentical transplantation using post-transplant cyclophosphamide in children with acute myeloid leukemia: a study on behalf of the PDWP-EBMT

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Background: Children with acute myeloid leukemia (AML) in need of allograft and lacking an HLA identical sibling can benefit of matched unrelated donor transplantation (MUD) or HLA-haploidentical (haplo-HCT) transplant. In haplo-HSCT, different techniques to overcome the HLA barrier have been developed for improving immune reconstitution and graft-versus-leukemia, such as the use of post-transplant cyclophosphamide (PTCy), which have been firstly reported in the adult setting.

Methods: We compared outcomes of patients ≤18 years with AML in first complete remission (CR1) undergoing either MUD with anti-thymocyte globuline (ATG) ($n = 315$) or haplo-HCT with PTCy ($n = 77$) after a myelo-ablative conditioning regimen (MAC) from 2011 to 2020, reported to EBMT. To adjust for the difference among groups, a matched pair analysis was performed with 2 MUD for each Haplo matching on source of cells, age at HCT, year of HCT, cytogenetic risk, female to male donor and CMV status. Final analysis was performed on 142 MUD and 71 Haplo-HCT. Median follow-up was censored at 2 years.

Results: In the matched cohort, median age at HCT was 10.5 and 9.1 years and median year of HCT was 2017 and 2018, in MUD and Haplo-HCT recipients, respectively. Median time from diagnosis to HCT was 5.2 months in both groups, and unfavorable cytogenetic group was reported in 32% and 25% of MUD and Haplo-HCT. Conditioning regimen was MAC mainly based on busulfan (Bu), with BuCy and BuCy-melphalan being the most common in MUD, and Bu+Fludarabine in the haplo-HCT group. Stem cell source was bone marrow (BM) in 67% of patients. For MUD and Haplo-HCT, cumulative incidence (CI) of day 60 neutrophil recovery was 98.5% and 91.4%, CI of 100-day grade II–IV acute (a)GvHD and grade III–IV was 34% vs 34%, and 5 vs 12.9%, respectively. The 2-year CI of relapse (RI) were 17.8% vs 21.8%, and non-relapse-mortality (NRM) were 5.7% vs 9.8%, after MUD and haplo-HCT, respectively.

According to donor type, no significant differences were found in overall survival (OS) (2-year: 82.4% vs 76.6%, HR 1.45 (95% CI 0.74–2.86, $p = 0.28$) and leukemia-free-survival (LFS) (2-year: 76.6% vs 68.5%, HR 1.45 (95% CI 0.81–2.59, $p = 0.21$), whereas higher GvHD-free-relapse-free-survival (GRFS) was observed in MUD (2-year: 64.5% vs 55.9%, HR 1.66 (95% CI 1.02–2.72, $p = 0.04$).

Conclusions: Our data show comparable OS and LFS between MUD and Haplo-HCT with PT-Cy recipients. Haplo-HCT was associated with higher risk of grade III–IV aGVHD, and lower GRFS, while relapse and NRM were not significantly different.

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to declare

O142

Predictors of long term response with CD28-based CD19 CAR T-cells in children and young adults with B-ALL

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Background: CD28-based CD19 CAR T-cells were recently FDA approved for adult ALL, driving a spotlight on long-term effects of such constructs in pediatric ALL, and especially long term follow-up.

Methods: We conducted a phase 2 clinical trial of autologous CAR T-cells manufactured with a retroviral vector containing an FMC63-CD28-CD3zeta construct. The pediatric ALL cohort is reported. Patients were referred to CAR T-cell therapy after failing two or more previous lines of therapy. Lymphodepletion consisted of fludarabine and cyclophosphamide, followed by an infusion of 1×10^6 CAR+ T cells/kg. Cytokine release syndrome (CRS) and neurotoxicity grading were evaluated per the 2019 ASTCT criteria. Cytopenia were graded per CTCAE v5.0.

Results: Between 2016 and 2020, 37 children and young adults with ALL were enrolled on the clinical trial. The median age was 12. Patients had a median of 3 prior lines of therapy (range, 1–6) and 32% had a prior allogeneic HSCT. CAR T-cells were manufactured within 9–11 days, and the time between leukapheresis and infusion ranged between 9 and 45 days. The was one production failure.

CRS and neurotoxicity occurred in 83% and 55%, respectively, and were grade 3 or higher in 17% and 28%, respectively. One patient treated for active CNS leukemia died of neurotoxicity on day +8. Cytopeia occurred in all patients but one, and grade 4 neutropenia and thrombocytopenia occurred in 88% and 30% of patients, respectively.

Thirty-five patients were evaluable for response: 30 achieved CR: 20 had PCR MRD-negativity in 20, 5 had flow-cytometry MRD-negativity, and 5 had PCR-MRD positivity.

We were able to demonstrate CAR T-cell trafficking into sanctuary sites such as the CNS, anterior chamber of the eye and ovaries. Twenty-six patients proceeded to HSCT. Eleven patients had a CD19-postive relapse (8 post HSCT and 3 without)

and one had a CD19-negative relapse. All relapse events occurred within 2 years from cell therapy. Three patients died in remission from HSCT-related toxicity.

With a median follow-up of 3 years, the median event-free survival (EFS) is 17 months, and the median overall-survival (OS) is not reached. The 3 year EFS is 41% and OS is 56%. Patients with >5% blasts in the bone marrow prior to lymphodepletion had an inferior EFS. All patients with a PCR MRD positive result at day 28 had relapsed disease after CAR T-cells therapy. A prior HSCT did not significantly affect outcome, but a consolidative transplant after achieving remission improved long term results, as all patients who were not transplanted had relapsed but one, who was maintained on tyrosine-kinase inhibitor therapy.

Conclusions: We provide here long term data with a median follow-up of >3 years, showing the ability of CD28-based CAR T-cells to achieve good remission rates, and to lead to long term survival when followed by a consolidative HSCT. Toxicity is significant and higher than reported in real-world use of tisagenlecleucel. Disease burden prior to lymphodepletion and molecular MRD-negativity following CAR T-cells were the strongest predictors for outcome. All relapse events occurred within 2 years, highlighting the significance of the long term follow-up of these patients.

Clinical Trial Registry: ClinicalTrials.gov NCT02772198.

Disclosure: EJ reports participation on advisory board and speakers fee from Novartis. Other speakers have nothing to disclose.

