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19 - Acute Leukaemia

O009

GILTERITINIB AND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IMPROVE OUTCOME IN RELAPSED/ REFRACTORY *FLT3*-MUTATED ACUTE MYELOID LEUKEMIA PATIENTS: REAL-WORLD DATA FROM A MULTICENTER ANALYSIS

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Background: Gilteritinib for *FLT3* mutated (*FLT3*^{mut}) relapsed or refractory AML (r/r AML) patients is a promising on-target therapy improving survival. However, robust real-world data are lacking and details on the use of gilteritinib in the context of allogeneic hematopoietic cell transplantation (alloHCT) have yet to be determined.

Methods: R/R AML patients aged >18 years harboring *FLT3* mutations (*FLT3*^{mut}) and receiving salvage treatment with gilteritinib were included in this analysis. All patients provided written informed consent on data analyses. The study was approved by the respective ethics committees and conducted in accordance to the Declaration of Helsinki. Statistical analysis was performed using R (Version 4.1.3) and standard statistical methods (Kruskal–Wallis test, Chi-square test, log rank test, Cox regression). CR and survival rates (overall survival, OS; relapse and progression-free survival, RPFS) were evaluated.

Results: All 156 patients with relapsed ($n = 87$) or refractory ($n = 69$) *FLT3*^{mut} AML salvaged with gilteritinib were analyzed. Median age was 58.5 years (range 21–84). According to the ELN2017 classification, 19.9% harbored favorable-, 43.6% intermediate- and 36.5% adverse-risk genetic aberrations at initial diagnosis. Eighty-two percent of patients had a history of intensive induction chemotherapy and 66.7% had received alloHCT before relapse or refractory disease occurred, which was followed by gilteritinib treatment. Forty-seven percent of patients received at least one FLT3 inhibitor before gilteritinib.

The majority of r/r *FLT3*^{mut} AML patients ($n = 116$; 74.4%) received gilteritinib as single treatment. The remaining 40 patients (25.6%) additionally underwent first or second alloHCT. Forty-three percent ($n = 17$) of transplanted patients further received gilteritinib as maintenance after alloHCT. Considering best response to gilteritinib, 43.6% showed CR/CRi, 23.7% partial response and 25% progress or refractory disease. With a median follow-up of 6.4 months (range 0.7–61.2), median OS and RPFS for the whole cohort was 6.2 months (range 0.6–60.2) and 4.8 months (range 0.5–60.2).

Focusing on the different therapeutic sequences, patients receiving gilteritinib only had a 2-year OS of 30% (95% CI: 21–43%). Survival rates were better for patients who underwent alloHCT after gilteritinib treatment with a 2-year OS probability of 75% (95% CI: 59–97%) from alloHCT. Patients who received gilteritinib as maintenance therapy after alloHCT had a 2-year OS rate of 90% (95% CI: 73–100%). Accordingly, 2-year RPFS probability was lowest in the gilteritinib only cohort (24%, 95% CI: 15–37%), with better rates when gilteritinib was followed by alloHCT (44%, 95% CI: 18–100%) or if gilteritinib was applied as maintenance therapy after alloHCT (74%, 95% CI: 52–100%), respectively. Significantly more patients achieved CR/CRi when receiving gilteritinib maintenance after transplantation ($p < 0.0001$).

Conclusions: Dismal prognosis of *FLT3*^{mut} r/r AML could significantly be mitigated by alloHCT as a combinational strategy in this retrospective analysis. Survival was best for patients who also received gilteritinib as maintenance after alloHCT. Therefore, we suggest that gilteritinib either as a bridging concept to alloHCT or continued after transplantation could potentially improve outcome for *FLT3*^{mut} r/r AML patients. However, results from prospective clinical trials are needed to clarify the prognostic role of gilteritinib as maintenance after alloHCT.

Disclosure: Nicolaus Kröger: Advisory Board and honorarium - Astellas

19 - Acute Leukaemia

O010

DETECTION OF PRE-TRANSPLANT LEUKEMIC STEM CELLS IS MORE PREDICTIVE FOR EARLY RELAPSES THAN FLOW MRD IN AML PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION IN CR

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Background: Several studies have shown that the leukemic stem cells (LSCs: CD34$^+$CD38$^-$CD45RA$^+$/Combi-6$^+$) plays a crucial role in the development of relapses in AML patients (pts). LSCs are less sensitive to conventional therapy; moreover their phenotypical characteristics may allow immune evasion promoting relapses after allo-SCT. Recent ELN guidelines recommend to include the LSCs into MRD assessment, but this approach has not yet been using routinely. In this study we investigated the impact of pre-transplant LSCs assessment on post-transplant outcomes in AML patients and correlated it with conventional flow-MRD.

Methods: 52 pts (male, $n = 26$; median, 60.5 years, 20–74) with AML in CR and available pre-transplant MRD data (multicolored flow cytometry, "different from normal" approach, according to ELN guidelines), who received allografts (matched, $n = 45$; mismatched, $n = 7$) during 2019–2022 years at the Department of Stem Cell Transplantation University Medical Centre Hamburg were included. The MRD assessment in all patients included pre-transplant LSCs detection (Zeijlemaker et al. 2019). Both, MRD method and LSCs detection were investigated solely and combined for their prognostic impact.

Results: Majority of pts had de novo AML (73%), normal cytogenetics (65%), intermediate ELN risk (67%), received matched grafts (related, $n = 14$, 27%; unrelated, $n = 31$, 60%) and MAC regimen ($n = 33$, 63%). ATG was used as GvHD prophylaxis in 43 pts (83%). Fifteen pts (29%) received venetoclax-based therapy immediately pre-SCT. There were 22 MRD$^-$ (42%) and 30 MRD$^+$ (58%) pts.

LSCs were detected in 29 (56%) pts (21 (70%) MRD$^+$ and eight (36%) MRD$^-$, $p = 0.016$). The median proportion of LSCs were 0.01% (0.005–0.37%) of WBC. There was no correlation between LSCs proportion and MRD status. We observed higher rate of LSCs negativity among pts who received venetoclax-based therapy (24/37, 65% vs 5/15, 33%, $p = 0.039$). Pts with iCR tended to have higher levels of LSCs comparing to those in CR (7/11, 64% vs 5/18, 28%, $p = 0.065$) as well as pts with abnormal cytogenetics at diagnosis (7/11, 64% vs 5/17, 29%, $p = 0.081$).

The 1-year OS and LFS were significantly higher in LSCs negative patients: 100% vs 75% (55–88%), $p = 0.021$; and 92% (64–99%) vs 41% (21–64%), $p = 0.001$, due to a higher relapse rate at 1-year: 42% (22–65%) vs 8% (1–36%), $p = 0.02$. The median time to relapse was 165 days (40–395). The difference in NRM was not significant. The area under the ROC curve for relapses was 0.75 (0.62–0.89, $p = 0.005$).

During the median follow up of 9 months (2–22), six of 21 (29%) MRD$^+$LSCs$^+$ pts developed relapse and four (19%) an NRM event; all MRD$^+$/LSCs$^-$ pts ($n = 9$) survived without relapses; three of eight (38%) MRD$^-$LSCs$^+$ pts developed relapses; one of 14 (7%) MRD$^-$LSCs$^+$ developed relapse.

Conclusions: Pre-transplant detection of LSCs has a stronger predictive value for early post-transplant relapses in AML patients than conventional flow MRD.

Clinical Trial Registry: not applicable

Disclosure: The authors disclose no potential conflict of interest.

19 - Acute Leukaemia

O011

COMPLEX KARYOTYPE NOT OTHER CYTOGENETIC ABNORMALITIES AFFECTS POST-TRANSPLANT SURVIVAL OF PATIENTS WITH NPM1-MUTATED ACUTE MYELOID LEUKEMIA: A STUDY FROM THE EBMT ACUTE LEUKEMIA WORKING PARTY

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Background: Acute myeloid leukemia (AML) with nucleophosmin-1 (NPM1) gene mutation, is a distinct entity in the 2017-European LeukemiaNet (ELN) guidelines, with a favorable prognosis in patients with normal cytogenetics (CG) and absence/low allelic ratio of FLT3 ITD and an intermediate prognosis in those with high allelic ratio of FLT3 ITD. In the 2022 ELN classification, patients with NPM1-mutated AML were reclassified to the adverse-risk category in the presence of high-risk CG regardless of the FLT3 ITD mutation status. Nonetheless, the impact of various CG aberrations on post-transplant outcomes remains to be unraveled.

Methods: We retrospectively analyzed adult patients(≥18 years) with NPM1-mutated de-novo AML, with intermediate/adverse risk CG and known FLT3 ITD mutation status, who underwent their first allogeneic-hematopoietic-stem-cell-transplantation (alloHCT) in first complete remission (CR1) from 2005-2021, from a matched sibling donor (MSD), unrelated donor (UD), or T-cell-replete haploidentical donor (Haplo), whose data were reported to the EBMT registry. We analyzed outcomes of patients according to CG. Multivariate analysis adjusting for differences between the groups was performed using a Cox proportional-hazards regression model.

Results: 3275 patients were identified, 2782 had normal karyotype, 493 had chromosomal aberrations including 160 with adverse risk CG, of which 72 had complex karyotype(CK), 66 had monosomal karyotype(MK), 38 had other abnormalities. Overall, 898 (27.4%) patients had wild-type FLT3. In univariate analysis, post-transplant outcomes were only affected by FLT3 ITD mutation status and CK, while other adverse risk CGs including MK, showed so significant impact on outcomes. In multivariate analysis, CK was associated with lower overall survival (OS)(hazard ratio[HR]1.7; $p = 0.01$), while FLT3 ITD mutation was predictive of higher relapse(HR 1.39; $p = 0.0005$), worse leukemia free survival (LFS) (HR 1.26; $p = 0.002$) and OS(HR 1.18; $p = 0.043$). For the subgroup with chromosomal aberrations, the 2-year LFS and OS were 61.4% and 68.1%, respectively. In univariate analysis, relapse risk (RR), LFS, OS, and GVHD-free, and relapse-free survival (GRFS) were only affected by CK(RR 44% versus 24.3%, $p = 0.003$; LFS 44.9% versus 64.1%, $p = 0.005$; OS 51% versus 71%; $p = 0.001$; and GRFS 34.6% versus 50.5%, $p = 0.018$) whereas FLT3 ITD mutation status, CG risk category, or any of the CG abnormality subgroups had no significant effects. In multivariate analysis, CK was associated with higher RR(HR 1.7; $p = 0.025$), worse LFS (HR 1.58; $p = 0.025$) and OS (HR 1.85; $p = 0.004$), with no interaction with FLT3 mutation status, monosomal karyotype, or any other CG abnormality.

Conclusions: This data assist in risk-stratification of patients allografted for NPM1-mutated AML in the setting of CG aberrations. With the recent ELN reclassification of AML with NPM1 mutation with high-risk CG as adverse-risk, this data indicates that in the transplant setting, CK not other adverse-risk CG is a predictor of worse outcomes. Nevertheless, even for this subgroup, a significant proportion of patients can achieve long-term post-transplant survival.

Clinical Trial Registry: NA

Disclosure: The authors have no conflict of interest to declare

19 - Acute Leukaemia

O012

IMPACT OF ALLO-HCT IN FIRST COMPLETE REMISSION (CR1) IN ADDITION TO FLT3 INHIBITION WITH QUIZARTINIB IN AML WITH *FLT3*-ITD: RESULTS FROM THE QUANTUM-FIRST TRIAL

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Background: Patients with AML and *FLT3*-ITD+ or *FLT3* mutations face poor outcomes. The randomized, double-blind, placebo-controlled, phase 3 QuANTUM-First (NCT02668653) trial evaluated the novel, highly potent, and selective type II FLT3 inhibitor, quizartinib, with standard chemotherapy in patients with newly diagnosed *FLT3*-ITD + AML. Quizartinib plus standard intensive induction, consolidation that may include allo-HCT in CR1, followed by single-agent continuation therapy for up to 3 years significantly improved overall survival (OS). We evaluated the impact of allo-HCT in CR1 and the interrelationship with quizartinib on clinical results and the association between *FLT3*-ITD minimal residual disease (MRD) pre–allo-HCT and OS.

Methods: Eligible patients (aged 18–75 years) were randomized to quizartinib (40 mg/d) or placebo and stratified by region, age, and white blood cell (WBC) at diagnosis. Patients achieving complete remission (CR) or CR with incomplete hematologic recovery (CRi) received up to 4 cycles of high-dose cytarabine plus quizartinib (40 mg/d) or placebo and/or allo-HCT followed by up to 3 years of quizartinib continuation therapy (30–60 mg/d) or placebo. The primary endpoint was OS. We assessed the impact of allo-HCT in CR1 on OS as a time-dependent covariable in multivariable regression analyses. *P* values were not adjusted for multiplicity.

Results: In QuANTUM-First, 539 patients (median age, 56 years) were randomized to quizartinib ($n = 268$) or placebo ($n = 271$); 147 patients (54.9%) on quizartinib and 150 (55.4%) on placebo achieved CR, while 45 (16.8%) on quizartinib and 26 (9.6%) on placebo achieved CRi after induction. Among 147 CR patients, 84 (57.1%) on quizartinib and 73 (48.7%) on placebo underwent allo-HCT in CR1. The median time to allo-HCT in CR1 was 3.5 months in 84 quizartinib patients and 3.3 months in 73 placebo patients. After completion of allo-HCT, 61 patients (72.6%) on quizartinib and 36 (49.3%) on placebo started 3 years of continuation therapy. Another 115 allo-HCTs were performed outside CR1 (quizartinib, $n = 60$; placebo, $n = 55$). A multivariable extended Cox regression was conducted in all randomized patients, stratified by region, age, and WBC, including allo-HCT in CR1 as time dependent and adjusted for *FLT3*-ITD variant allele frequency and sex. This analysis revealed quizartinib treatment (hazard ratio [HR], 0.770; 95% CI: 0.609–0.973; $P = 0.0284$) and allo-HCT in CR1 (HR, 0.424; 95% CI: 0.301–0.597; $P < 0.0001$) as favorable factors to OS. Simon–Makuch plot, used to analyze time-dependent effect of allo-HCT in CR1 on OS, showed that CR patients on quizartinib had longer OS regardless of undergoing allo-HCT in CR1 or not. Kaplan–Meier plot of OS in patients undergoing allo-HCT in CR1 by latest pre–allo-HCT *FLT3*-ITD MRD status (cutoff 10^{-4}) showed longer OS with quizartinib versus placebo, particularly in patients with pre–allo-HCT MRD+ status.

Conclusions: Patients on quizartinib had longer OS than patients on placebo, irrespective of allo-HCT in CR1. Patients on quizartinib who underwent allo-HCT in CR1 had longer OS than patients on placebo, irrespective of pre–allo-HCT MRD status.