O143

T-cell depleted haploidentical transplantation in children with hematological malignancies: a comparison of transplant outcomes between CD3+/CD19+ and TCRαβ+/CD19+ depletion platforms

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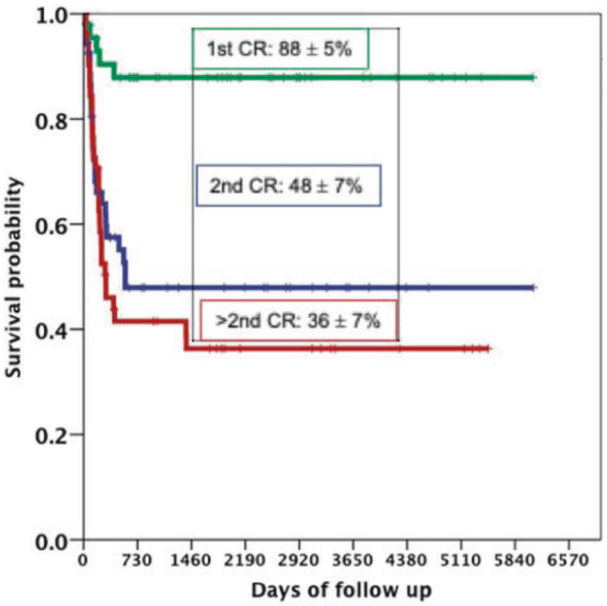
Background: T-cell depleted (TCD) haploidentical transplantation using "ex vivo" CD3+/CD19+ and TCRαβ+/CD19+ depletion techniques have been increasingly used in pediatric patients with hematological malignancies over the last two decades. Considering that there are no prospective studies comparing transplant outcomes of these TCD haploidentical transplant platforms, data from retrospective studies could be useful in guiding which TCD approach should be chosen. Herein we present a retrospective study aimed to analyze and compare transplant outcomes in pediatric patients with hematological malignancies receiving a TCD haploidentical transplant using either CD3+/CD19+ or TCRαβ+/CD19+ platforms.

Methods: A total of 159 children with hematological malignancies (ALL = 80) (AML = 79) that received a TCD haploidentical transplantation using either CD3+/CD19+($n = 79$) or TCRαβ+/CD19+ ($n = 80$) platforms between 2005 and 2020 were included in this study. Median age was 9 years in both groups with 65% males.There were no differences in patient, donor and transplant characteristics between groups except for more patients transplanted in first CR (38%) in TCRαβ+/CD19+ group than in CD3+/CD19+ group (30%) ($p = 0.03$), KIR B genotype more frequent in TCRαβ+/CD19+ group (91%) than in CD3+/CD19+ group (76%) ($p = 0.009$) and high number of NK+ cells with lower CD19+ cells infused in TCRαβ+/CD19+ group (35.32×10^6/kg and 0.06×10^6/kg) than in CD3+/CD19 group (24.6×10^6/kg and 0.25×10^6/kg), respectively ($p = 0.04$ and $p = 0.0001$). The conditioning used were similar in both groups, mainly based in TBF. Median follow-up was 11 years (range; 8–16 years) in CD3+/CD19+ group and 5 years (range; 2–9 years) in TCRαβ+/CD19+ group.

Results: Engraftment kinetics were similar in both groups (13 days for neutrophils and 10 days for platelets). Immune reconstitution kinetics were not different in both groups except higher CD8+ on day +60 in CD3+/CD19+ group. There was no difference in incidence of acute GvHD II–IV ($29 \pm 4\%$ vs $37 \pm 5\%$, respectively, $p =$ ns). A trend to lower incidence of chronic GvHD was observed in TCRαβ+/CD19+ group ($23 \pm 4\%$ vs $32 \pm 5\%$). TRM was $23 \pm 5\%$ in CD3+/CD19+ group vs $21 \pm 4\%$ in TCRαβ+/CD19+ group ($p =$ ns). Relapse incidence was also similar $32 \pm 5\%$ vs $34 \pm 6\%$, respectively ($p =$ ns). DFS and OS were not different ($45 \pm 5\%$ vs $45 \pm 6\%$ and $53 \pm 6\%$ vs $58 \pm 6\%$, respectively ($p =$ ns). As there were no differences on transplant outcomes between groups, we analyzed all patients together for risk factors associated with DFS. On multivariate analysis, early disease status at transplant (HR: 0.16; 95% CI (0.07–0.35) ($p = 0.0001$) (Fig. 1), presence of cGvHD (HR: 0.38; 95% CI (0.20–0.70) ($p = 0.002$) and high number (>300/μL) of NK cells on day+ 30 after transplant (HR: 0.38; 95% CI (0.34–0.90) ($p = 0.02$) were associated with better DFS because of lower relapse incidence.



Conclusions: Our data suggest that there are no advantages in transplant outcomes between TCD platforms. Risk factors for survival are clearly dependent on disease characteristic, early immune reconstitution and chronic GvHD rather TCD platform used.

Disclosure: Nothing to declare

O144

A randomised clinical phase 2 trial to compare treosulfan with busulfan based conditioning prior to allogeneic haematopoietic stem cell transplantation in children with non-malignant diseases

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Background: Myeloablative conditioning regimens are usually recommended for allogeneic haematopoietic stem cell transplantation (alloHSCT) in children suffering from a variety of non-malignant diseases (NMD). Here we present efficacy and safety results from a prospective, open label, randomised (1:1) phase 2 trial comparing treosulfan versus busulfan based preparative regimens in children with inborn errors of metabolism, primary immunodeficiencies, haemoglobinopathies, or bone marrow failure syndromes.

Methods: Children with NMD received either treosulfan (10 [17.6%], 12 [62.7%], or 14 [19.6%] g/m^2/day on days −6, −5 and −4, adapted to actual body surface area of ≤0.5, >0.5–1.0, or >1.0 m^2) or intravenous busulfan (4.8–3.2 mg/kg/day on days −7, −6, −5, and −4, according to the actual body weight). Thiotepa (2 × 5 mg/kg on day −2) was additionally administered in 84% of children. Other concomitant medications were administered according to local hospital practice. Matched sibling, family, unrelated or umbilical cord blood (MSD, MFD, MUD or UCB) donors were accepted for first alloHSCT. No formal confirmatory testing approach for efficacy was planned. Primary endpoint was "freedom from transplantation (treatment)-related mortality (TRM)", defined as death from any cause between days −7 and +100. Comparative exploratory analysis included engraftment, treatment-related mortality (TRM), overall survival (OS), acute and chronic graft-versus-host disease (GvHD), and safety.

Results: Results of all 101 treated patients (busulfan 50, treosulfan 51, median age: 5.5 years) with at least 12 (median 25) months follow-up are presented. Randomization imbalances were seen for subjects with PID (busulfan 28, treosulfan 23 patients) and Hb-pathies (busulfan 13, treosulfan 21 patients). "Freedom from TRM" until Day +100 was 90.0% (90% CI: 80.1%, 96.0%) after busulfan and 100.0% (90% CI: 94.3%, 100.0%) after treosulfan ($p = 0.0528$). TRM at 12 months was 12.0% (90% CI: 6.3%, 22.1%) and 3.9% (90% CI: 1.2%, 12.0%), respectively ($p = 0.1244$, HR of 0.29, 90% CI: 0.08, 1.09) showing a trend towards less TRM after treosulfan. OS at 12 months was 88.0% (90% CI: 77.9%, 93.7%) versus 96.1% (90% CI: 88.0%, 98.8%), also a trend favouring treosulfan. Cumulative incidence of primary and secondary graft failure was 4.0% (90% CI: 0.0%, 8.6%) after busulfan and 15.8% (90% CI: 7.4%, 24.3%) after treosulfan ($p = 0.0366$, HR of 5.48 (90% CI: 1.44, 20.91), favouring busulfan. Chronic GvHD-free survival at 12 months was 69.4% (90% CI: 57.1%, 78.8%) versus 89.3% (90% CI: 79.0%, 94.7%), $p = 0.0308$, HR of 0.32 (90% CI: 0.14, 0.76), a trend favouring treosulfan. Incidences of treatment emergent adverse events of at least CTCAE grade III were similar (busulfan: 82.0%, treosulfan: 80.4%).

Conclusions: In this comparative, explorative analysis, children transplanted for non-malignant disorders with treosulfan-based conditioning had improved survival, including cGvHD-free survival, but a higher risk of secondary graft failure when compared with busulfan conditioned children. Nevertheless, all subjects with graft failure after treosulfan were alive at last follow-up and maintained the opportunity to be rescued. This comparative trial provides relevant data to support clinical risk-benefit analysis of conditioning regimens for individual paediatric transplant candidates with non-malignant diseases.

Clinical Trial Registry: EudraCT number 2013-005508-33; Clinicaltrials.gov Identifier NCT02349906.

Disclosure: This study is part of the medac pediatric investigation plan for Treosulfan in HSCT. It was sponsored and fully financed by medac AG, Wedel, Germany. K-WS: speaker fees Jazz, research and travel grants medac, travel grant Neovii. RB: research and travel grants medac, travel grant Neovii. KK: speaker's bureau: JazzPharma, medac, Novartis. All other co-authors have no relevant disclosures to make.

O145

Radio-immunotherapy with ^{90}Yttrium labelled anti-CD66 monoclonal antibody in children with relapsed/refractory acute leukemia: a UK phase 1 study

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Background: Radioimmunotherapy (RIT) may allow targeted dose escalation in the amount of radiation delivered to the bone marrow (BM) of patients with leukemia undergoing allogeneic hematopoietic cell transplantation (allo-HCT), but toxicity and efficacy data in children are lacking.

Methods: This was a 3 + 3, dose escalation, phase I clinical study using a radiolabeled anti-CD66 monoclonal antibody (besilesomab – Telix Pharmaceuticals) conjugated with Yttrium-90 (^{90}Y, a pure beta emitter), as part of the conditioning regimen prior to allo-HCT in children with relapsed/refractory leukemia treated at Great Ormond Street Hospital and University College London Hospitals, UK.

All patients received an initial infusion of indium-111 (^{111}In)-labelled anti-CD66 antibody for bio-distribution and dosimetry determination. If the dosimetry was favorable, children went on to receive a therapeutic dose of ^{90}Y-labelled anti-CD66 antibody with a planned escalation dose from 35 to 45 MBq/kg. The dose was adjusted so as not to exceed the maximum allowed exposure to non-hematopoietic organs. The primary endpoint of the study was dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of ^{90}Y anti-CD66.

Results: Between 2016 and 2019, nine patients with relapsed leukemia were treated. Patient characteristics: median age 9 years (range 4–16); diagnoses: acute lymphoblastic leukemia (4) and acute myeloid leukemia (5); all 9 patients had relapsed after previous allo-HCT; 6/9 patients had detectable disease at the time of transplant. Patients received ^{90}Y anti-CD66 antibody on day −14, followed by fludarabine/melphalan (4) or treosulfan/fludarabine/thiotepa (5). Donors were HLA matched related (2), matched unrelated (5) or mismatched unrelated (2). Umbilical cord blood was used in 5/9 patients.

RIT was well tolerated, with no infusion-related toxicity and no DLT or MTD was found. One patient with pre-allo-HCT aspergillosis died of fungal infection. Three patients experienced grade 3 acute graft versus host disease (GvHD), followed by chronic GVHD in one. Excellent BM targeting was seen in all patients and 9/9

children developed neutropenia within 7 days from ^{90}Y anti-CD66. Organ-specific absorbed radiation doses are described in Table 1. All patients engrafted and, at last follow-up, 4/9 patients were alive. Minimal residual disease (MRD) negative remission was achieved in 8/9, 4/9 and 2/9 patients at 3, 6, 12 months post RIT, respectively. Seven patients subsequently relapsed and 1/9 patient remains in MRD negative remission 2 years post-RIT. A trend to longer duration of remission with higher doses of radiation to BM was observed.

Table 1. Correlation between infused activity of Y-90 and estimated absorbed organ radiation.

	Patients								
	1	2	3	4	5	6	7	8	9
Infused activity (MBq/kg)	35	35	35	45	45	47	30.9	40	20
BM dose (Gy)	15.7	12.3	32.1	29.8	28.7	25.2	43.9	47.6	32.2
Spleen dose (Gy)	6.4	3.4	8.6	20.3	12.6	20.7	10.6	11.1	13.7
Liver dose (Gy)	7.0	1.7	3.7	4.4	4.4	11.7	5.2	7.4	2.3
Kidney dose (Gy)	3.9	1.6	3.4	4.0	3.2	2.8	3.1	5.4	8.1

Conclusions: RIT had a good safety profile in children with relapsed/refractory leukemia and no DLT or MTD was found. A phase 2 study will assess RIT efficacy with a maximized BM dose.

Clinical Trial Registry: NCT04082286. https://clinicaltrials.gov/ct2/show/NCT04082286

Disclosure: Nothing to declare

O146

Population pharmacokinetic analysis of alemtuzumab in in children with non-malignant diseases undergoing allogeneic HSCT: towards model informed precision dosing

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Background: Alemtuzumab is a humanized monoclonal antibody targeting the CD52 glycoprotein expressed on most lymphocytes, thereby inducing complement- and antibody-mediated cytotoxicity. Although optimal dosing is still unknown, alemtuzumab is increasingly administered off-label in children with non-malignant diseases prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) to prevent graft rejection and graft-versus-host disease (GvHD) through profound lympho-depletion. Prior studies have shown a correlation between alemtuzumab levels at alloHSCT and both incidence of GvHD and immune reconstitution, supporting the need for therapeutic drug monitoring. In selected patient groups, pilot projects on individualized alemtuzumab dosing are currently based on extended drug measurements to estimate when alemtuzumab level falls below the lympholytic level of 0.1 mcg/ml, in order to schedule the graft infusion accordingly. However, this approach includes important logistic and clinical challenges, i.e., eventual postponement or freezing of the graft and the necessity of real-time drug measurements. Moreover, large in vivo interindividual variability of exposure despite uniform dosing regimens based on body weight is known and may significantly impact biological efficacy. Novel strategies such as model informed precision dosing which uses mathematical models combined with measured drug concentrations are urgently needed to overcome these challenges, thereby further improving clinical outcome.