Clinical Trial Registry: NCT02668653

Disclosure: QuANTUM-First was conducted in compliance with Helsinki Declaration and Good-Clinical-Practice guidelines per International Council for Harmonization.

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ARA, PZ, PNW, SA: no competing interests.

19 - Acute Leukaemia

O013

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR EARLY PRECURSOR T-CELL (ETP) AND NEAR-ETP ACUTE LYMPHOBLASTIC LEUKEMIA/LYMPHOMA (ALL/LBL) IN REMISSION: A MULTICENTER PHASE III STUDY

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Background: The outcome of adults with T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) originating from early T-cell precursors (ETP) and near-ETP is poor following standard chemotherapy, and allogeneic hematopoietic cell transplantation (allo-HCT) has been recommended as preferred consolidation treatment. We developed multi-institutional, prospective phase III trials (NCT02042690, from2014; NCT03756675 from 2018) to investigate: 1) if the outcomes of patients with ETP, near-ETP and non-ETP ALL/LBL in complete remission (CR) are comparable post-HCT, 2) if allo-HCT with haploidentical donors (HIDs) would achieve similar results compared to HLA identical siblings (ISDs) in ETP or near-ETP T-ALL/LBL.

Methods: **Inclusion criteria**:

1) T-ALL/LBL(stage IV) in CR1 or CR2;
2) age 2–65;
3) no HSCT history, available donor of MSDs or HIDs;
4) ECOG 0-2, HCT-CI *(Blood 2005)* 0-3. ETP was defined as *Lancet Oncol* 2009 *(WHO 2016)* and updated according to *International Consensus Classification 2022* in the final analysis.

Patients were biologically randomized to HIDs or MSDs according to the donor availability on an intent-to-treat (ITT) basis. Two uniform conditioning regimens were available in the trial: intravenous(iv.) cytarabine+ busulfan+ cyclophosphamide +/− fludarabine, oral semustine (Bu/Cy); or total body irradiation (TBI,770 cGy) +iv cyclophosphamide(TBI/Cy). The primary endpoint was disease-free survival (DFS). The competing risk of relapse and non-relapse mortality(NRM) was evaluated by Gray's test and Fine-Gray model. Statistical analyses were performed using R software 4.2.1.

Results: Between Jan 2014 to Dec 2021, patients ($n = 367$) with T-ALL/LBL were consecutively enrolled at participating centers, and 10 patients who received unrelated HCT were excluded from the following ITT analysis. Patients **($n = 357$)** were categorized into three subgroups: ETP ($n = 70$), near-ETP ($n = 52$), and non-ETP ALL/LBL ($n = 235$), patients with ETP or near-ETP had a higher incidence of pre-HCT measurable residual disease(MRD, by 10-color flow cytometry). Median follow-up was 34.5 months post-HCT, estimated by the reverse Kaplan–Meier method. Neutrophil recovery was achieved in 99.4% of patients. The 3-year cumulative incidence of relapse (CIR), NRM, DFS and OS were 19.5% (95% Confidence Interval, CI 15.3-24.1%), 14.9% (95%CI 11.3-19.0%), 65.6% (95% CI: 60.6–71.1%) and 69.7% (95% CI: 64.8–75.0%), respectively. Patients with ETP (63.3%, 95% CI: 52.3–76.5%) or near-ETP (65.1%, 95% CI: 52.9–80.2%) had comparable 3-year DFS with non-ETP (66.4%, 95% CI: 60.3–73.2%, $p = 0.9$). Patients following allo-HCT with HIDs (64.2%, 95% CI: 58.7–70.1%) had comparable 3-year DFS with MSDs (75.8%, 95% CI: 64.3–89.3%; $p = 0.2$), HID-HSCT was superior to MSD-HSCT for 3-year DFS in patients with ETP (66.2% vs. 33.3%, $p = 0.041$) or with positive pre-

Table

		ETP $n = 70$	Near-ETP $n = 52$	Non-ETP $n = 235$	p-value
		n (%); Median (Inter Quartile Range)			
Sex	Female	14 (20%)	14 (27%)	57 (24%)	0.6
	Male	56 (80%)	38 (73%)	178 (76%)	
Age		27 (20, 33)	27 (20, 33)	22 (15, 30)	0.044
Diagnosis	ALL	42 (81%)	62 (89%)	182 (77%)	0.12
	LBL (Stage IV)	8 (11%)	8 (11%)	53 (23%)	
Remission	CR1	66 (94%)	48 (92%)	211 (90%)	0.5
	CR2	66 (94%)	4 (7.7%)	24 (10%)	
Pre-HCT MRD	Positive	26 (37%)	22 (42%)	61 (26%)	0.028
Conditioning	Bu/Cy	60 (86%)	49 (94%)	200 (85%)	0.3
	TBI/Cy	10(15%)	3(6%)	35 (15%)	
Donor	MSDs	6 (8.6%)	10 (19%)	30 (13%)	0.2
	HIDs	64 (91%)	42 (81%)	205 (87%)	
Graft	BM + PB	47 (67%)	38 (73%)	171(73%)	0.6
	PB	23 (33%)	14 (27%)	64 (27%)	

P-value with Pearson's Chi-squared test; Kruskal–Wallis rank sum test; Fisher's exact test

HSCT MRD (65.4% vs. 27.3%, $p = 0.008$). 3-year DFS was similar between HID-HSCT and MSD-HSCT in patients with near-ETP (66.7 vs. 60.0%, $p = 0.7$). In the multivariable analysis (MVA) of DFS by adjusting age, sex, diagnosis, pre-HCT MRD, cytogenetics, molecular biomarkers, conditioning, donor and graft, ETP (Hazard Ratio, HR 1.01, 95% CI: 0.62–1.64, $p > 0.9$) or Near-ETP (HR1.11, 95% CI: 0.65–1.90, $p = 0.7$) was comparable to non-ETP, while HID was comparable to MSD (HR1.36, 95% CI: 0.72–2.59, $p = 0.3$).

Conclusions: Allo-HCT might overcome the negative effect of ETP or near-ETP on outcomes of ALL/LBL with traditional chemotherapy. HIDs are feasible alternative donors for patients of ETP or near-ETP if MSDs are unavailable.

Clinical Trial Registry: NCT02042690; NCT03756675

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19 - Acute Leukaemia

O014

USE OF CYCLOSPORIN A VERSUS TACROLIMUS COMBINED WITH POST-TRANSPLANTATION CYCLOPHOSPHAMIDE FOR AML IN FIRST COMPLETE REMISSION: A STUDY FROM THE ACUTE LEUKEMIA WORKING PARTY (EBMT)

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Background: Graft-versus-host disease (GVHD) prophylaxis with post-transplantation cyclophosphamide (PT-Cy) is increasingly used to treat patients with AML. Although the original Baltimore protocol for haploidentical (haplo) donors combined PT-Cy with tacrolimus (TAC) and mycophenolate mofetil (MMF), many transplant centers administer cyclosporin A (CSA) instead of TAC. It is not known if the choice of calcineurin inhibitor (CNI) impacts outcome. Thus, we compared GVHD prophylaxis with PT-Cy/MMF/CSA and PT-Cy/MMF/TAC in a homogeneous cohort of patients with AML in first complete remission (CR1).

Methods: This large retrospective study from the European Society for Blood and Marrow Transplantation (EBMT) registry included 2427 AML patients who had received a first unmanipulated hematopoietic cell transplant (HCT) from a haplo ($n = 1844$, 76%) or unrelated donor (UD, $n = 583$, 24%) in 2010–2021. GVHD prophylaxis consisted of PT-Cy/MMF/CSA ($n = 1528$) or PT-Cy/MMF/TAC ($n = 899$) without in vivo T-cell depletion.

Results: Patient characteristics were well balanced in the CSA and TAC groups with respect to age (median 55.1 [range, 18–75] vs. 54.9 [range, 18–78] years), Karnofsky performance score <90 (20.8% vs 21.8%), and adverse risk cytogenetics (22.1% vs 21.6%), respectively. Stem cell source and donor type differed between groups, with patients on CSA-based GVHD prophylaxis were more likely to receive bone marrow (31.3% vs 16.1%) from a haplo-donor (81% vs 67.4%), $p < 0.0001$ each. Negative measurable residual disease status prior to HCT (62.6% vs

65.7% of 1164 patients) and use of myeloablative conditioning (49.8% vs 47.9%) were similar in both cohorts. The conditioning regimen most frequently combined with CSA was thiotepa/busulfan/fludarabine (TBF, 56.3% of patients), followed by fludarabine/busulfan (FluBu, 19.9%) and fludarabine/total body irradiation (Flu/TBI, 13.5%). TAC was mostly given after Flu/Bu (35.9%), Flu/TBI (20.8%) and TBF (18.4%) conditioning. Graft failure occurred in 3.9% and 5.4% of HCT with CSA and TAC, respectively, p=ns.

Using univariate analysis and Cox regression, no difference between groups was observed with regard to 2-year leukemia-free survival and overall survival (LFS, CSA: 60.5% vs TAC: 60.3%, hazard ratio (HR) 0.95, $p = 0.59$, and OS, 66.3% vs 64.5%, HR 0.97, $p = 0.76$, respectively) as well as cumulative incidence (CI) of relapse (21.1% vs 21.7%, HR 1.07, $p = 0.57$) and non-relapse mortality (NRM, 18.5% vs 18.0%, HR 0.87, $p = 0.31$). Overall, leukemia and infections contributed to 43.4% and 27.4% of deaths, respectively.

TAC-based immunosuppression was associated with a lower CI of severe acute GVHD grade III-IV (6.6% vs 9.1%, HR 0.63, $p = 0.02$), without difference in acute GVHD grade II-IV (25.2% vs 27.3%, HR 0.84, $p = 0.20$) and survival free of relapse, severe acute or extensive chronic GVHD (GRFS, 50.2% vs 51.3%, HR 0.97, $p = 0.68$). In multivariate analysis, other risk factors for outcome were adverse cytogenetics and patient age which were associated with a higher risk of relapse and NRM, respectively, and both factors were associated with lower LFS and OS. No interaction was found between GVHD prophylaxis and donor type.

Conclusions: In the setting of a haplo- or MUD-HCT, PT-Cy/MMF-based GVHD prophylaxis resulted in favorable OS and GRFS irrespective of which CNI was added. TAC seemed to prevent severe acute GVHD more effectively without impact on other outcome parameters.

Disclosure: Nothing to declare

19 - Acute Leukaemia

O015

THE IMPACT OF ALLOGENEIC STEM CELL TRANSPLANTATION IN PH-LIKE PATIENTS: A REPORT FROM THE NATIONAL TREATMENT PROTOCOLS GIMEMA 1913 AND GIMEMA 2317

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Background: Philadelphia (Ph)-like acute lymphoblastic leukemia (ALL) is characterized by a gene-expression signature resembling true Ph-positive ALL and treated with standard chemotherapy shows poorer outcomes compared with other B precursors ALL (BCP-ALL). Although allogeneic hematopoietic stem cell transplant (alloHSCT) is the most effective strategy to overcome chemoresistance in ALL settings, its benefit in Ph-like ALL subgroup remains to be investigated, due to the paucity of studies specifically addressing this issue. The aim of this study was to investigate the impact of alloHSCT on prognosis of Ph-like ALL within a cohort of BCP-ALL patients consecutively enrolled in two consecutive Italian national phase II trials (GIMEMA 1913, NCT02067143 and GIMEMA 2317, NCT03367299).

Methods: In the present analysis, 197 patients, 88 enrolled in the GIMEMA1913 protocol (Bassan EHA 2022) and 109 in the GIMEMA 2317 (Bassan EHA 2021), with available characterization of Ph-like signature, were considered. The Ph-like status was evaluated according to "*BCR/ABL1*-like predictor" as previously reported (Chiaretti et al. BJH 2018, Haematologica 2021), but was not part of transplant allocation decision-making, due to the translational research nature of this aspect in both trials. At variance, patients were considered eligible to alloHSCT in CR1 based on the joint assessment of the conventional disease risk profile at diagnosis and post-consolidation MRD status.

Results: A Ph-like signature was identified in 58/197 (29.4%) BCP-ALL patients. Patients' characteristics were similar between Ph-like and non-Ph-like patients, except for a higher white blood cell count and a higher proportion of patients carrying Ikaros deletions (Table 1). Complete remission (CR) was achieved in 88% of non-Ph-like and 81% of Ph-like patients ($p = 0.26$),while MRD negativity at TP2, after the first 3 cycles of chemotherapy, was overall lower in Ph-like group (61% vs 77%, $p = 0.074$). In terms of 2-year disease-free survival (DFS) and overall survival (OS) Ph-like patients did markedly worse than non-Ph-like patients (DFS 48% (95% CI: 35–68%) vs 78% (95% CI: 71–87%), $p < 0.0001$); OS 61% (95% CI: 47–78%) vs 79% (95% CI: 72–87%), $P = 0.107$). Forty-five patients received alloHSCT: 38% were Ph-like and 62% were non-Ph-like ALL. A consolidative alloHSCT improved outcomes mostly in non-Ph-like compared to Ph-like group (2-year OS 81.4% (95% CI: 64–100%) vs 50.4% (95% CI: 28–90.4%), $P = 0.062$ and 2- year DFS 79.8% (95% CI 63.8–99.9%) vs 40.3% (95% CI: 19.4–90.4%), $P = 0.034$, respectively). In the Ph-like group, the potential benefit of alloHSCT was largely hampered by a high incidence of leukemia relapse during the first 2 years after transplantation (28%, 95% CI: 0–57.5%).

Conclusions: Ph-like signature defines a distinct very high-risk group of ALL characterized by worse OS and DFS. The benefit gained by an alloHSCT in patients at high risk of relapse was greater for non-Ph-like compared to Ph-like cases, due to a very high risk for relapse during the first 2 years after alloHSCT in Ph-like patients. These findings strengthen the need to detect this subset at diagnosis in order to optimize treatment and to obtain deeper remission – as in the currently ongoing GIMEMA 2922 trial -before transplantation and to evaluate experimental preemptive treatments after transplantation to prevent relapse.