Methods: Alemtuzumab concentration-time data was obtained in a multicenter combined prospective/retrospective pharmacokinetic (PK) and pharmacodynamic (PD) study conducted between 2010 and 2020 at two university children's hospitals (Zurich, Switzerland, and Leiden, The Netherlands) in children (<18 years old) with severe non-malignant diseases of the blood or immune system (BASEC-2018-00794/NL8185). Alemtuzumab was given at treating physician's discretion (mean cumulative dose 0.7 mg/kg, range 0.3–1.4) as part of a busulfan- or treosulfan-based conditioning regimen prior to alloHSCT. Alemtuzumab levels were measured in serum with an internally developed and validated ELISA assay. Data was used to develop a population pharmacokinetic model using non-linear mixed effects modelling (NONMEM). Monitoring of lymphocyte count and extended immune phenotyping was performed at baseline and on a regular basis after lymphatic engraftment.

Results: A total of 46 children aged 2.5 months to 16.5 years at alloHSCT were included and provided a total of 622 samples for extended population PK analysis. A 2-compartment PK model with parallel linear and non-linear elimination best described the concentration-time data. High inter-individual variability in clearance was identified (CV 97.6%). Total body weight (allometrically scaled) and lymphocyte count at baseline were significant predictors of alemtuzumab clearance. However, considerable unexplained variability in PK remained after inclusion of these covariates. Model derived cumulative alemtuzumab exposure ($AUC_{0-\infty}$) mean value was 1.23 mg/L*day (range 0.09–12.14). Lympholytic alemtuzumab levels (>0.1 µg/ml) were estimated to circulate on average over 38 days (range 12–95) in patients. On average, estimated alemtuzumab concentration at transplant date was above the drug lympholytic level (mean 1.84 mcg/ml, range 0.02–12.84).

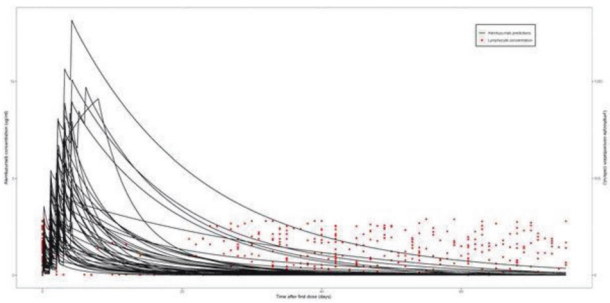

Figure 1. Alemtuzumab predictions (black lines) in correlation with lymphocyte reconstitution (red dots) over time.

Conclusions: Alemtuzumab is associated with substantial pharmacokinetic variability in pediatric alloHSCT recipients which can partly be explained by bodyweight and lymphocyte count at baseline. The population PK model can be used for informed precision dosing to optimize alemtuzumab therapy.

Clinical Trial Registry: Swiss registry: BASEC-2018-00794, https://ongoingprojects.swissethics.ch/runningProjects_list.php?q=%28ProjectTitle~contains~Alemtuzumab%29&orderby=dBASECID. Dutch registry: NL8185, https://www.trialregister.nl/trial/8185

Disclosure: Nothing to declare

Stem cell donor

O148

Matching beyond the HLA name: a new classification of HLA-allele mismatches based on peptide binding profile

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Background: HLA-matched unrelated donors (UD) are available for a limited proportion of patients in the need of allogeneic hematopoietic stem cell transplantation (HSCT). Historically, the use of HLA-mismatched UD has been associated with poor outcome. Criteria to classify HLA-allele mismatches are lacking. We developed a new classification to categorize HLA-allele mismatches according to their peptide binding profile and, therefore, functionality.

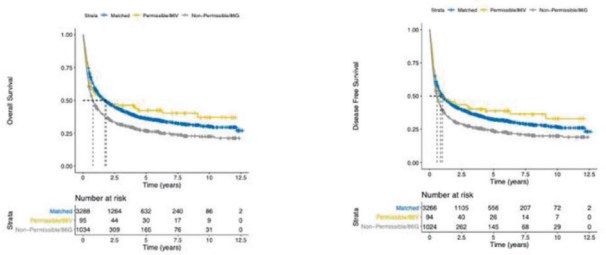
Methods: We hypothesized that HLA-mismatches at HLA-A, B, C and DRB1 loci presenting only amino acid differences at residues that do not determine peptide binding and, therefore, carrying identical structure in the antigen recognition site (distal membrane domains) are not immunogenic. Other postulated non-immunogenic directional HLA-mismatches involve DRB1 alleles differing only at amino acid residue 86 in which the patient carries Valine (V) and the donor carries Glycine (G). HSCT from UD carrying these permissible HLA-mismatches may result in significantly better outcomes than HSCT with other HLA-mismatches. We included in the study 4417 patients reported to the CIBMTR, aged 0-60, receiving their first 8/8 or 7/8 UD HSCT for hematological malignancies between 2003-2011. Transplant pairs were resolution typed for HLA-A, B, C, DRB1, DQB1 and DPB1 through the NMDP retrospective high-resolution typing program. HSCT were grouped in two discovery cohorts: putative permissible ($N = 95$) and non-permissible ($N = 1034$), and an HLA-matched cohort ($N = 3288$).

We compared clinical outcomes [OS, DFS, NRM, grade III–IV acute (a)GvHD] of patients receiving a permissible/86V or non-permissible/86G HSCT versus HLA-matched HSCT, and of patients receiving a permissible/86V versus a non-permissible/86G HSCT. For the multiple regression analyses, we adjusted for variables with an absolute standardize difference (ADS) ≥0.2 between groups in a Cox proportional hazards model.

Results: No significative differences in OS, DFS, NRM and aGvHD were observed between HLA-matched and permissible cohorts (p value = 0.4, 0.4, 0.7, 0.3, respectively). However, based on Cox model, the permissible cohort had a 11% lower risk of death [HR = 0.89 (0.68, 1.16)]. Conversely, when compared to the HLA-matched cohort, the non-permissible cohort had dismal OS, DFS, NRM, and higher aGvHD (p value < 0.0001). In line with our hypothesis, we observed a significant difference in OS between the HLA-matched and non-permissible cohorts (p value < 0.0001, Fig. 1). On a Cox model, the non-permissible cohort has a 38% higher risk of death [HR (95% CI) = 1.38 (1.26–1.5)]. As speculated, we also observed a significant difference in OS between permissible and non-permissible cohorts (p value = 0.004). In the non-permissible cohort—based on Cox model—the risk of death was 51% higher [HR = 1.51 (1.15–1.99)].

As expected, the lower OS in the non-permissible versus the HLA-matched and permissible cohorts is sustained by an increased incidence of aGvHD (27.8% vs 18%, p value < 0.0001; 27.8% vs 22.1%, p value < 0.05, respectively). Interestingly, no differences in relapse incidence have been observed between the three cohorts.

Figure 1
Kaplan Meier probability estimates of OS (panel A) and DFS (panel B), and Cox Proportional Hazards model (panel C).



C: Hazard ratio estimates (95% CI) from Cox Proportional Hazards model for each pairwise group comparison.

Model		HR	2.50%	97.50%
Matched vs Permissible/86V	**Group: Permissible/86V**	**0.89**	**0.68**	**1.16**
	Sex: Female	0.93	0.86	1.02
	Disease: ALL	1.01	0.89	1.13
	CML	0.65	0.57	0.75
	MDS	0.92	0.8	1.05
	Year of HSCT: 2003-2006	1.09	0.85	1.38
	2007 -2011	0.98	0.76	1.25
	GVHD prophylaxis: CsA based	1.01	0.91	1.12
	Other	1.24	0.7	2.19
	Race/Ethnicity: All others	0.99	0.83	1.17
	Unknown	1.14	0.9	1.44
Matched vs non-Permissible/86G	**Group = non-Permissible/86G**	**1.38**	**1.26**	**1.5**
	Race/Ethnicity = All others	0.91	0.8	1.04
	Unknown	1.04	0.94	1.14
Permissible vs non-Permissible/86G	**Group = non-Permissible/86G**	**1.51**	**1.15**	**1.99**
	Year of HSCT. 2003-2006	1.09	0.81	1.48
	2007 -2011	0.95	0.7	1.29
	Race/Ethnicity = All others	0.87	0.72	1.07
	Unknown	0.96	0.71	1.31

Conclusions: We developed a new classification of HLA-allele mismatches considering differences in peptide binding profiles that will likely change clinical practice for donor eligibility, prioritization and selection. Based on this dataset, at least 8.4% of 7/8 UDs was functionally equivalent to 8/8 UDs.

Disclosure: Nothing to declare

O149

Haplo or unrelated donor (UD) allogeneic hematopoietic stem cell transplantation (allo HSCT) for patients older than 55 years: a randomized multicenter phase III study

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Background: We performed a prospective, multicenter, open label, randomized controlled trial (NCT02623309) comparing allo HSCT after conducting a search for haploidentical (Haplo) or unrelated donors (UD) for patients with hematological malignancies aged older than 55 years, as soon as the absence of MRD was established.

Methods: In the case of an alternative donor from the assigned group not being identified in time, cross-over was allowed. The primary endpoint was the comparison of chronic graft-versus-host disease-free and relapse-free survival (cGRFS) from time of randomization. Conditioning was reduced intensity conditioning (RIC). Patients receiving Haplo-HSCT and UD-HSCT received GVHD prophylaxis based on HD-PTCy (100 mg/kg) and ATG (5 mg/kg), respectively. Additional GVHD prophylaxis consisted of cyclosporin A and MMF for all patients.

Results: The study enrolled 108 patients, of which 106 were analyzed (due to 2 patients withdrawing consent). Median follow-up was 27 (range, 14–34) months and median age was 65 (range, 55–70) years. Disease was myeloid malignancy in 84 (79%) patients. Disease risk index (DRI) was low, intermediate, and high in 5 (5%), 59 (55%), and 42 (40%), respectively. Fifty-five and 51 patients were assigned to Haplo and UD groups, respectively. Fifteen (27%) patients in the Haplo group could not proceed to allo-HSCT because of progression ($n = 9$), patient contraindication ($n = 5$), and absence of donor ($n = 1$); and 14 (27%) patients in the UD group could not proceed because of progression ($n = 8$), and patient contraindication ($n = 6$).

In the intent-to-treat analysis, from date of randomization, 2-year GRFS, PFS and OS did not differ between the two donor groups (Haplo vs UD): 29% vs 37%, $p = 0.22$; 45% vs 49%, $p = 0.56$; 50% vs 59%, $p = 0.47$, respectively. The original search revealed 31 (56%) and 26 (51%) transplants from the initial Haplo and UD groups, respectively, that satisfied the desired transplant criteria within 63 (21–153) and 89 [MM1] (37–288) days ($p = NS$), respectively. In addition, 9 and 11 patients were transplanted from a UD or a Haplo in Haplo and UD search groups, respectively, resulting in a total 40 Haplo and 37 UD transplants (73% in both groups).

With a median follow-up of 24 months after transplant, 2-year GRFS, PFS and OS did not differ between Haplo and UD transplants: 40% vs 34%, $p = 0.66$; 48% vs 45%, $p = 0.78$; 55% vs 54%, $p = 0.90$, respectively. No statistical differences were evident for the outcomes of grade 2–4 acute GVHD, severe cGVHD, NRM, and relapse incidence.

Conclusions: This prospective trial using an alternative donor search-initiation time-point establishes for the first time that when a MRD is not available, a HaploD search results in the same donor identification and the same outcomes as a UD search in older patients with hematological malignancies. In addition, although 77% of the patients can achieve a transplant using either strategy, only half of the patients will receive a transplant from the original prospective donor type. As outcomes are similar after Haplo and UD transplants, performing a search for both types of donor may avoid potential delays with secondary searches..

Clinical Trial Registry: NCT02623309.

Disclosure: None

Stem cell mobilization, collection and engineering

O150

UM171 expansion of small cord bloods provides access to safe transplantation for donorless patients with excellent longterm follow-up

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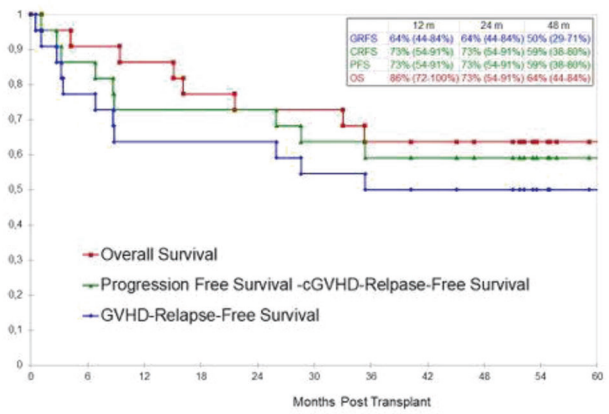
Background: Approximately 10–15% of patients do not have an optimal donor for allogeneic stem cell transplantation for various reasons: absence of HLA identical donor, high titer donor specific HLA antibodies, older aged donor, donor with prohibitive medical issues, absence of adequately sized and HLA matched cord blood (CB) and absence of haploidentical donor. CB transplants have fallen into disfavor because of high transplant related mortality (TRM) and prolonged hospitalizations largely due to small CB size forcing selection of larger, poorly HLA matched units. UM171-based expansion allows selection of smaller, better HLA matched CBs all the while maintaining CB's advantages of low risk of chronic (c) GVHD and relapse.