		Ph-like		
Characteristic	**Overall, *N* = 197**	**Yes, *N* = 58**	**No, *N* = 139**	***p*-value**
Sex, *n* (%)				0.35
M	111 (56%)	36 (62%)	75 (54%)	
F	86 (44%)	22 (38%)	64 (46%)	
Age, median (range)	40 (18, 65)	39 (18, 65)	40 (18, 65)	0.65
WBC, *n* (%)				**0.001**
WBC > 30 × 10^−9/L	54 (28%)	25 (45%)	29 (21%)	
WBC < 30 × 10^−9/L	140 (72%)	31 (55%)	109 (79%)	
Risk, *n* (%)				0.091
SR	120 (64%)	28 (54%)	92 (68%)	
NO SR	68 (36%)	24 (46%)	44 (32%)	
All category, *n* (%)				0.11
De novo	187 (96%)	57 (100%)	130 (94%)	
Secondary	8 (4.1%)	0 (0%)	8 (5.8%)	
Ikaros^{plus}, *n* (%)	41 (27%)	24 (51%)	17 (16%)	<0.001
Protocol, *n* (%)				0.53
LAL2317	109 (55%)	30 (27.2%)	79 (72.57%)	
LAL1913	88 (45%)	28 (31.8%)	60 (68.2%)	

Clinical Trial Registry: NCT02067143 and NCT03367299
Disclosure: Nothing to declare

19 - Acute Leukaemia

O016

SPECIFIC CYTOGENETIC ABNORMALITIES AT DIAGNOSIS PREDICT SURVIVAL AFTER HEMATOPOIETIC CELL TRANSPLANT IN POOR-RISK PEDIATRIC ACUTE MYELOID LEUKEMIA: A PDWP/EBMT STUDY

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Background: We evaluated whether poor risk (PR) cytogenetic abnormalities in children with AML at diagnosis were predictive of outcomes after allogeneic hematopoietic stem cell transplant (HSCT).

Methods: We included all patients <18 years of age at HSCT reported to the European Society for Blood and Marrow Transplantation (EBMT) registry, who had received their first allogeneic HSCT for AML in CR1 between 2005 and 2020 with an evaluable diagnostic karyotype. Patients were subgrouped as (a) monosomy 7/del7q or monosomy 5/del5q, (b) 11q23 abnormality excluding t (9; 11), (c) complex or monosomal karyotype, or (d) "other". A complex karyotype was defined as three or more structural abnormalities, and a monosomal karyotype as a monosomy with one or more structural abnormalities, excluding WHO-designated recurring translocations or inversions (2017 ELN recommendations). The "other" subgroup included t(6;9), t(3;5), t(9;22), t(8;16), inv(3) or t(3;3), t(16;21), abn(11p15), and del(12p) or abn(12p13). Cytogenetic subgroup, age at HSCT, female donor to male recipient, patient/donor CMV status, time from AML diagnosis to HSCT, and year of HSCT were included as predictors for OS, RI and non-relapse mortality (NRM) in multivariate analysis.

Results: Included were 744 children (42.2% female; median age at HSCT: 8.6 years [0.3–18 years]) from 139 participating centers. Median follow-up after HSCT was 4.4 years. Thirty-seven percent had an 11q23 abnormality, 24% monosomy 7/del7q or 5/del5q, 24% a complex or monosomal karyotype, and 15% "other" PR cytogenetic abnormalities. Donor sources were matched related donor (27%), mismatched related donor (11%), unrelated donor (46%), or cord blood donor (16%); stem cells sources were bone marrow (55%), peripheral blood stem cells (29%) and cord blood (16%) ; 97% of patients received myeloablative conditioning.

The OS and leukemia free survival for the entire cohort was 76% and 70% respectively at 2 years. In a multivariate model, 11q23 (hazard ratio [HR] = 0.59, $P = 0.01$) and "other" PR cytogenetic abnormalities (HR = 0.49, $P < 0.01$) were associated with significantly better OS compared to monosomy 7/del7q or 5/del5q. The "other" PR cytogenetic abnormalities category was also associated

with a lower risk of disease relapse after HSCT (HR = 0.4, $P = 0.01$). Receipt of an unrelated donor was associated with lower RI (HR = 0.58, $P = 0.03$). Older age at HSCT (12–18 years) carried the highest risk of NRM (HR = 1.95, $P = 0.02$) and a worse OS (HR = 1.71, $P < 0.01$) compared to younger patients (aged 4–12 years).

Conclusions: PR cytogenetic abnormalities at diagnosis remain predictive of OS after HSCT for AML in children . Monosomy 7/del7q or monosomy 5/del5q confer a poor prognosis even after HSCT, whereas 11q23 abnormality and "other" PR cytogenetic abnormalities predict a more favorable outcome. Whether HSCT from an unrelated donor offers greater protection against relapse than an HSCT from a matched related donor requires further validation. Efforts for improving conditioning regimens and transplant techniques should focus on reducing NRM and RI.

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Locatelli: *BlueBird bio:* Speakers Bureau; *Miltenyi:* Speakers Bureau; *Medac:* Speakers Bureau; *Novartis:* Honoraria, Speakers Bureau; *Amgen:* Speakers Bureau; *SOBI:* Speakers Bureau; *Jazz Pharmaceuticals:* Honoraria; *Neovii:* Speakers Bureau.

Fagioli: *NOVARTIS:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *JAZZ PHARMA:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *AMGEN:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *CLINIGEN:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *PFIZER:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *GENZYME SANOFI:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *TAKEDA:* Membership on an entity's Board of Directors or advisory committees, Research Funding.

Biffi: *Altheia Science:* Consultancy.

Tambaro: *Gilead:* Speakers Bureau; *Jazz:* Other: Meeting Participation Fees, Speakers Bureau; *Novartis:* Other: Meeting Participation fes.

Bhatt: *Rite Aid Corp.:* Divested equity in a private or publicly-traded company in the past 24 months; *Johnson & Johnson:* Divested equity in a private or publicly-traded company in the past 24 months; *Moderna Inc.:* Divested equity in a private or publicly-traded company in the past 24 months; *Pfizer Inc.:* Divested equity in a private or publicly-traded company in the past 24 months.

Table. Multivariable analysis showing hazard ratios of various variables included in the model for various outcomes.

Variables	Modalities	OS		Relapse Incidence		NRM	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Poor-risk abnormality group	Monosomy 7/del7q or monosomy 5/del5q	1		1		1	
	11q23 abnormality	0.59 (0.39–0.88)	**0.01**	0.85 (0.52–1.40)	0.53	0.72 (0.41–1.27)	0.26
	Complex or monosomal karyotype	0.94 (0.62–1.42)	0.76	1.00 (0.59–1.71)	0.99	1.00 (0.56–1.80)	1
	Other poor risk	0.49 (0.29–0.84)	**0.009**	0.40 (0.19–0.83)	**0.01**	0.67 (0.32–1.37)	0.27
Age at HCT	4-12 years	1		1		1	
	0-4 years	1.16 (0.75–1.79)	0.5	0.73 (0.44–1.22)	0.23	1.48 (0.81–2.71)	0.2
	12-18 years	1.71 (1.16–2.52)	**0.006**	1.04 (0.67–1.63)	0.86	1.95 (1.11–3.40)	**0.02**
Donor type	Matched related donor	1		1		1	
	Unrelated donor	0.80 (0.53–1.19)	0.26	0.58 (0.36–0.93)	**0.03**	0.90 (0.51–1.58)	0.71
	Mismatched related donor	0.83 (0.47–1.45)	0.51	0.64 (0.32–1.28)	0.21	1.23 (0.61–2.50)	0.57
	Umbilical cord blood	1.19 (0.72–1.97)	0.5	0.91 (0.50–1.69)	0.78	1.28 (0.64–2.59)	0.49
CMV status	Neg to Neg	1		1		1	
	Neg to Pos	0.87 (0.56–1.36)	0.55	0.95 (0.54–1.68)	0.87	0.91 (0.50–1.66)	0.76
	Pos to Neg	1.05 (0.63–1.75)	0.84	1.17 (0.62–2.21)	0.63	0.91 (0.44–1.85)	0.79
	Pos to Pos	0.85 (0.57–1.27)	0.43	1.10 (0.67–1.80)	0.71	0.82 (0.48–1.40)	0.47
Diagnosis to HCT (effect for 3-month increment)		0.98 (0.79-1.22)	0.87	0.91 (0.69–1.19)	0.48	1.04 (0.78–1.38)	0.79
Year of HCT (effect for 5-year increment)		0.91 (0.74-1.12)	0.37	0.93 (0.72–1.19)	0.55	0.94 (0.71–1.24)	0.65

19 - Acute Leukaemia

O017

T REPLETE HAPLOIDENTICAL TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE IN PATIENTS WITH SECONDARY VERSUS DE NOVO AML: A STUDY FROM THE ALWP /EBMT

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Background: Allogeneic stem cell transplantation (HSCT) is the only curative therapy in secondary AML (sAML). However, outcomes of matched siblings or unrelated transplants in sAML are inferior in comparison to those achieved in de novo AML, partially due to a higher relapse rate (Blood Cancer J. 2020). Results with non-T-depleted haploidentical transplants (HaploSCT) with post-transplant cyclophosphamide (PTCy) may differ in view of the potential more potent graft versus leukemia effect mediated by a haploidentical graft.

Methods: We compared outcomes of HaploSCT with PTCy in adult (≥18 years) patients (pts) with sAML vs de novo AML using the EBMT registry. Multivariate analysis was performed using a Cox proportional hazards model. A propensity score matching was also performed to reduce confounding effects.

Results: 1925 AML patients (sAML-285, de novo-1640) in the first CR that undergo haploSCT with PTCy from 2010–2021, were evaluated. Pts with de novo AML were younger, with a median age of 55.5 (range 18.1–82.5) vs 60 (19.9–75.7) years, ($p < 0.0001$). The median year of the transplant was 2019 in both groups. Follow-up was 25.6 (range, 24–27.8) and 28 (range, 22.3–33.9) months, respectively ($p = 0.38$). Cytogenetics risk was intermediate in ~2/3 and poor in ~1/3 of pts in both groups. The two patient groups did not differ with regard to gender, CMV serostatus, pre-haploSCT measurable residual disease (MRD), and type of graft (PB in 71.9% and 76.5% of pts, respectively). Karnofsky performance status (KPS) was lower in the sAML group, with KPS < 90 in 78.6% and 70.4%, respectively ($p = 0.003$). Time from diagnosis to haploSCT was longer in pts with de novo AML; median 5.2(range, 1–23.9) vs 5.1 (range,1.3–22.8) ($p = 0.04$). Fewer sAML pts received myeloablative conditioning (37.2% vs 49.5.2%, $p < 10^{-3}$). All pts received PTCy as GVHD prophylaxis. Engraftment at day 60 was similar 95.2% vs 93.3%, respectively ($p = 0.18$). By multivariate analysis, no difference was observed in any HSCT outcome parameter between the sAML vs de novo AML groups; NRM hazard ratio (HR) = 1.03 (95% CI: 0.77–1.38 $p = 0.83$), RI HR = 1.3 (95% CI: 0.97–1.73, $p = 0.08$), LFS HR = 1.15 (95% CI: 0.94–1.42, $p = 018$), OS HR = 1.12 (95% CI: 0.9–1.4, $p = 0.32$) and GRFS HR = 1.05 (95% CI: 0.87–1.28, $p = 0.59$), respectively. Similarly, day 180 incidence of acute (a) GVHD II-IV HR = 1 (95% CI: 0.75–1.32, $p = 0.98$), aGVHD III-IV HR = 1 (95% CI: 0.73 0.43–1.25, $p = 0.25$), 2-year chronic(c)GVHD all grades HR = 0.99 (95% CI: 0.75–1.29, $p = 0.93$), extensive cGVHD HR = 0.67 (95% CI: 0.42–1.07, $p = 0.098$) did not differ between the two groups as well. Causes of death were leukemia (35.9% vs 43.4%), infection (30.5% vs 27.4%) and GVHD (14.3% vs 10.4%), respectively. The results were confirmed by propensity score matching two de novo AML ($n = 464$) with each sAML patient ($n = 245$). We did not find any significant difference between the 2 groups.

Conclusions: haploSCT with PTCy may be able to overcome the bad prognosis of sAML as results are similar to those of haploSCT in de novo AML in contrast to previous studies of transplants from MDS and UD reporting inferior outcomes in sAML compared to de novo AML.

Disclosure: Nothing to declare

19 - Acute Leukaemia

O018

OUTCOMES OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM DIFFERENT DONOR TYPES IN PRIMARY REFRACTORY ACUTE MYELOID LEUKEMIA: A REPORT FROM THE ALWP OF THE EBMT

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Background: Primary refractory acute myeloid leukemia (prAML) is a poor prognosis disease for which allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative option available. We aimed to estimate outcomes according to different donor types and to identify the most relevant predictive factors for allo-HSCT in prAML in the recent period.

Methods: We conducted a retrospective multicenter study of adult patients reported to the European Society for Blood and Marrow Transplantation (EBMT) registry allografted between 2015 and 2020 for prAML. We considered HSCT from matched sibling donors (MSD), 10/10 unrelated donors (UD 10/10), UD 9/10 and haploidentical donors. The primary endpoint was leukemia-free survival (LFS), secondary endpoints were overall survival (OS), relapse incidence (RI) and non-relapse mortality (NRM). A Cox proportional-hazards model was used for multivariate analysis.

Results: We included 1574 patients. Median age was 56.9 years (range 18.1–77.9). Cytogenetic risk was intermediate in 855 (54.3%), adverse in 679 (43.2%) and favorable in 40 (2.5%) patients. Donor type was distributed as follows: MSD $n = 521$ (33.1%), UD 10/10 $n = 540$ (34.3%), UD 9/10 $n = 153$ (9.7%), haploidentical $n = 360$ (22.9%). Patients allografted from an MSD were younger, allografted sooner after diagnosis, more often received MAC and had less secondary AML. Use of PTCy and bone marrow as a stem cell source were more frequent in haploidentical transplants.

2-years LFS was 35.2% (95% CI: 30.6–39.9) in MSD, 37.6% (95% CI: 33.2–42.1) in UD 10/10, 35.2% (95% CI: 27.1–43.5) in UD 9/10 and 27% (95% CI: 22–32.2) in haploidentical transplants ($p = 0.003$). In multivariate analysis LFS was significantly lower in haploidentical transplants compared to MSD (HR = 1.22, $p = 0.044$), to UD 10/10 (1.43, $p = 0.002$) and to UD 9/10 (1.43, $p = 0.011$).2-years OS was 40.9% in MSD, 45.7% in UD 10/10, 43% in UD 9/10 and 31.2% in haploidentical transplants ($p = 0.001$). In multivariate analysis, haploidentical transplants also resulted in inferior OS compared to MSD (HR = 1.3, $p = 0.015$), to UD 10/10 (1.49, $p = 0.001$) and to UD 9/10 (1.38, $p = 0.033$).

The UD 9/10 group experienced the lowest RI (33.5% compared with 46.7% in MSD, 42.7% in UD 10/10, and 46.8% in haploidentical [$p = 0.013$]), and the highest NRM (31.2% compared with 18.1% in MSD, 19.7% in UD 10/10, and 26.2% in haploidentical [$p = 0.001$]).

In multivariate analysis, other factors associated with poor LFS were adverse cytogenetic risk (HR 1.73, $p < 0.0001$) and longer time from diagnosis to allo-HSCT (HR 1.03, $p = 0.009$), whereas factors associated with a better LFS were RIC (HR 0.85, $p = 0.031$) and good Karnofsky performance status (KPS ≥ 80) (HR 0.74, $p = 0.0009$). Adverse cytogenetic risk was associated with higher RI (HR 1.89, $p < 0.0001$), higher NRM (HR 1.47, $p = 0.002$), lower LFS (aforementioned) and lower OS (HR 1.82, $p < 0.0001$).

Conclusions: Our study identified adverse cytogenetic risk, haploidentical donor and longer time from diagnosis to HSCT as factors associated with worse outcomes in the setting of allo-HSCT for prAML. Use of RIC and KPS ≥80 showed an improved LFS. With respect to secondary endpoints, unrelated donors achieved better OS compared to other donor types, and UD 9/10 showed the lowest RI and the highest NRM.

Disclosure: Nothing to declare

19 - Acute Leukaemia

O019

COMPARATIVE STUDY FOR HAPLO-, MSD AND MUD ALLO-HCTS FOR AML PATIENTS WITH KMT2A REARRANGEMENT: A STUDY ON BEHALF OF THE EBMT GLOBAL COMMITTEE AND ALWP

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Background: Balanced rearrangements involving the *KMT2A* gene, located at 11q23, are among the most frequent chromosome aberrations in acute myeloid leukemia (AML) with adverse prognosis. We compared in a EBMT global multi-center registry-based analysis the outcomes following an allogeneic stem cell transplantation (allo-HCT) with either matched siblings (MSD), matched unrelated (MUD) or haploidentical (haplo) donors.

Methods: 759 AML patients with KMT2A rearrangement receiving a first allo-HCT in 225 EBMT centers from 2010–2021 were analyzed. All patients achieved first complete remission (CR1) before transplant. Patients with t (9;11), patients receiving mismatched UD (<10/10), umbilical cord blood or grafts with ex-vivo manipulation were excluded. Univariant analysis and Cox regression models were used.

Results: Results from 309 MSD, 335 10/10 MUD, and 115 haplo were analyzed. Female-to-male transplants was more common in MSD (20.6%) and haplo (22.6%) than in MUD HCTs (11.6%). Peripheral blood (PB) was the major graft source (85.8%). Engraftment rates were comparable in the three cohorts (MSD 99.7%, MUD 97.9% and haplo 97.3% $p = 0.06$). Original disease was the major cause of deaths for the three cohorts. The transplant outcomes of the entire cohort was shown in **Table 1**.

In univariate analysis, haplo was associated with a lower 2-year relapse incidence (RI) (MSD 41.5%, MUD 37.8%, haplo 21.6%, $p < 0.01$) but higher 2-year non-relapse mortality (NRM) (MSD 7.3%, UD 16.9%, haplo 22.1%, $p < 0.01$). Meanwhile, the 180-day cumulative incidence (CI) of grade II-IV acute GVHD (aGVHD) was lower in MSD (19.6%) than in MUD (28.2%) or haplo (23.6%), respectively ($p = 0.036$). Similarly, the 2-year CIs of chronic GVHD (cGVHD) was lower in MSDs (19.6%) than in MUD (28.2%) or haplo- (23.6%) ($p = 0.034$). Incidence of extensive cGVHD was 18.4% 12.3% and 17.9% in MSD, MUD and haplo, respectively ($p = 0.12$). Finally, the 2-year leukemia-free survival (LFS), overall survival (OS) and GVHD-free/relapse free survival (GRFS) in MSD/MUD/haplo were 51.2%/45.3%/56.3%, 61.2%/54.6%/59.7% and 39.6%/38.1%/42.1%, without significant difference between the three cohorts.

In multivariate analysis, compared to MSD (reference), MUD was associated with higher incidence of grade II-IV acute GVHD (HR = 1.87, 95% CI: 1.26–2,76; $p < 0.01$), NRM (HR = 2.55, 95% CI: 1.51–4.33; $p < 0.01$), and lower LFS (HR = 1.28, 95% CI: 1–1.63; $p < 0.05$). Haplo was associated with lower RI (HR = 0.51, 95% CI: 0.33–0.81; $p < 0.01$), higher NRM (HR = 3.08, 95% CI: 1.62–5.85; $p < 0.01$), higher II-IV acute GVHD (HR = 1. 7, 95% CI: 1–2.87; $p < 0.05$). Both CK and MK were associated with higher RI, lower LFS and GRFS. In addition, PB stem cell source was associated with a higher incidence of grade II-IV acute GVHD (HR = 2.17, 95% CI: 1.18–3.97; $p = 0.012$), and female-to-male transplants with a higher risk of chronic GVHD (HR = 1.49, 95% CI: 1.03–2.15; $p = 0.033$).

Conclusions: For AML patients with KMT2A rearrangement, haplo was associated with a lower RI but higher NRM, leading to similar LFS, OS and GRFS as compared to MUD and MSD HCTs. With improvement in GVHD prophylaxis/treatment, haplo might bring potential benefit to these patients through relapse prevention.

Table 1 Transplant outcomes of all KMT2A^r AML patients.

Estimation (95% CI%)	2 years	5 years
RI	36.9 (33.1–40.6)	43.1 (39–47.1)
NRM	13.8 (11.3–16.5)	16.8 (13.9–20)
OS	58.1 (54.1–61.9)	44.7 (40.2–49)
LFS	49.4 (45.4–53.2)	40.1 (35.9–44.2)
GRFS	39.4 (35.5–43.1)	30.5 (26.6–34.4)
chronic GVHD	36 (32.2–39.7)	37.8 (33.9–41.6)
Extensive chronic GVHD	15.6 (12.9–18.7)	19.2 (16–22.7)

Disclosure: Nothing to declare.

19 - Acute Leukaemia

O020

PRE-TRANSPLANT BLINATUMOMAB DECREASES TRANSPLANT RELATED MORTALITY IN B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS WHO UNDERGO ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Blinatumomab is a bispecific monoclonal antibody which has shown effectiveness in controlling refractory B-cell acute lymphoblastic leukemia (ALL) and achieving measurable residual disease (MRD) negativity [1]. Emerging data suggests it improves survival when used in consolidation in Philadelphia chromosome (Ph)-negative ALL patients who achieve MRD negativity. Blinatumomab increases the fraction of B-ALL patients eligible for allogeneic hematopoietic cell transplantation (HCT). This study examined the outcomes of allogeneic HCT in B-cell ALL patients who received blinatumomab pre-transplant.

Methods: In a study of 117 adults who underwent allogeneic HCT for B-cell ALL at Princess Margaret Hospital, Toronto, 2010–2021 we compared transplant outcomes in individuals who received blinatumomab pre-transplant to those who did not. Overall survival (OS) and GVHD- and relapse-free survival (GRFS) were calculated using the Kaplan–Meier and log-rank methods. Cumulative incidences of relapse (CIR), transplant-related mortality (TRM), acute graft-vs-host disease (aGVHD), and chronic GVHD (cGVHD) were calculated using the Fine and Gray model.

Results: Median follow-up for the whole cohort (**Table 1**) was 13 months (range: 1–144). Thirty-one patients (26.5%) received blinatumomab. More individuals in the blinatumomab group received T-cell depletion (96.8% vs 62.8%, $P < 0.001$), had high disease risk index (DRI) (61.3% vs 19.8%, $P < 0.001$) and primary induction failure as transplant indication (45.2% vs 7.2, $P < 0.001$). There were fewer Ph+ ALL patients in the blinatumomab group (22.6% vs 50.0%, $P = 0.01$).

Two-year OS, GRFS, TRM, and CIR in the blinatumomab and non-blinatumomab groups were, respectively: 65.4% vs 45.6% ($P = 0.$ 0.04) [HR: 0.50 (95% CI: 0.26–1.00); $P = 0.05$], 42.2% vs 17.3% ($P = 0.006$) [HR: 0.50 (95% CI: 0.29–0.84); $P = 0.01$], 3.2% vs 43.0% ($P = 0.0001$) [HR: 0.06 (95% CI: 0.008–0.47); $P = 0.007$] and 34.4% vs 14.4% ($P = 0.02$) [HR: 2.6 (95% CI: 1.2–5.9); $P = 0.02$]. Blinatumomab was associated with a lower incidence of day-100 grade 2–4 and grade 3-4 aGVHD: 27.5% vs 56.7% ($P = 0.005$) [HR: 0.38 (95% CI: 0.19–0.78); $P = 0.009$], and 10.9% vs 34.7% ($P = 0.02$) [HR: 0.28 (95% CI: 0.08–0.94); $P = 0.04$], respectively. There was no difference in 2-y all-grade or moderate-severe cGVHD, 31.7% vs 33.0% ($P = 0.9$), and 17.8% vs 29.5% ($P = 0.4$), respectively, between patients who received blinatumomab and those who did not. In multivariate analysis (MVA), blinatumomab remained associated with TRM [HR: 0.09 (95% CI: 0.01–0.69); $P = 0.02$] but not OS or CIR. The most common cause of TRM in non-blinatumomab group was infection (15 patients, 48.4%) followed by GVHD (11 patients, 35.5%). The cause of TRM in the case of one patient in the blinatumomab group was sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD).

Conclusions: Pre-transplant blinatumomab is associated with improved OS, GRFS, TRM and control of aGVHD in B-cell ALL patients who undergo allogeneic HCT, at the cost of increased relapse risk. The effect of blinatumomab on TRM is confirmed in MVA suggesting that the reduction in TRM possibly reflects lower burden of treatment-related toxicity experienced by patients who receive less cytotoxic agents during induction. The major limitation of this study is the small number of subjects. Larger and prospective trials are needed.

Disclosure: Nothing to disclose

Table 1. Patient demographic and clinical characteristics.

Variable	Whole cohort ($n = 117$)	Blinatumomab ($n = 31$)	No Blinatumomab ($n = 86$)	*P*-value
Age (median, range)	40 (18–70)	35 (18–65)	40 (19–70)	0.9
Gender (*n*, %)				1.0
Female	60 (51.3%)	16 (51.6%)	44 (51.2%)	
Male	57 (48.7%)	15 (48.4%)	42 (48.8%)	
Diagnosis (*n*, %)				0.01
Ph+ve	50 (42.7%)	7 (22.6%)	43 (50.0%)	
Ph-ve	67 (57.3%)	24 (77.4%)	43 (50.0%)	
Pediatric inspired protocol (*n*, %)				0.61
Yes	112 (95.7%)	29 (93.5%)	83 (96.5%)	
No	5 (4.3%)	2 (6.5%)	3 (3.5%)	
Indication of transplant (*n*, %)				<0.001
Relapse	33 (28.9%)	16 (51.6%)	17 (20.5%)	
Primary induction failure	20 (17.5%)	14 (45.2%)	6 (7.2%)	
Chemotherapy intolerance	2 (1.8 %)	0 (0.0%)	2 (2.4%)	
High-risk features	45 (39.5%)	0 (0.0%)	45 (54.2%)	
Therapy-related	10 (8.8%)	1 (3.2%)	9 (10.8%)	
MRD positivity after chemotherapy	4 (3.5%)	0 (0.0%)	4 (4.8%)	
Donor (*n*, %)				0.13
MRD	36 (30.8%)	10 (32.3%)	26 (30.2%)	
MUD	47 (40.2%)	11 (35.5%)	36 (41.9%)	
MMUD	17 (14.5%)	2 (6.5%)	15 (17.4%)	
HID	17 (14.5%)	8 (25.8%)	9 (10.5%)	
Graft (*n*, %)				1.0
PBSC	112 (95.7%)	30 (96.8%)	82 (95.3%)	
BMSC	5 (4.3%)	1 (3.2%)	4 (4.7%)	
CMV discordance				0.5
No	74 (63.2%)	18 (58.1%)	56 (65.1%)	
Yes	43 (36.8%)	13 (41.9%)	30 (34.9%)	
HCT-CI (median, range)	1 (0–8)	1 (0-8)	1 (0-7)	1.0
KPS (median, range)	90 (60-100)	90 (60-100)	90 (70-100)	0.3
DRI (*n*, %)				<0.001
Intermediate	80 (68.4%)	11 (35.5%)	69 (80.2%)	
High	36 (30.8%)	19 (61.3%)	17 (19.8%)	
Very high	1 (0.8%)	1 (3.2%)	0 (0.0%)	
Conditioning (*n*, %)				0.08
MAC	77 (65.8%)	16 (51.6%)	61 (70.9%)	
RIC	40 (34.2%)	15 (48.4%)	25 (29.1%)	
GVHD prophylaxis (*n*, %)				<0.001
T-Cell depletion	84 (71.8%)	30 (96.8%)	54 (62.8%)	
Other	33 (28.2%)	1 (3.2%)	32 (37.2%)	
TBI 1200 (*n*, %)				0.2
Yes	49 (41.9%)	16 (51.6%)	33 (38.4%)	
No	68 (58.1%)	15 (48.4%)	53 (61.6%)	
Inotuzumab (*n*, %)				0.01
Yes	7 (6.0%)	5 (16.1%)	2 (2.3)	
No	110 (94.0%)	26 (83.9%)	84 (97.7%)	

BMSC bone marrow stem cells, *CMV* cytomegalovirus, *DRI* disease risk index, *HCT-CI* hematopoietic cell transplant comorbidity index, *HID* haploidentical donor, *KPS* Karnofsky performance status, *MAC* myeloablative conditioning, *MMUD* mismatched unrelated donor, *MRD* matched related donor, *MUD* matched unrelated donor, *PBSC* peripheral blood stem cells, *RIC* reduced intensity conditioning, *TBI* total body irradiation.

19 - Acute Leukaemia

O021

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) IS EQUALLY EFFECTIVE IN THERAPY-RELATED ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) COMPARED TO DE-NOVO ALL – A REPORT FROM THE EBMT REGISTRY

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Background: Therapy-related acute lymphoblastic leukemia (tr-ALL) is a rare treatment complication in patients treated for a solid tumor (ST) or hematological disease (HD). The prognosis of tr-ALL is generally poor due to the greater frequency of high-risk molecular and cytogenetic changes compared to de novo ALL (dn-ALL). We compared: RI, NRM, acute and chronic GvHD, LFS, GRFS and OS, between tr-ALL and dn-ALL patients receiving allo-HCT who were registered in the EBMT database.

Methods: Between 2010–2021, among 9720 ALL patients treated with allo-HCT 351 (3.6%) were reported as tr-ALL out of whom 268 were transplanted in 1st complete remission (CR1), 46 in ≥CR2, and 37 with active disease. For detailed analyses, we chose 80 patients in CR1 with a known precedent primary diagnosis. Among them, 58.8% had STs (40% with breast cancer) the rest (41.2%) had HDs including lymphomas (20%), CLL (2.5%), myeloma (2.5%), MDS/MPN (11.2%), AML (3.8%) and sAA (1.2%). We used a matched-pair propensity score to compare the outcomes of dn-ALL and tr-ALL in a 2:1 ratio.