Methods: In 2016, we initiated a phase I–II clinical trial of UM171 expanded CB for patients who lacked an optimal HLA identical donor. The goal was to select smaller, better HLA matched CBs to improve TRM. CB was thawed, $CD34^+$ selected and placed into culture with UM171 and 4 cytokines for 7 days, and then infused to the patient along with the T cell containing CD34- fraction. Patients underwent a myeloablative regimen.

Results: Twenty-two patients with a median age of 45 years received a single UM171 CB transplant. The underlying diseases were at high risk of relapse: 5 (23%) had failed a prior allogeneic transplant, 3 (14%) had acute leukemia not in remission, and 2 (9%) had aggressive lymphoma not in CR/PR. Eight patients (36%) had a comorbidity index ≥3. Median CD34 infused cell dose was 2.88 x10^6/kg. Median time to 100 and 500 neutrophils was 9 and 18 days, respectively. Patients appeared to derive clinical benefit from early appearance of 100 neutrophils with early resolution of febrile neutropenia. Duration of hospitalization was reduced by 2 weeks compared to same institution conventional CBs transplants. More than 80% of patients received a 6/8 HLA matched CB as opposed to >80% of our conventional CB transplants who got a 5/8 matched CB. The cumulative incidences of acute grade III-IV GVHD and moderate-severe cGVHD were 64% and 0%, respectively. Median time to discontinuation of immunosuppression was 6 months and immune reconstitution was prompt with median CD4 count at 3 months of 251/mcL. With a median follow-up beyond 4 years, cumulative incidence of TRM is 5%. Overall, progression-free, GVHD-relapse-free, cGVHD-relapse free survival at 4 years are 64%, 59%, 50%, and 59%, respectively.



Conclusions: We conclude that we were able to achieve our goal of transplanting smaller, better HLA matched CBs in a safe manner with a low TRM of 5%. For the 10–15% of patients who lack an optimal donor, UM171 expanded CB offers an excellent alternative with results comparable to matched donor transplantation all the while maintaining CB's advantages of low risk of cGVHD and relapse. We are currently studying the antileukemia effect of UM171 CB in very high risk acute leukemias.

Clinical Trial Registry: https://clinicaltrials.gov/ct2/show/NCT02668315

Disclosure: SC: royalties from sales of UM171, consulting fees from ExCellThera (company which holds license for UM171). JR: royalties from sales of UM171. GS: major stockholder of ExCellThera and CEO of ExCellThera (company which holds license for UM171).

O151

Graft engineering: how long can you wait, how low can you go, and pandemic readiness

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Background: Little information is available on how long grafts can be handled until they are infused to the patient, or on how many $CD34^+$ cells must be harvested from a donor to attain a sufficient allograft resulting in profound engraftment. Graft engineering usually requires higher cell numbers, as the engineering process results in partial loss of cells. Finally, the option to cryopreserve an engineered graft remains essential during the time of an ongoing global pandemic (1), and more information is needed on whether the freezing procedure of an engineered allograft compromises either, cell numbers, cell composition or engraftment.

Methods: To address the questions "how long you can wait" until infusion, "how low can you go" with $CD34^+$ cell numbers, and whether cryopreservation puts patients at risk for primary graft failure, all adults who received an αβT cell depleted allo-SCT product between 2013 and 2021 ($n = 212$ fresh grafts, 22 frozen grafts) at the University Medical Center Utrecht (UMCU) were included in this retrospective analysis. Written informed consent was obtained in accordance with the JACIE guidelines, and clinical data was reported to and extracted from the EBMT registry. αβT cell reduction was performed as previously reported (deWitte Blood Adv. 2021:240–9).

Results: The median time to neutrophil recovery was 14 days in the fresh cohort (range 4–26), and 15 days in the frozen cohort (range 10–29) ($p = 0.018$). For platelets, the median time to recovery was also 14 days in the fresh cohort (range 9–440) and 15 days in the frozen cohort (range 11–110) ($p = 0.2$). In the fresh cohort, three primary graft failures were observed (1.4%), versus none in the cryopreservation cohort.

To assess the impact of time from apheresis to either infusion ('fresh cohort'), or time to cryopreservation ('frozen cohort') on primary engraftment, we first analyzed the median time to infusion for the fresh products (46 h, range 25–68). We found no impact of time from apheresis to infusion on neutrophil or platelet engraftment for fresh products, implying that out of spec (OOS) procedures can be omitted up to 68 h from apheresis to infusion. As expected, the median time from apheresis to cryopreservation of the engineered product ('frozen cohort') was shorter (31 h, range 24–54, $p = 0.054$). All frozen products were infused, and again no impact of time from apheresis to cryopreservation on neutrophil or platelet engraftment was observed.

For fresh and for frozen allografts, infused cell numbers did not correlate with neutrophil engraftment (fresh $\rho = 0.049$; $p = 0.58$ and frozen $\rho = -0.28$; $p = 0.23$). A total of 14% of the infused grafts had less than 4×10^6/kg $CD34^+$cells. However, no differences in primary engraftment data were observed as compared to the subgroup that met the EBMT recommendations (3) of more than 4×10^6/kg $CD34^+$cells.

Conclusions: We show for the first time that infusing stem cell products until 68 h after apheresis is feasible, and numbers as low as 1.7×10^6 $CD34^+$cells/kg in a T cell depleted transplantation platform did not impact engraftment. Cryopreservation did not harm primary engraftment, demonstrating that a global pandemic does not necessarily hamper the transplantation procedure with engineered grafts.

Disclosure: 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 and MdW received research, advisor and clinical study support from Miltenyi Biotech. JK received further research support from Novartis and Gadeta.

O152

PBSC allogeneic graft cryopreservation during COVID-19 pandemic: analysis of the SFGM-TC center experience

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Background: Besides risks and logistical constraints, PBSC allogeneic grafts are, in the vast majority, infused fresh, in the following hours from apheresis, without cryopreservation. COVID-19 pandemic disturbed regular practices because of potential shipment issues for unrelated donor grafts, the risk of SARS-Cov2 transmission from the donor, and the potential risk of mobilization with rh-G-CSF in a SARS-Cov2 infected donor.

As of march 2020, SFGM-TC endorsed EBMT guidelines and recommended to cryopreserve allogeneic grafts before beginning of the conditioning regimen. With this unique experience, we intended to analyze this change of practices and evaluate its impact on PBSC graft quality and clinical outcome, as available data are scarce.

Methods: We collected PBSC graft quality/control (QC) performed before and after cryopreservation, potential adverse events, as well as ANC recovery.