Results: The median age of tr-ALL patients was 51.8 (range 21.7–75.8) years. Most of them (67.5%) were female. Phenotypically, 64 (80%) had B-ALL (half of them were Ph+) and 16 (20%) had T-ALL. The median time from first disease diagnosis to tr-ALL was 60.1 months [IQR:18.1–99.8], whereas the time from tr-ALL diagnosis to allo-HCT was 5.6 months [IQR: 4.7–6.5]. Peripheral blood cells were used in 87.5% of recipients. The majority of donors were matched unrelated (58.8%), the rest comprised matched siblings (33.8%) or other related (7.5%). Total body irradiation (TBI) based conditioning was applied in 51.2% of cases. Myeloablative conditioning received 57.5% of patients, despite a high score(≥3) HCT-specific comorbidity index in 68% of recipients. The most common immunosuppression was CSA + MTX (45%) or CSA + MMF (25%), in vivo T-cell depletion was performed in 48.8% of cases. All, except 2 patients, (97.5%) engrafted. Acute GVHD ≥grade II was diagnosed in 26.4% of cases. The median follow-up was 37.4 months [IQR: 17.26–48.97]. During follow-up 31 (21.1%) patients died due to underlying disease, GVHD (32.1%), infection (14.4%) or other transplant-related complications (10.7%). Estimated 2-year RI and LFS were 19.1% (95% CI: 11–28.9) and 52.1% (95% CI: 39.6–63.2), respectively; NRM 28.8% (95% CI: 18.4–40), GFRS and OS were 39.4% (95% CI: 27.8–50.7) and 60.8% (95% CI: 47.9–71.4), respectively. There was no difference in RI, GFRS, NRM, and OS in patients with STs and HDs. In univariate analysis no variable affected RI, GFRS, and OS. However, NRM was higher in male donor ($p = 0.016$) and in patients with T-ALL (50.7%) and Ph(+) B-ALL (33.7%) compared to Ph(-) B-ALL ($p = 0.034$).Para ID="Par124">

Conclusions: The prevalence of tr-ALL in the EBMT registry (3.6%) is lower than the estimated 9% among the general ALL population, which suggests that most of the patients are not intensively treated and referred for allo-HCT. However, those who received allo-HCT in CR1, despite high HCT-CI scores, had comparable outcomes to patients with dn-ALL but an increased cGVHD incidence.

Clinical Trial Registry: N/A

Disclosure: nothing to disclose

20 - Aplastic Anaemia

O022

HAPLOIDENTICAL HEMATOPOIETIC CELL TRANSPLANTATION USING EX VIVO T CELL-DEPLETED GRAFT FOR PEDIATRIC PATIENTS WITH ACQUIRED SEVERE APLASTIC ANEMIA

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Background: Allogeneic hematopoietic cell transplantation (HCT) is a curative treatment for patients with acquired severe aplastic anemia (SAA). With the recent improvement in the outcome of HCT, matched URD is now accepted as a frontline treatment in

Table 1.

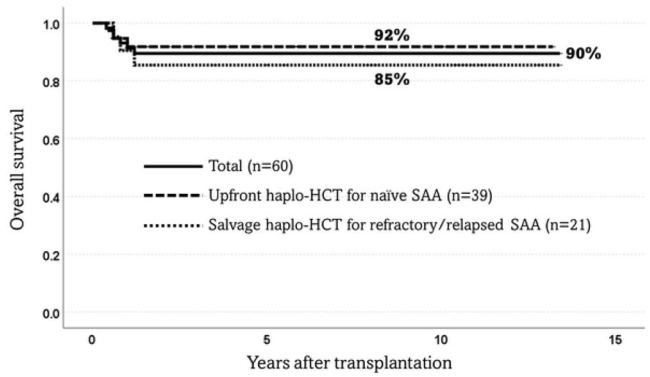
	De-novo ALL	tr-ALL	HR (95% CI)	*P* value
RI	25.7%	19.9%	0.97 (0.51–1.82)	0.92
GRFS	42.9%	40.7%	1.26 (0.89–1.76)	0.19
NRM	18.3%	26%	1.25 (0.67–2.32)	0.48
LFS	56.1%	54.1%	1.09 (0.71–1.67)	0.69
OS	67.7%	63.1%	1.18 (0.75–1.86)	0.48
cGvHD	31.4%	51.9%	2.07 (1.37–3.12)	0.0006
Extensive cGvHD	12.5%	20.8%	1.98 (1.02–3.82)	0.042

children with SAA. Allogeneic HCT from haploidentical family donor (haplo-HSCT) has made significant progress and is now widely used in patients mostly with hematologic malignancy who do not have a suitable MSD or URD. However, haplo-HSCT for pediatric patients with SAA requires more evidence. In this study, we evaluated the outcome of haplo-HCT using an ex vivo T cell-depleted graft in pediatric patients with acquired SAA.

Methods: Between October 2009 and October 2022, 60 pediatric patients with SAA received haplo-HCT using ex vivo T cell-depleted grafts [16 from CD3-depleted PBSC (CD3-HCT) and 44 from TCRαβ-depleted graft (αβ-HCT)] at Asan Medical Center Children's Hospital. Of 60 patients, 37 were male and the median age at transplant was 12.6 years (range, 1.4–22.6). Donors were father in 16, mother in 26 and sibling in 18. Of the 60 patients, 39 received upfront haplo-HSCT for treatment-naïve SAA and 21 received salvage haplo-HCT for refractory/relapsed SAA.

Results: Fifty-eight of 60 patients achieved neutrophil engraftment at a median of +10 days (range, 9–13 days). Two patients experienced primary graft failure (GF) and additional 4 patients developed graft rejection within 30 days post-transplant. One more patient developed late GF at +125 days. As a result, a total of 7 patients (5 from CD3-HCT and 2 from αβ-HCT) experienced GF, leading to cumulative incidence (CI) of 11.7%. All the 7 patients received rescue transplantations and achieved neutrophil engraftment. The CI of GF is significantly higher in CD3-HCT than in αβ-HCT (31.2% vs 4.6%, $P = 0.004$). The CI of acute GVHD ≥ grade 2 and ≥ grade 3 were 36% and 16%, respectively. No patient developed grade 4. Two patients developed moderate/severe chronic GVHD. Six patients died at a median of 254 days after receiving haplo-HSCT (CMV disease in 2, and pure red cell aplasia, TMA, pneumonia, MOF in 1 each). At a median follow-up of 5.8 years (range, 0.3–13.4), the disease-free survival (DFS) was 90 ± 4.1% (Fig. 1). DFS was comparable between upfront and salvage haplo-HCT (naïve 92 ± 4.5% vs salvage 85 ± 7.8%, $P > 0.05$, Fig. 1).

Figure 1. Outcomes of haploidentical HCT for pediatric patients with acquired SAA.



Conclusions: This study demonstrated that our current haploidentical HSCT using ex vivo T cell-depleted graft is a viable treatment option for pediatric patients with acquired SAA. Given that the outcome of upfront haplo-HCT was comparable to that of salvage transplant, upfront haplo-HCT could be offered for the pediatric patients with SAA.

Clinical Trial Registry: NCT01759732
NCT02014506

Disclosure: Authors have no personal or financial interest to declare.

20 - Aplastic Anaemia

O023

CONDITIONAL SURVIVAL AND STANDARDIZED MORTALITY RATIOS OF PATIENTS WITH SEVERE APLASTIC ANEMIA SURVIVING AT LEAST ONE YEAR AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION OR IMMUNOSUPPRESSIVE THERAPY

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Background: Immunosuppressive treatment (IST) and allogeneic hematopoietic cell transplant (HCT) are standard therapies for severe aplastic anemia (SAA). While outcomes after initial IST or HCT have been well described, limited data are available regarding the temporal variations of mortality risks on survivors of SAA after IST or HCT. Previous HCT registry studies had limited data on conditional survival and standardized mortality ratios (SMR) after alternative donor HCTs. Moreover, no studies to date have evaluated conditional survival or SMR in SAA after IST.

Methods: SAA patients who received their first HCT ($n = 3571$), reported to the Center for International Blood and Marrow Transplantation Registry (CIBMTR), or received anti-thymocyte globulin (ATG)-based IST at the Clinical Center, NIH ($n = 395$) between 2000 and 2018 were eligible for the study. Those who survived less than 1 year after their treatment (677 [19%] for HCT and 12 [3%] for IST) were excluded, resulting in 2894 HCT patients and 383 IST patients available for analysis. During the study period, 2000–2018, there were changes to treatment regimens and follow-up times differed. Consequently, treatment periods 2000–2010 and 2011–2018 were studied separately. Eighty-three (22%) patients who received IST also received an HCT for recurrent disease after IST. Patients in the HCT group were not censored at 2nd HCT and patients in the IST group were not censored for HCT.

Results: The median age (range) of patients during 2000–2010 was 30 years (range: 2–82) for IST, 17.3 years (0.1–70) for matched sibling HCT, and 15.9 years (0.1–66) for alternative donor HCT. The corresponding median age (range) for the period 2011–2018 were 30 year (3–82), 18.5 years (0–76), and 17.9 years (0–74), respectively. Non-Hispanic White represented 51% of the IST cohort and 74% of the HCT cohort in 2000–2010 while 58% of the IST cohort and 57% of the HCT cohort were non-Hispanic White in 2011–2018. In the earlier period, 2000–2010, and in the later period, 2011–2018, matched siblings were the predominant donors and accounted for 735 of 1282 (57%) and 693 of 1612 (43%) of HCTs, respectively. In the IST cohort, all patients were treated with horse ATG in combination with cyclosporine (CSA), 158 with ATG/CSA with addition of eltrombopag. The SMR of patients treated during the period 2000–2010 and survived 1 year was 3.50 (95% confidence interval: 2.62–4.58), 4.12 (3.20–5.21), and 8.62 (6.88–10.67) after IST, matched related donor HCT, and alternative donor HCT, respectively. For the period 2011–2018, the corresponding SMRs were 2.89 (1.54–4.94), 3.12 (1.90–4.82), and 4.75 (3.45–6.38), respectively. The mortality risk decreased over time, and became comparable to the general population by 5 years in IST patients. For HCT recipients during 2000–2010 and 2011–2018, the mortality risk became comparable to the general population after 10 years and after 5 years, respectively.

Conclusions: Our data indicate long-term survival is excellent and improving over time for 1-year survivors after IST or HCT. However, their mortality risks remain greater than the general

population, warranting further studies in cause-specific mortality/morbidity and patient-reported outcomes.

Disclosure: Nothing to declare

20 - Aplastic Anaemia

O024

THE IMPACT OF PATIENT-REPORTED ETHNICITY ON HAEMATOPOIETIC CELL TRANSPLANT OUTCOME: THE UK EXPERIENCE

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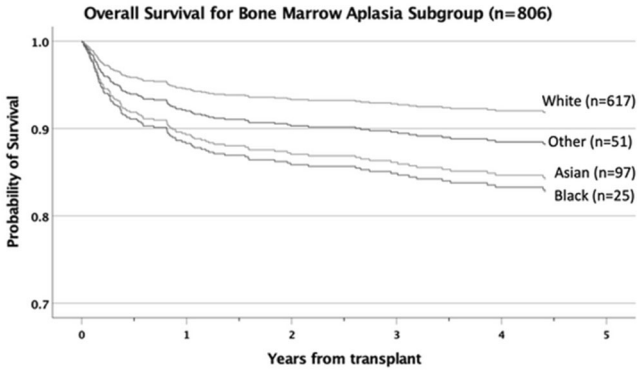
Background: Patient-reported ethnicity has been associated with differences in haematopoietic cell transplant (HCT) outcomes in both autologous and allogeneic settings, with patients from minority ethnic and mixed heritage backgrounds often showing increased risks of complications and mortality. To date, most large studies have been performed on cohorts of US patients where differences in healthcare models and access to primary healthcare may have additional socioeconomic impacts, and translation of such findings to countries with different healthcare systems, like the UK, may not be straightforward. We therefore aimed to determine the impact of patient-reported ethnicity on the outcome of HCT in the UK.

Methods: All patients receiving a first autologous ($n = 20{,}119$) or allogeneic ($n = 13{,}978$) transplant for a haematological disorder between January 2009 and December 2020 at a UK transplant centre with patient-reported ethnicity were included. Ethnicity categories were pre-determined by the EBMT registry criteria, and were limited to Asian, Black, Other (including mixed heritage) and White. All ethnicities were reported on the ProMISe patient outcome database by transplant centres and are based on patient self-defined ethnicity. The primary outcome was 5-year overall survival (OS), as estimated by the Kaplan-Meier method. Univariate and multivariate analyses were carried out using the log-rank test and Cox model, respectively.

Results: After adjustment for known prognostic factors, there were no statistically significant associations between ethnicity and 5-year OS, in either the whole autologous cohort or in different disease subgroups. Similarly, there were no associations observed in the full allogeneic cohort. Given the heterogeneity of the full allogeneic cohort, OS probability was determined for the malignant ($n = 12{,}158$) and non-malignant ($n = 1820$) disease subgroups. No significant association between ethnicity and OS was observed for the malignant dataset ($p = 0.83$). However, a significant association between ethnicity and OS was observed for the non-malignant cohort ($P = 0.002$) with patients from Asian and Other ethnic backgrounds having significantly worse OS than White patients ($P \le 0.001$, HR 1.8; and $P = 0.016$, HR 1.7, respectively). These effects were predominantly from the bone marrow aplasia subgroup with White patients ($n = 617$) having significantly better 5-year OS than Asian patients ($n = 97$; HR 2.0, $P = 0.023$). There were no significant differences in OS for any other ethnic group in this analysis, nor in any other disease subgroup. The predominant cause of death for patients in the bone marrow aplasia subgroup was HCT-related factors (67%), with no significant variation between ethnic groups.



Conclusions: Overall, this relatively large UK study did not find significant differences in survival outcomes between ethnic groups in the majority of indications for HCT. However, the reported difference in OS between White and Asian patients undergoing allogeneic HCT for a bone marrow aplasia requires further investigation. Differences in healthcare models, mix of ethnic groups and other socio-economic factors impacting on access to healthcare may explain variation in findings internationally. [DNM1] As with previous studies, there are limitations. Ethnicity data reporting should be harmonised and data capture processes improved to enable thorough comparative analyses to identify and address health inequalities on national and international levels.