Results: From March 2020 to August 2021, 1146 allo-HSCT were performed in 24 centers. A total of 438 (38%) allografts were related (RD), and 708 (62%) were unrelated (UD). Median time from apheresis to cryopreservation was 20 h for RD, and 28h for UD ($p < 0.01$). CD34+ cell dose pre-cryopreservation and after thawing was not different between RD and UD. Viability of CD34+ at reception was 100% for RD and 99% for UD ($p = 0.054$). CD34+ recovery was 78% (33–107%) for RD and 76% (14–108%) for UD ($p = 0.007$). TNC cell dose pre-cryopreservation and after thawing was not different between RD and UD. Viability of TNC at reception was inferior for UD compared to RD, with 98% and 99% ($p < 0.01$) respectively. No difference was observed between the two groups for CFU.

To better understand the difference observed between RD and UD groups, we sought for a potential impact of graft transit time between donor and transplant centers. We divided transit time in three groups (<24, 24–48, and >48 h) and analyzed graft QC between these three groups. We observed a significant reduction in terms of CD34+ cell dose (5.9, 5.9 and 5.3, respectively, $p = 0.01$), CD34+ viability at infusion (93%, 91% and 90%, respectively, $p = 0.02$) and CD34+ recovery (79%, 75% and 74%, respectively, $p = 0.04$). This deleterious impact of the cryopreservation process according to transit time on CD34+ recovery was confirmed after adjustment with center effect (75%, 73% and 70%, respectively, $p = 0.02$). As cryopreservation process can be incriminated at different steps, we ruled out the impact of washing step (no difference between the two groups), but observed a negative impact of using >2 cryopreservation bags in both RD and UD groups ($p < 0.05$). Finally, we recorded only 2.8% of total allogeneic PBSC grafts that were cryopreserved and not infused, which compares favorably with recruited/not infused UCB graft during the same period in France.

Conclusions: This is the first multicentric study with complete QC pre and post-cryopreservation, describing the impact of transit time and cryopreservation on allogeneic PBSC grafts. Our data provide evidence for deleterious impact of cryopreservation for UD graft, especially with transit time >48 h. Clinical correlatives (ANC and platelet recovery, chimerism, acute GvHD incidence and 1-year OS/NRM) will be compared with fresh PBSC allografts from the same period and presented at the meeting.

Disclosure: Nothing to declare

O153

Does graft cryopreservation affect the outcomes of allogeneic haematopoietic cell transplants? A UK multicentre case control study during COVID19 pandemic

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Background: Whether graft cryopreservation has any effect on patient outcome in allogeneic haematopoietic cell transplantation (HCT) remains unclear. Further evidence in this field is critical because of the continued cryopreservation of HSC grafts during the COVID-19 pandemic[1–6].

Methods: Adult and paediatric patients receiving an unrelated or sibling donor allogeneic cryopreserved HCT (excluding cord blood) in the UK from 1 March 2020 to 31 May 2020 were included. Patients receiving fresh HSC grafts in the same period were controls.

Data were collected from individual transplant centres by British Society of Blood and Marrow Transplantation (BSBMTCT) registry.

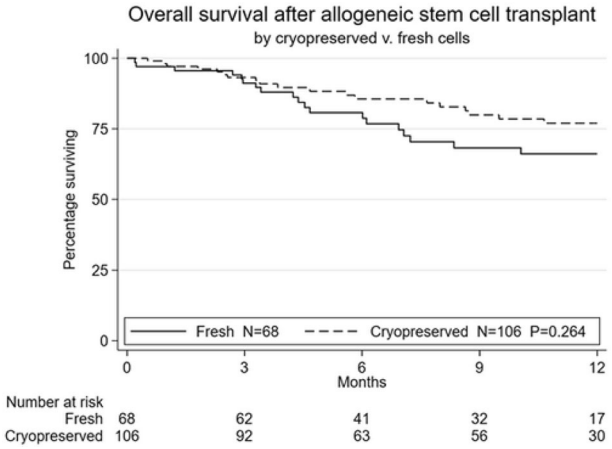
Engraftment, graft failure, GvHD, relapse, PFS and OS were analysed.

Results: During the study, 106 patients received cryopreserved HSC grafts, of which 13 (12%) were BM harvests (11 paediatric, 2 adult) and 68 patients received fresh HSC grafts, of which 11 (16%) were BM harvests (all paediatric). The median follow-up time for both groups was 12 months. There was no statistically significant difference in neutrophil or platelet engraftment between fresh or cryopreserved grafts. The median time to neutrophil engraftment was 15 days in both (range, 8–45; $p = 0.84$). Platelet engraftment was 18 days (range, 3–129) and 19 days (range, 9–267) for patients receiving fresh and cryopreserved grafts, respectively ($p = 0.37$). The frequency of graft failure was also similar, with two patients having primary and one having secondary graft failure in both groups.

Acute GvHD occurred in 22% (95% CI: 14–34%) of HCT with fresh and 19% (95% CI: 12–28%) with cryopreserved grafts ($p = 0.70$). Disease relapse occurred in 12 patients receiving fresh grafts and 11 patients with cryopreserved cells. PFS at 12 months post-HCT was 66% (95% CI: 52–77%) and 75% (95% CI: 64–83%) with fresh and cryopreserved grafts, respectively ($p = 0.35$).

There was no statistically significant difference in OS at 12 months ($p = 0.26$); 66% (95% CI: 52–77%) in patients who received fresh versus 77% (95% CI: 66–85%) in patients with cryopreserved grafts (Fig. 1).

Figure 1. Twelve-month OS of patients receiving fresh versus cryopreserved grafts.



Conclusions: Our retrospective, multicentre UK study of allogeneic HCT patients did not find a statistically significant difference in engraftment, graft failure, aGVHD, PFS or OS for patients receiving fresh versus cryopreserved HSC grafts. A larger follow-up study is underway.

Clinical Trial Registry: Not applicable.

Disclosure: None of the authors have any conflict of interest to declare.

Stem cell source

O154

Comparison of mobilized peripheral blood stem cells versus unmanipulated bone marrow haploidentical transplantation using post-transplant cyclophosphamide with or without ATG

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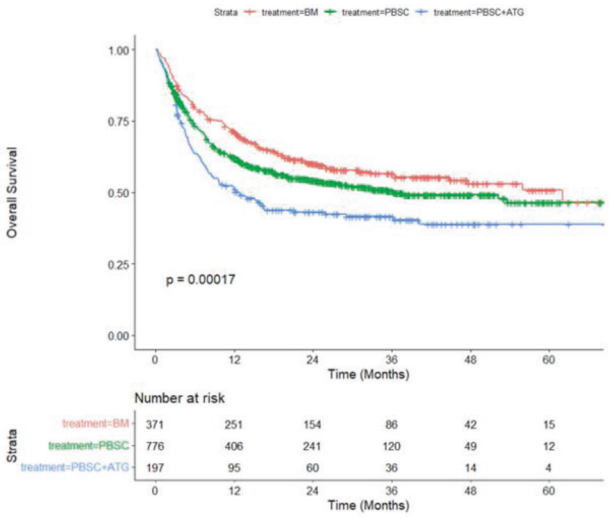
Background: Using peripheral blood mobilized stem cells (PB) or bone marrow (BM) graft after haplo-transplant is debated. The value of adding ATG to high dose post-transplant cyclophosphamide (PT-Cy) is unknown.

Methods: This study is a retrospective registry-based analysis of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). 1344 adult patients received an unmanipulated haplo-identical transplant in 37 centers from May 2012 to December 2019. Outcome were overall survival (OS), GVH and Relapse free survival (GRFS), cumulative incidence of Relapse and cumulative incidence of severe (grade 3–4) acute GVH or extensive chronic GVH. To account for the observational design, causal effect of treatment was estimated within each pairwise comparison using propensity score weighting with overlap weights

Results: A total of 371 patients (27.6%) received BM, 776 (57.7%) received PB without ATG and 197 (14.7%) received PB +ATG. Median age at transplant was 56 years (40.7–63.7). Patients were treated for an acute leukemia (56%) or another myeloid (24%) or lymphoid (20%) hemopathy. GVHD prophylaxis consisted in PT-Cy and a combination of anticalcineurin and mycophenolate in all patients. BM patients were younger (median age 51 years old) than in PB (58 years old) and in PB-ATG groups (56 years old) ($p < 0.0001$). PB+ATG patients had a high disease risk index (DRI) score in 29.9% vs 19.1% (BM) and 19.7% (PB), and very high in 6.7% vs 1.5% (BM) and 2.2% (PB) ($p < 0.0001$). As expected, median CD34+/kg in the graft were higher for PB (6.3×10^6) and PB+ATG (6×10^6) than BM (2.64×10^6) ($p < 0.0001$). MAC was more frequently used in the BM group (41.8%) than PB (24.7%) and PB+ATG (35.5%) ($p < 0.0001$). Median follow-up was 28.4 months. Overall survival at 2 years was 60%, 54% and 43% ($p = 0.0001$); 2-year cumulative incidence of acute GVH grade 3–4 or extGVHc was 17%, 24% and 22% ($p = 0.028$); 2-year cumulative incidence of relapse was: 31%, 26% and 38% ($p = 0.017$), resulting in a 2-year GRFS of 46%, 42% and 33% ($p = 0.0014$) for BM, PB and PB+ATG, respectively. Infection-related deaths were significantly higher in PB+ATG and PB than in BM (22.3% vs 16.5% vs 8.9% ($p < 0.0001$) respectively. In weighted analysis, OS was significantly better for BM vs PB (HR 0.75; IC [0.56–0.99]). There was also a non-significant better GRFS in BM vs PB group (HR 0.8; IC [0.62–1.02]), and a non-significant higher risk of relapse in BM vs PB group (HR 1.16; IC [0.81–1.67]). OS (HR 0.67; IC [0.46–0.96]) and GRFS (HR 0.67; IC [0.49–0.93]) were statistically better in BM vs PB +ATG group, while the risk of relapse was similar (HR 0.98; IC [0.62–1.55]). Interestingly, outcomes were similar in PB and PB +ATG groups (HR between 0.88 and 1.04 for OS, severe GVHD, relapse, GRFS).



Conclusions: In this large cohort and using propensity score weighted analysis, patients receiving haploidentical marrow grafts had improved survival compared to PB and PB+ATG grafts. In particular, the addition of ATG did not appear to provide any benefit. Prospective studies are needed to establish the respective positions of BM and PB after haploidentical-transplantation.

Disclosure: Nothing to declare

O155

Cord blood significantly outperforms other cell sources in clearing residual host hematologic and lymphoid tissues

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Background: Cord blood (CB) as a donor cell source in hematopoietic stem cell transplant (HCT) has declined in recent years, mirrored by the rise in haplo-identical donor transplant. However, it has retained specific utility in high risk myeloid malignancy and in those non-malignant conditions where time to transplant is critical and where full donor engraftment is advantageous. We studied whole blood and lineage-specific chimerism patterns in children undergoing allogeneic HCT with CB and other cell sources.

Methods: We retrospectively analysed serial donor chimerism of patients aged 0–16 years, treated with allogeneic HCT using CB, bone marrow (BM) or mobilised peripheral blood stem cells (PBSC) at Royal Manchester Children's Hospital for malignant and non-malignant indications between 2010 and 2020. Patients were categorised into CB and non-CB groups, and whole blood and lineage-specific chimerism was recorded and compared. Patients who had primary graft failure and who had relapsed leukaemia post-HCT were excluded from the study. GraphPad Prism 9.3 was used for all statistical analysis

Results: Analysis was restricted to the 445 long-term surviving patients. CB, BM and PBSC were used as stem cell source in 125, 227 and 93 patients, respectively. Four percent patients (5/125) in the cord group had primary graft failure (PGF), compared to 0.9% (3/320) in the non-cord groups. Twenty-four patients experienced late graft failure (LGF) with late autologous reconstitution. The proportion of patients with late graft failure was significantly lower in cord group (5 vs 19). 23 patients were re-transplanted successfully of both PGF and LGF. Serial engraftment patterns were studied in both groups. At engraftment, there was no statistical difference in the mean whole blood donor chimerism between the CB and non-CB groups (98.1% v

98.9%; $p = 0.6$). However, similar comparison at 6 and 12 months post-HCT showed cords had a higher percentage of donor chimerism with mean 98.4% vs 93.9% ($p = 0.03$) and 98.9% vs 91.1% ($p < 0.0001$) respectively.

Lineage specific chimerism was analysed at 6 and 12 months. An unpaired two tailed *t*-test showed that there was significant statistical difference in myeloid (CD15+) chimerism data between the CB and non-CB groups (mean 100% vs 85.3% at 6mths, 99% vs 86.4% at 12 months; $p = 0.003$). The CB group also had higher T cell chimerism (Mean CD3: 93.4% vs 69.8% at 6 months; $p \leq 0.0001$).

"Last recorded" chimerism values >2 years post HCT were analysed, mean whole blood chimerism was strikingly greater in the CB cohort to the non-CB cohort (mean 99.3% vs 75.6%, $p \leq 0.0001$).

Conclusions: Complete donor chimerism is much higher in CB transplant recipients than those who have received a BM or PBSC allograft. This represents an enhanced "graft versus marrow" effect mediated by CB transplants. This is of utility in difficult-to-cure leukemia and in this non-malignant conditions where full donor chimerism translates to a clinical benefit, such as in metabolic conditions, including MPSI, since it is associated with superior donor-derived enzyme delivery. CB has higher rates of primary graft failure and procedure-related morbidity compared to these other cell sources but retains significant benefit compared to other cell sources.

Disclosure: Nothing to declare