Disclosure: Nothing to declare

20 - Aplastic Anaemia

O025

OBSERVATIONAL STUDY OF 361 NON-TRANSPLANT APLASTIC ANAEMIA AND/OR PNH PATIENTS WHO RECEIVED COVID-19 VACCINATION;JOINT REPORT FROM SEVERE APLASTIC ANAEMIA & INFECTIOUS DISEASES EBMT WORKING PARTIES

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	Baseline ($n = 361$)		3 months ($N = 361$)		6 months ($N = 361$)		12 months ($n = 361$)	
	Missing	Median (IQR)	Missing	Median (IQR)	Missing	Median (IQR)	Missing	Median (IQR)
Hb (g/l; IQR)	3 (0.8%)	116.5 (98–129.8)	36 (10%)	114 (96–128)	25 (6.9%)	115.5 (97–130)	56 (15. 5%)	119 (101–132)
WCC (x10*9/l; IQR)	8 (2.2%)	4 (2.9–5.2)	42 (11.6%)	4 (3–5)	30 (8.3%)	3.9 (3–5.1)	60 (16.6%)	4 (3.2–5)
Neutrophil (x10*9/l; IQR)	5 (1.4%)	2 (1.4–2.9)	44 (12.2%)	2 (1.4–2.7)	30 (8.3%)	2 (1.4–2.9)	61(16.9%)	2 (1.5–2.8)
Platelets (x10*9/l; IQR)	4 (1.1%)	123 (74–171)	41 (11.4%)	122.5 (73.8–169.2)	27 (7.5%)	122 (79–172)	55 (15.2%)	128 (87–174.8)

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Background: SARS-CoV-2 vaccinations were developed rapidly following the identification of the novel coronavirus responsible for the COVID-19 pandemic 2019. Vaccination of patients with aplastic anaemia (AA) and/or Paroxysmal Nocturnal Hemoglobinuria (PNH) is complex due to concerns regarding risks of AA relapse and those with PNH may have complications due to complement activation.

We proceeded with an observational prospective study of non-transplant patients with AA and PNH who were invited to receive COVID-19 vaccination to provide an evidence-based approach for patients and physicians.

Methods: Physicians treating AA and/or PNH within the EBMT AA working party were invited to participate, data was collected until September 2022 with all patients having had 12-month follow-up post first vaccination.

Patients consented to the EBMT registry, data collected included demographics, disease status, vaccination status, vaccine complications and disease status follow-up at 3, 6- and 12-months post vaccination.

Results: 361 patients from 20 centres (from 13 countries) were included, 206 (57.1%) female and a median age at vaccination of 55.1 years (IQR 37.6–68.9).

At the time of the study (within a year after first COVID-19 vaccination), 99 (27.4%) patients received treatment for PNH only, 149 (41.3%) patients received treatment for AA only, 30 (8.3%) patients were treated for both PNH and AA, and 83 (23.0%) patients received no treatment.

139 patients were on active immunosuppression (IST) at time of 1st vaccination.

Overall survival at 12 months post vaccination was 99% (97–100%), with no difference between patients on active immunosuppression compared to patients with no active immunosuppression (12 month survival 99% in both groups, $p = 0.9$).

AA relapse free survival was 97% (94–99%).

9 patients relapsed, 6 due to concomitant reduction in immunosuppression, 1 unknown and 1 due to transformation to MDS. 1 relapse was considered possibly vaccine related with a fall in platelet count (72×10*9/l to 12×10*9/l 1 week post vaccination) responding to an increase in oxymetholone.

Immediate vaccine side effects were experienced by 117 (32.4%) patients, with PNH specific complications in 19 (5.3%). There was no difference between complications experienced by those without IST (9.7%) and those on IST (4.3%) ($p = 0.27$).

15% of patients experienced SARS-CoV-2 infection post vaccination by 12 months, of which 76.8% experienced symptoms. No patients died from COVID-19 in this cohort.

Median blood counts at time of vaccination and 12 months later were minimally changed (see table I).

Conclusions: This is the largest report to date assessing patients with aplastic anaemia and/or PNH receiving vaccination for SARS-CoV-2 infection. Vaccine related relapse of AA and PNH related complications were extremely low. There was no difference in outcome of those on active immunosuppression compared to patients who were on no active immunosuppression, and no deaths from SARS-CoV-2 infection observed post vaccination. This cohort would suggest patients with AA and/or PNH should be reassured regarding vaccination for SARS-CoV-2.

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Dr D Eikema: Nothing to declare

Dr I Verheggen: Nothing to declare

Prof A Kulagin: Nothing to declare

Dr J Tjon:Nothing to declare

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Dr U Zaidi: Nothing to declare

Dr L Desnica: Nothing to declare

Dr S Giammarco: Nothing to declare

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Dr F Beier: Nothing to declare

Dr A Cignetti: Nothing to declare

Dr B Dexler: Nothing to declare

Dr E Gavriilaki: Nothing to declare

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20 - Aplastic Anaemia

O026

THE PNH CLONE SIZE AT THE START OF APLASTIC ANEMIA ARE CLOSELY ASSOCIATED WITH TRANSFORMATION IN CLINICAL SIGNIFICANT PNH

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Background: It is known, that PNH clones escape immune attack and closely associated with bone marrow failure syndromes. Current immunosuppressive therapy (IST) proved to be effective in 70-90% of patients with AA. Nevertheless, the PNH clone increases and becomes clinically significant even with the development of remission of AA. The purpose of this study is select the group of AA pts, association with high progression in to clinical significant PNH.

Methods: We evaluated PNH-clone expansion in 138 treatment-naïve (TN) AA patients between May 2012 and October 2022: 74 males and 64 females at median age 26 years (range 18–62 years). PNH-clone had been assessed by flow cytometry before treatment and then monitored during IST. PNH clone of more than 10% in association with an increased activity of LDH >1.5 x ULN was referred to as "PNH syndrome" at the disease onset. Combined IST consisted of horse ATG (20 mg/kg x 5 days or 40 mg/kg x 4 days) and two years of Cyclosporin A (CsA) treatment (at least one year after remission achievement).

Results: PNH clone was detected in 92/138 patients (67%). Only 32/138 (23%) had PNH-clone more than 10% (among granulocytes) and 18/138 (13%) had AA with PNH syndrome. Clonal evolution observed in 22 pts (16%): in 16 pts to classic PNH, in 6 pts to MDS (monosomy 7 ($n = 4$), trisomy 6 ($n = 1$), trisomy 8 ($n = 1$).

Five-years probability for evolution to hemolytic PNH was 16.5%, and 18.3% in 10-years. Of note that 5-year progression rate to hemolytic PNH was 50% in AA patients with PNH clone greater than 10%. High LDH activity (1.5 x ULN) in TN AA patients with PNH-clone greater than 10% was not significant for progression to hemolytic PNH: the median time to transformation was higher in AA pts with PNH syndrome (60 versus 38 months with LDH < 1.5N).

Conclusions: Treatment-naïve AA patients with PNH-clone greater than 10% are more likely to develop hemolytic PNH after hematopoiesis recovery. The results of our study indicate that half of AA patients with PNH-clone >10% develop hemolytic PNH in 5 years.

Disclosure: Nothing to declare

20 - Aplastic Anaemia

O027

CURRENT USE OF ANDROGENS IN BONE MARROW FAILURE DISORDERS: A REPORT FROM THE SEVERE APLASTIC ANEMIA WORKING PARTY (SAAWP) OF THE EBMT

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Background: Anabolic steroids have been in use for several decades as a class of therapeutics in both inherited and acquired bone marrow failure (BMF). However, their role has been rarely analyzed in prospective setting and systematic and long-term data are currently unavailable to clearly state on their use, efficacy and toxicity in acquired and inherited contexts.

Methods: Here, taking advantage of a unique disease-specific international dataset, we retrospectively analyzed the so far largest cohort of BMF patients who received androgenic compounds, reappraising their current use in these disorders.

Results: Between 1990 and 2021 we identified 274 patients across 82 EBMT-affiliated centers, 193 with acquired and 81 with inherited BMF. In most of the cases, patients had a severe disorder. Median age at the time of androgen start was 32 (18–52) years for acquired and 8 (6–12) years for inherited BMF, while median time from diagnosis to first androgen use was 4 (0.3–17.6) and 8.5 (0.4–34.9) months respectively. Especially when given in idiopathic setting, androgens were often associated with other immunosuppressive treatments. Oxymetholone was the most common anabolic steroid used in acquired context (33%) while norethandrolone (15%) and danazol (15%) were instead more frequently administrated in inherited diseases. Median duration of androgen treatment in patients with acquired BMF was 5.6 (2.2–20.4) months. In this group, after three months of treatment, complete (CR) and partial remissions (PR) were observed in 6% and 29% of patients, respectively, with most of the patients remaining in stable disease. With a median follow-up from androgen initiation of 73.7 months (IQR: 57.1–96.4), 5-year overall survival (OS) was 63% (95% CI: 56–71%) and failure-free survival (FFS) was 23% (16–30%). In inherited context androgens were given for a median duration of 20 months (IQR: 7–37.7). Here, CR and PR rates were observed respectively in 7 and 26% of patients at 3 months. In this group median follow-up from androgen start was 82.3 months, with 5-year OS and FFS respectively of 78% (68–87%) and 14% (6–22%). Initiation after >2 lines of therapy for acquired and a delay of >12 months from diagnosis for inherited BMF were identified as factors associated with improved FFS in univariable and multivariable analysis. For acquired group, 5-year cumulative incidence (CI) of toxicity was 13% for liver, 4% for gastrointestinal, 3% for renal, 1% for psychiatric disorders, with most of the events occurring within the first year. For inherited BMF, median time to toxicity from androgen initiation was more delayed: 22.8 and 15.1 months for respectively liver and endocrinological toxicities with 5-year CI of

13% and 6%. Five-year CI of secondary neoplasms after androgenic treatment was 1% for both groups, while 5-year CI of myeloid clonal evolution was 3% in acquired and 8% in inherited group.

Conclusions: Powered by a multicenter effort, this study provides a unique opportunity to re-examine the role of androgens in a real-life cohort of BMF patients setting the stage for future studies and guidelines.

Disclosure: No relevant conflict of interest to disclose

21 - Autoimmune Diseases

O028

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR TREATMENT OF MULTIPLE SCLEROSIS IN SWEDEN: AN OBSERVATIONAL COHORT STUDY

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Background: Autologous hematopoietic stem cell transplantation (AHCT) has been used to treat multiple sclerosis (MS) since the 1995. Although there is an increasing evidence base for the safety and efficacy of AHSCT for MS, it is still considered experimental therapy in many European countries. The aim of this study was to provide data on safety and effect of AHCT for MS when used in routine health care.

Methods: We conducted a retrospective analysis of prospectively collected registry data from the Swedish MS register of all patients with relapsing-remitting MS (RRMS) treated with AHCT in Sweden before January 1st 2020. All outcome data in the register were retrospectively scrutinized by a specialist in neurology at each transplantation center. Data on adverse events were collected through systematic analysis of medical records.

Results: The cohort comprised 174 RRMS patients, with a median age of 31 years (interquartile range, IQR 26–36), a mean disease duration of 4.6 (±4.4) years before AHCT, and a median expanded disability status scale (EDSS) score of 3.5 (IQR 2–4). The annualized relapse rate in the year prior to AHCT was 1.7 (±1.9). The median patient had received 2 (IQR 1-3) disease-modifying treatments prior to AHCT.

All patients received mobilization with cyclophosphamide + G-CSF. 33 patients were treated with BEAM-ATG as conditioning regimen and 141 received Cy-ATG. The median time to engraftment was 12 days (8–21, IQR 11–13.5) and the patients were hospitalized for the transplantation for a median of 20 days (IQR 19–22). The mean number of serious adverse events was 1.5 per patient for grade 3 and 0.08 per patient for grade 4. Febrile neutropenia was the most common adverse event occurring in 68% of patients. 18% did not experience any serious adverse event. Five patients were admitted for intensive care with a maximum duration of two days. Only one patient in the cohort needed treatment for Epstein–Barr virus and one patient needed intravenous treatment for cytomegalovirus. There was no treatment related mortality.

The mean follow-up time was 5.9 (±3.2) years. The Kaplan-Meier estimate of 'no evidence of disease activity' (freedom from disease) was 73% (95% CI 66–81%) at five years and 65% (95% CI 57–75%) at ten years. The annualized relapse rate during the follow-up period was 0.035 (±0.12), significantly lower than at baseline ($p < 0.0001$). At last follow-up, the EDSS was 2 (IQR 1–3.5), significantly lower than at baseline ($p < 0.0001$). Of the 149 patients with disability at baseline (EDSS ≥2), 80 (54%) improved in disability, 55 (37%) were stable, and 14 (9%) deteriorated.

Table 1. Most common grade 3 and 4 adverse events

n = 174	Grade 3 (%)	Grade 4 (%)
Febrile neutropenia	119 (68.4)	6 (2.9)
Hypokalemia[Ψ]	31 (17.8)	-
Nausea	14 (8.0)	-
Serum sickness	11 (6.3)	-
Diarrhea	9 (5.1)	-
Oral mucositis	9 (5.1)	-
Elevated AST/ALT	9 (5.1)	-
Hypoalbuminemia	7 (4.0)	-
Hypotension	6 (3.4)	-
Thromboembolic event	5 (2.9)	1 (0.6)
Fatigue	5 (2.9)	-
Anorexia	5 (2.9)	-
Hyperglycemia	5 (2.9)	-
Skin/soft tissue infection	4 (2.3)	-
Pericarditis	2 (1.1)	1 (0.6)
Pneumonia	3 (1.7)	-
Cytokine release syndrome	3 (1.7)	-

The table presents the most common grade 3 and 4 adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 for all patients from start of mobilization to day +100 after AHCT. Anemia, neutropenia and thrombocytopenia as well as transient alopecia and amenorrhea were expected the first weeks after AHCT and were excluded. Neurological adverse events assessed as manifestations of MS were not included. There were no grade 5 adverse events.
[Ψ]Hypokalemia was associated with furosemide treatment after hyperhydration in 15 patients.

Conclusions: Our results from this cohort study of AHCT for RRMS concludes that this procedure is a feasible, safe and very effective treatment for MS in routine health care. More than half of the patients improved in disability and there was no treatment related mortality. AHCT could benefit considerably more patients with MS and should be included as standard of care for patients with highly active MS.

Clinical Trial Registry: The study is registered at clinicaltrials.gov with NTC number 05029206 and can be found at https://clinicaltrials.gov/ct2/show/NCT05029206

Disclosure: The study was funded by the Swedish Society of Medicine, the Center for Clinical Research Dalarna, the Uppsala-Örebro Regional Research Council and Region Stockholm.

All individual authors have nothing to declare.

21 - Autoimmune Diseases

O029

AUTOLOGOUS STEM CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES AT ST VINCENTS HOSPITAL, SYDNEY – 25 YEARS AND 159 PATIENTS: AN ANALYSIS OF DISEASE SPECIFIC OUTCOMES AND SAFETY

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Background: To describe the patient cohorts treated with autologous haematopoietic stem cell transplantation (HSCT) for severe autoimmune diseases (ADs) from 1997 to 2022.

Methods: All studies were approved by the St Vincents Hospital ethics committee (HREC: 96/014,00/03,99/102,08/106,10/206,16/221). Data collected included clinical and quality of life (QOL) data pre HSCT and 3, 6, 12 months post HSCT then yearly. Safety was the primary endpoint (as measured by Transplant Related Mortality - TRM) with disease specific efficacy as secondary endpoints (skin score/change in FVC for scleroderma, NEDA for MS, ACR criteria for RA and Visual analogue scales/DMARD use for other diseases).

Results: Between Jan 1997 and February 2022, 159 patients received HSCT for severe ADs. The major indications were systemic sclerosis (SSc – 65 patients), multiple sclerosis (MS- 63 patients), rheumatoid arthritis (RA – 15 patients) and other conditions (16 patients).Median follow up for theses indications was 4 years (SSc), 5 years (MS), 11.2 years (RA) and 4.6 years (others).TRM in SSc patients was 7.7% (5/65) at D100 and 1 year with no TRM in the other ADs, confirming an overall TRM of 3.1%. Overall survival at 5 years was 86%(95% CI: 73.7–92.8) for SSc, 100% for MS, 100% for RA and 100% for other indications. Response rate was 85% for SSc, 85.7% for MS, 78.6% for RA and 68% for others. In contrast, disease free survival at 5 years was SSc: 53.7% (95% CI: 38.9–66.4), MS 45.5% (95% CI: 30.3–59.6), RA:0% and Others 58.6% (95% CI: 25.1–81.3). There were five late malignancies—Hodgkin Lymphoma, PTLD, lung carcinoma, renal cell carcinoma and melanoma.

Conclusions: HSCT for autoimmune conditions provides meaningful long term disease free survival for the vast majority of patients (except RA). Data from our centre mirrors the world experience in both phase II and III trials suggesting that HSCT can be considered in patients who fail conventional therapies. Further work is required to improve short term safety in SSc and to elucidate the mechanisms of action of the procedure.

Clinical Trial Registry: ANZCTR12613000339752

Disclosure: Nil

21 - Autoimmune Diseases

O030

OUTCOME OF SARS-COV2 INFECTION IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS FOR AUTOIMMUNE DISEASES

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Background: Hematopoietic stem cell transplant (HSCT) recipients may be at high risk of mortality from coronavirus disease 2019 (COVID-19). During the pandemic, European Society for Blood and Marrow Transplantation (EBMT) provided specific recommendations to properly guide the delivery of HSCT in this context, whilst maintaining quality and cautiously balancing risks and benefits against alternative non-transplant treatment options. However, specific data on COVID-19 after treatment with HSCT in patients affected by autoimmune diseases (ADs), using more immunosuppressive transplant regimens than other indications, are still lacking.

Methods: This multicenter observational study of the EBMT reported clinical data on COVID-19 infection in 11 patients affected by severe ADs treated with HSCT ($n = 3$ allogeneic transplant; n = 8 autologous transplant). Underlying disease were Systemic Sclerosis ($n = 5$), Multiple Sclerosis ($n = 3$), Behcet syndrome ($n = 1$), juvenile idiopathic arthritis (systemic Still's disease, $n = 1$), neuromyelitis optica ($n = 1$). At time of COVID-19, eight patients were in complete disease remission and 3 patients in disease activity/progression. The median age of patients at COVID-19 diagnosis was 41 years (range 13–67; only one patient with age <18 years).

Results: COVID-19 diagnosis (Table 1) were reported between March 2020 and May 2022 (4 cases in 2020, 3 cases in 2021 and 4 cases in 2022). Median time from transplant to COVID-19 diagnosis was 422 days (range 8–4736). Overall, 3 patients were vaccinated against SARS-Cov-2 with the BNT162b2 vaccine (Pfizer, BioNTech), and developed the infection at a median 228 days between first dose vaccine and COVID-19. Levels of vaccine-specific antibodies before infection were not evaluated. All patients were symptomatic with 5 patients reporting upper respiratory symptoms, 3 patients cough without oxygen requirement, and 6 patients exhibited other symptoms ($n = 6$ fever, $n = 3$ asthenia, $n = 2$ myalgia and/or arthralgia, $n = 2$ gastrointestinal symptoms, $n = 2$ loss of taste and smell). At COVID-19 onset, 2 patients had neutrophil counts below 0.5×109/L, while one patient had lymphocyte counts below 0.5 x 109/L and 3 patients had lymphocyte counts between 0.5 and 1.0×109/L. Four cases developed a lower respiratory tract disease (LRTD). Hospitalization was required in 6 cases, without necessity of intensive care unit (ICU) admission and/or ventilation/oxygen. Different interventions were adopted: remdesivir ($n = 1$), nirmatrelvir/ritonavir ($n = 1$), sotrovimab ($n = 1$), immunoglobulins ($n = 1$). No additional steroid use was administered during the infection. At the last follow-up, all patients clinically solved the infection and are alive. Ten patients had virologic and one patient had clinical resolution but was not retested with PCR. Finally, all cases were classified as having mild/moderate COVID-19.

	Allogeneic ($N = 3$)	Autologous ($N = 8$)	Overall ($N = 11$)
Asymptomatic			
No	3 (100%)	8 (100%)	11 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
COVID-19 treatment			
No	1 (33.3%)	6 (75.0%)	7 (63.6%)
Yes	2 (66.7%)	2 (25.0%)	4 (36.4%)

	Allogeneic (N = 3)	Autologous (N = 8)	Overall (N = 11)
Hospitalization during COVID -19			
No (outpatient)	2 (66.7%)	3 (37.5%)	5 (45.5%)
Yes	1 (33.3%)	5 (62.5%)	6 (54.5%)
Intensive care unit admission			
No	3 (100%)	8 (100%)	11 (100%)
LRTD			
Possible	0 (0%)	2 (25.0%)	2 (18.2%)
Proven	1 (33.3%)	1 (12.5%)	2 (18.2%)
Use of ventilation			
No	3 (100%)	8 (100%)	11 (100%)
Last known COVID-19 status			
Alive, virologically and clinically resolved	3 (100%)	7 (87.5%)	10 (90.9%)
Alive, clinically resolved	0 (0%)	1 (12.5%)	1 (9.1%)?

Conclusions: Specific EBMT guidelines have potentially contributed to contain numbers of COVID-19 in AD population treated with HSCT. The current analysis describing the mild-moderate course of COVID-19 and 100% survival after infection in transplant recipients affected by ADs, similar to the course observed in ADs under standard treatments, provides useful information to support the delivery of HSCT programs in the context of pandemic. Vaccination and new treatments available for SARS-CoV-2 infection may be useful to further minimize the infectious risks.

Clinical Trial Registry: NA. The study was conducted on behalf of the European Society for Blood and Marrow Transplantation (EBMT) COVID19 Task Force, Autoimmune Diseases Working Party (ADWP) and Infectious Diseases Working Party (IDWP).

Disclosure: All authors have no competing interests directly related to this manuscript.

21 - Autoimmune Diseases

O031

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR MS. THE DUTCH EXPERIENCE OF PATIENTS GOING ABROAD

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Background: Until very recently, autologous hematopoietic stem cell transplantation (aHSCT) for MS was not provided in the Netherlands, resulting in numerous Dutch patients with MS going abroad at their own expense to fee for service clinics for aHSCT.

There is no insight into the number of patients and their diagnosis who have undergone an HSCT abroad, and in the number of people who have plans to go.

Methods: Via (social) media communities and the Dutch MS society, patients with MS were requested to fill out a questionnaire about aHSCT treatment abroad.

Results: 481 patients responded to the call (386 female, 80%). Of these, 135 (28.1%) had undergone aHSCT (treated group) and 346 (71.9%) had considered treatment (planned group).

Of the planned group, 10.9% ultimately decided not to undergo aHSCT, and 176 (51.9%) patients indicated that they are waiting with their final decision until aHSCT in the Netherlands has been approved.

The treated group consisted of 51 (38%) patients with RRMS, 46 (38%) with SPMS, and 31 (34%) with PPMS. The planned group consisted of 241 (70%) patients with RRMS, 50 (14%) with SPMS, and 41 (12%) with PPMS Most patients were treated in Russia 76 (57%) or Mexico 42 (31%). Eight were treated in India (6%) and the remaining 6% elsewhere.

Most patients rely on social media to choose a particular clinic. Remarkable is the high EDSS score in the treated group: 62% has an EDSS score of 5,5 or higher. Within the treated group, 77% decided for aHSCT regardless of their treating neurologist's opinion. 24% of patients who returned home didn't receive aftercare from a hematologist or neurologist.

Within the treated group, 22 patients (16%) were treatment naïve and 56 (42%) were on second line MS treatment. Two patients died during treatment (India), and two underwent euthanasia in a later stage after aHSCT. In the planned group, 125 (93%) patients indicated that, in hindsight, they would make the same decision. Four patients indicated that it was too early after the treatment to answer this question. Two patients regretted their decision. 84% reported no new disease activity since aHSCT and 57% reported an improvement in disability. 24% of patients who returned home after aHSCT did not receive aftercare from a neurology or hematology clinic.

In none of the cases, the health insurance contributed to financing the treatment.

Conclusions: Many Dutch MS patients seek aHSCT treatment abroad, usually regardless of the advice of their treating physician. While in the past years many patients had progressive MS in recent years there seems to be a shift towards RRMS. A striking number of patients had not undergone any previous treatment.

Although HSCT will very soon be available in the Netherlands for selected cases, we expect the flow of patients going abroad to continue. Expert coaching with the attention to aftercare of people going abroad for this high-risk treatment remains necessary for better safety. A central registration is needed for the registration of side effects.

Disclosure: This study was not sponsored.

P.A. Kramer and GJ Hengstman are members of the medical advisory committee of the Dutch MS society which is involved in the reimbursement application for AHSCT in The Netherlands. P.A. Kramer received a speakers fee from Sanofi Genzyme. G.J. Hengstman gives paid and unpaid, asked, and not- asked advice to several MS patient support groups and all pharmaceutical companies with licensed medications for MS. C.W. Choi, T Berkx and B. Platel have nothing to disclose related to this poster.

21 - Autoimmune Diseases

O032

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION MODULATES THE INFLAMMATION-FIBROSIS PATHOLOGICAL AXIS IN SYSTEMIC SCLEROSIS PATIENTS

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Background: Autologous hematopoietic stem cell transplantation (auto-HSCT) has shown substantial impact on skin fibrosis of systemic sclerosis (SSc) patients. However, how auto-HSCT affects the immune pathways associated with fibrosis is not entirely known. Here, we aimed to investigate if auto-HSCT affects mechanisms associated with the inflammation-fibrosis axis in the skin and serum of SSc patients.

Methods: Clinical data, serum samples, and skin biopsies from 24 SSc patients who underwent auto-HSCT were collected and retrospectively evaluated. Serum from SSc patients before and after (6 months) transplantation and serum from healthy control subjects were used to evaluate levels of chemokines (CCL-2 and CCL-3), epidermal growth factor (EGF), and hepatocyte growth factor (HGF) by Multiplex assay. Skin biopsies obtained from the dorsal mid-forearms of SSc patients were assessed for epidermal thickness.

Results: Most participants were female (87%), with a mean (standard deviation, SD) age of 39.13 (±8.94) years and a mean time from diagnosis of 39.38 (± 27.58) months. SSc patients after auto-HSCT had improvement of the skin fibrosis ($p = 0.006$) measured by modified Rodnan's skin score (from mean 27 at baseline to 18 post-transplantation). Histological analyses showed that epidermal thickness in SSc patients decreased ($p = 0.03$) significantly after auto-HSCT compared to baseline, indicating a decrease of irregular acanthosis. Serum levels of CCL-2 and HGF in SSc patients were not different from healthy controls and did not change after auto-HSCT. EGF and CCL-3 serum levels from SSc patients were higher at baseline ($p = 0.002$ and $p = 0.04$, respectively) compared to healthy controls, decreasing ($p = 0.04$ and $p = 0.03$, respectively) and normalizing after auto-HSCT.

Conclusions: Auto-HSCT for SSc improves cutaneous fibrosis, decreases epidermal thickness, and diminishes serum concentrations of EGF and CCL-3. These results suggest that auto-HSCT affects inflammation-fibrosis-related mechanisms. Decreasing CCL-3 may indicate less leukocyte homing, reflecting less inflammation and accumulation of extracellular matrix in the tissue. The reduced epidermal thickness and diminished EGF serum levels after auto-HSCT suggest an effect of the procedure on the epidermal compartment. Beyond immune resetting, auto-HSCT may have additional therapeutic pathways that target skin cells, mirroring the clinical outcomes of SSc patients.

Disclosure: Nothing to declare.

21 - Autoimmune Diseases

O033

THYROID DISEASES POST AUTOLOGOUS STEM CELL TRANSPLANTATION FOR AUTO-IMMUNE A DISEASE: A RETROSPECTIVE COHORT STUDY

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Background: Thyroid disorder is frequent after autologous stem cell transplantation (AHSCT) for autoimmune indications (AI) but the exact incidence and predisposing factors are unknown.

Methods: A retrospective analysis of all AHSCT recipients for AI at The Ottawa Hospital between March 1999 to December 2020 was performed to calculate the incidence and predisposing factors of thyroid disease (TD) after AHSCT, defined as hypo- or hyperthyroidism requiring treatment. The cut-off date for data extraction was May 31, 2021. The data extracted from the medical record included the age, sex, co-morbidities including pre-existing TD, smoking status, transplant indication, autologous hematopoietic stem cell (AHSC) mobilisation regimen, number of AHSC collections, year of AHSC collection, whether CD34 graft selection was performed, year of AHSCT, age at AHSCT, number of AHSCT, AHSCT conditioning regimen, CD34+ cell dose infused, year of onset of thyroid disorder, smoking status after aHSCT, final diagnosis of TD, and details of treatment of TD. Incidence of TD before and after AHSCT, in the first 5 years after AHSCT and from 5 years after AHSCT to the end of follow-up were calculated. Logistic regression was performed to estimate the association between individual, disease and AHSCT factors and the occurrence of TD.

Results: The incidence of TD before AHSCT was 2.6/1000 PY. Twenty-six patients (17.9% of the cohort) developed TD, 18 patients were treated for hypothyroidism, 8 for hyperthyroidism. The incidence of TD after AHSCT is 37.3/1000 patient-year (PY) follow-up. The incidence is 56.0/1000 PY in the first 5 years after AHSCT dropping to 7.5/1000 PY after 5 years until the end of the follow-up. Female sex (OR 2.71 [1.09–6.71] $p = 0.03$) was the sole factor associated with TD development.

Conclusions: TD is frequent especially in the 5 years after AHSCT. Female sex was the only predisposing factor identified although the size of the cohort may have precluded identification of other factors that may be related to the onset of TD after AHSCT. TD is common in this population before AHSCT, indicating a genetic and/or immunologic predisposition to developing TD. A screening of TD should be performed before and after AHSCT.

Disclosure: None

21 - Autoimmune Diseases

O034

INFLAMMATION AND IMMUNOREGULATION-RELATED MOLECULES IN THE SERUM OF PATIENTS WITH SYSTEMIC SCLEROSIS TREATED WITH AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Systemic sclerosis (SSc) is an autoimmune disease characterized by a pathological triad of microvasculopathy, immunological abnormalities, and excessive collagen production resulting in fibrosis of the skin and internal organs. Autologous hematopoietic stem cell transplantation (auto-HSCT) is a therapeutic option for patients with severe and progressive SSc, promoting the resetting of the immune system and the reestablishment of self-tolerance. Here, we aimed to investigate how auto-HSCT influences serum levels of molecules related to inflammation and immunoregulation in patients with SSc.

Methods: Serum samples and clinical data from 14 patients were collected before, 12, and 24 months after auto-HSCT. The concentrations of IL-4, IL-5, IL-6, IL-13, TNF-α, IL-2, IL-1, IL-17, IL-31,

IL-33, IL-35, IFN-γ, and IL-10 were measured by Multiplex assay. Eight healthy controls were included to compare serum markers.

Results: Most participants were female (78%), with mean (standard deviation, SD) age of 31 (± 11.2) years. After auto-HSCT, the modified Rodnan skin score (mRSS) decreased at 12 and 24 months ($p < 0.05$); ($p < 0.01$), compared to baseline (pre-transplant). Serum levels of IL-6, IL-17, IL-4, IL-1, IL-2, and IL-5 were elevated in all transplant periods compared to controls ($p < 0.05$) and did not change after auto-HSCT ($p > 0.05$). Serum IFN-γ levels were elevated only at baseline compared to healthy controls ($p = 0.0005$). After auto-HSCT, serum IFN-γ levels decreased at 12 months compared to baseline ($p < 0.05$). Serum IL-10 levels were elevated only at 12 months after auto-HSCT compared to healthy controls ($p > 0.05$). After auto-HSCT, serum IL-10 levels increased at 12 ($p < 0.05$); and 24 ($p < 0.01$) months compared to baseline, also increasing from 12 to 24 months ($p < 0.05$).

Conclusions: Our results show that some pro-inflammatory molecules were elevated at baseline, not returning to healthy control levels after auto-HSCT, except for IFN-γ. Auto-HSCT significantly increased serum concentrations of IL-10, an anti-inflammatory cytokine with an essential role in mechanisms of immunoregulation. Thus, we believe that IL-10 reflects an improvement in the regulatory network after transplantation, limiting inflammatory responses. This effect may be associated with better prognosis and disease remission in patients.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

O035

A REPRODUCIBLE INFLAMMATORY BIOMARKER SIGNATURE IDENTIFIES NON-HODGKIN LYMPHOMA PATIENTS AT HIGH RISK OF CAR-T TREATMENT FAILURE ACROSS DIFFERENT COHORTS

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Background: Relapse and progression affect over 50% of large-B cell lymphoma (LBCL) patients treated with CD19-directed CAR-T cells as an advanced treatment line. Here, using an unsupervised learning approach, we identify reproducible biological signatures associated with an increased risk of CAR-T treatment failure.

Methods: We applied an unsupervised Gaussian Mixture Model (GMM) to identify clusters based on standard laboratory and cytokine measurements collected from LBCL patients (Center 1 Development Cohort; $n = 171$ [**Table 1**]) on the day of (but preceding) CD19-CAR-T infusion. We then evaluated the clusters defined by this model in two validation cohorts including an independent cohort of CAR-T-treated LBCL and mantle cell lymphoma (MCL) patients from the same center (Center 1 Validation Cohort; $n = 54$), and an independent cohort of LBCL from another center (Center 2 Validation Cohort; $n = 141$). We evaluated the relationship between clusters and CAR-T efficacy-related outcomes in all three cohorts.

Table 1. Population Characteristics

	Center1 Development	Center1 Validation	Center2 Validation
Sample size, *n*	171	54	141
Disease, *n* (%)			
Large B-Cell Lymphoma	171 (100)	26 (48)	141 (100)
Mantle Cell Lymphoma	0 (0)	28 (52)	0 (0)
Age, median (IQR)	66 (56–72)	64 (56–72)	60 (48–70)
KPS ≥ 90, *n* (%)	42 (25)	19 (37)	117 (76)
Primary refractory disease, *n* (%)	59 (35)	25 (47)	82 (55)
CAR-T Product, *n* (%)			
Axicabtagene ciloleucel	90 (53)	19 (35)	39 (28)
Lisocabtagene maraleucel	25 (14)	23 (43)	0 (0)
Tisagenlecluecel	56 (33)	1 (2)	36 (26)
Point-of-care CD19-directed CAR-T	0 (0)	0 (0)	66 (47)
Brexucabtagene Autoleucel	0 (0)	11 (20)	0 (0)

Results: An unsupervised GMM approach, applied on day 0 laboratory and cytokine measurements, identified two distinct clusters termed as inflammatory ($n = 47$, 27%) and non-inflammatory ($n = 124$, 73%) in the Center 1 Development Cohort. The inflammatory cluster was enriched for elevated inflammatory markers (e.g., IL-6, TNFa, and ferritin) and lower blood counts and albumin. A similar distribution of inflammatory and non-inflammatory clusters was observed in the Center 1 Validation Cohort ($n = 21$ (36%) and $n = 38$ (64%), respectively). In the development and validation cohorts from Center 1, the inflammatory cluster had an increased likelihood of not achieving a complete response (CR) after CD19-CAR-T. Overall survival was also reduced in the inflammatory cluster in development cohort 1.

Since day 0 labs were absent for Center 2, we developed and validated in cohort 1 a machine learning (random forest) model to infer day 0 clusters. The model was based on pre-lymphodepletion features and had high discrimination (AUC = 0.92). In the Center 2 Validation Cohort, 98/141 of patients (64%) were predicted as non-inflammatory. As with the Center 1 Development Cohort 1, the predicted inflammatory cluster was associated with inferior response and overall survival.

Conclusions: Applying an unsupervised model towards pre-infusion laboratory biomarkers, we defined a cluster of patients with LBCL at high risk for CAR-T failure. This model is generalizable across treatment centers and to patients with mantle cell lymphoma and could guide decision-making prior to CAR-T infusion to preempt early inflammation and disease relapse in high-risk subgroups.

Disclosure: **Perales:** *Astellas:* Honoraria; *AbbVie:* Honoraria; *Sellas Life Sciences:* Consultancy; *Kite:* Honoraria, Research Funding; *Merck:* Consultancy; *Miltenyi Biotec:* Consultancy, Honoraria; *Novartis:* Honoraria; *Nektar Therapeutics:* Consultancy, Honoraria; *Omeros:* Consultancy; Honoraria; *VectivBio AG:* Honoraria; *Orca Bio:* Consultancy; *Karyopharm:* Honoraria; *Celgene:* Honoraria; *MorphoSys:* Consultancy, Honoraria; *Cidara Therapeutics:* Consultancy; *Takeda:* Honoraria; *Medigene:* Consultancy **Giralt:** *Amgen, Actinium, Celgene, Kite, Janssen, Spectrum Pharma, Takeda:* Membership on an entity's Board of Directors or advisory committees; *Amgen, Actinium, Celgene, Johnson & Johnson, Miltenyi, Omeros, Takeda:* Research Funding; *BMS, Sanofi, Pfizer, GSK:* Membership on an entity's Board of Directors or advisory committees. **Jacoby:** *Novartis:* Membership on an entity's Board

of Directors or advisory committees. **Lin:** *Magenta Therapeutics:* Consultancy; *Kite, A Gilead Company:* Consultancy. **Palomba:** *BeiGene:* Consultancy; *Ceramedix:* Consultancy. **Salles:** *Roche/Genentech, Gilead Sciences, Janssen, Celgene, Novartis, MorphoSys AG, Epizyme, Bristol Myers Squibb, Kite, a Gilead Company, Loxo, Rapt:* Consultancy; *Roche/Genentech, Janssen, Celgene, Gilead Sciences, Amgen, Bayer, Epizyme, Regeneron, Kite, a Gilead Company:* Honoraria; *AbbVie, BeiGene, Bristol Myers Squibb, Incyte, Kite, a Gilead Company, Miltenyi*, Membership on an entity's Board of Directors or advisory committees. **Scordo:** *Medscape, LCC:* Honoraria; *i3Health:* Honoraria; *Amgen, Inc.:* Research Funding; *Omeros Corporation:* Consultancy, Research Funding; *Angiocrine Bioscience, Inc.:* Consultancy, Research Funding; **hah:** *Amgen:* Research Funding; *Beyond Spring:* Research Funding; *Janssen:* Research Funding. **Slingerland:** *Seres Therapeutics:* **Avigdor:** *Takeda, Gilead, Novartis*. **van den Brink:** *Rheos Medicines:* Honoraria; *Pluto Therapeutics:* Current holder of *stock options* in a privately-held company, Honoraria; *Notch Therapeutics:* Current holder of *stock options* in a privately-held company, Honoraria; *Frazier Healthcare Partners:* Honoraria; *Nektar Therapeutics:* Honoraria; *Ceramedix:* Honoraria; *Lygenesis:* Honoraria; *GlaskoSmithKline:* Honoraria; *Da Volterra:* Honoraria; *Thymofox:* Honoraria; *Garuda:* Honoraria;: Honoraria; *Juno Therapeutics:* Other: IP Licensing ; *DKMS:* Other: fiduciary role on the Foundation Board ; *Wolters Kluwer:* Patents & Royalties; *Seres Therapeutics:* Current holder of *stock options* in a privately-held company, Honoraria. **Shouval:** *Medexus:* Consultancy; *MyBiotics:* Consultancy.

4 - CAR-based Cellular Therapy – Clinical

O036

DUAL ANTIGEN TARGETING WITH CO-TRANSDUCED CD19/22 CAR T CELLS MAY PREVENT ANTIGEN-NEGATIVE RELAPSE AFTER CAR T CELL THERAPY FOR RELAPSED/REFRACTORY ALL

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Background: CD19-negative escape is a major cause of relapse after CD19 CAR T cell therapy for relapsed/refractory (r/r) paediatric ALL and dual targeting of CD19/CD22 may overcome this. We developed AUTO1/22 an autologous CAR T cell product co-transduced with 2 different lentiviral vectors encoding a previously described fast-off rate CD19 CAR and a novel CD22CAR designed to recognise targets with low antigen density. We evaluated safety/efficacy of AUTO1/22 in a Phase I study in children/young adults with r/rALL (NCT02443831).

Methods: Patients with r/r B-ALL age <25 years who were ineligible for/relapsed after Tisagenlecleucel were recruited. Following fludarabine/cyclophosphamide lymphodepletion, patients received 1×10^6 /kg CAR^+ T cells. Primary endpoints were incidence of grade 3–5 toxicity and the proportion of patients achieving MRD negative remission.

Results: 12 patients have been treated and are evaluable with >1 month follow-up. The median age was 12 years and patients had a median of 3 (range 2–6) prior lines of therapy. Six of 12 patients had relapsed post allogeneic stem cell transplant (SCT), 6 had received prior Blinatumomab/Inotuzumab and 4 had relapsed after prior Tisagenlecleucel. Prior to lymphodepletion, 4 patients had >5% BM disease, 5 had MRD level disease, 3 were MRD negative. Six patients had extramedullary relapse and 3 had detectable CD19 negative disease. Cytokine release syndrome (CRS) occurred in 11/12 patients (grade 1 $n = 5$, grade 2 $n = 6$) requiring Tocilizumab in 4 cases, but there was no severe (≥ grade 3) CRS. Self-resolving grade 1-2 ICANS was observed in 5 patients. One patient had delayed onset grade 4 leucoencephalopathy (MRI/brain biopsy were more indicative of fludarabine toxicity than CAR T related) and has ongoing neurological recovery. Ten patients had grade 3–4 cytopenia persisting beyond/recurring after day 28, requiring a CD34+ stem cell top up in 1 case. Ten of 12 evaluable patients (83%) achieved MRD negative CR/CRi at 1 month post-infusion and 2 patients did not respond. Importantly 2/3 patients with CD19-ve disease achieved molecular CR. Of the 10 responding patients, 3 have relapsed with CD19 + CD22+ disease, 2 had emergence of MRD level disease and received further treatment, 2 had loss of CART cell persistence at 3 and 4 months post-infusion and went on to receive further treatment. With a median follow-up of 8.7 months, 5/10 responding patients remain alive in MRD negative CR. Median duration of remission in responding patients was 9.9 months. The overall survival rate at 6 and 12 months remained at 75% (95% CI: 41–91%). The 6 and 12 month EFS rate were 75% (95% CI: 41–91%) and 60% (95% CI: 23–84%), respectively, using the same definition of event free survival (EFS) as in the ELIANA study. Median persistence of CD19 CART and CD22 CART in peripheral blood was 5 and 7.5 months, respectively, and there was no evidence of antigen-negative relapse.

Conclusions: Dual CD19/22 targeting CAR T cells generated by co-transduction suggest a good safety profile and efficacy in a heavily pre-treated cohort of patients. Antigen-negative relapse has not been observed to date, indicating that dual targeting may be effective in preventing antigen evasion.

Clinical Trial Registry: NCT02443831

Disclosure: SG, MAP and PJA have patent rights for CAT CAR in targeting CD19 (patent application, World Intellectual Property Organization, WO 2016/139487 Al) and may receive royalties from Autolus PLC who have licensed the IP and knowhow from the CARPALL study. PJA has research funding from Bluebird Bio Inc. MAP is a shareholder in and employee of Autolus PLC, which has licensed CAT CAR.

4 - CAR-based Cellular Therapy – Clinical

O037

LONG-TERM SAFETY AND EFFICACY OF CD38-TARGETED CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY IN PATIENTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA: A SINGLE-ARM, OPEN-LABEL, PHASE 1-2 TRIAL

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Background: Chimeric antigen receptor (CAR)-T cell therapy has shown impressive results in relapsed/refractory (r/r) B cell malignancies. However, the antigenic heterogeneity, immunosuppressive milieu in the tumour microenvironment and on-target off-tumor toxicities pose barriers for clinical translation of successful immunotherapy for acute myeloid leukemia (AML). CD38 is an established immunotherapeutic target in multiple myeloma and under investigation as a target antigen in AML. Our prospective study aimed to assess the safety and efficacy of CD38-targeted chimeric antigen receptor T (CD38-CAR-T) cell therapy in patients with r/r AML.

Methods: Twenty patients with r/r AML were enrolled in this single-center, phase 1/2 clinical trial, including 9 (45%) who relapsed after allogeneic hematopoietic stem cell transplantation, and 11 patients (50%) had high-risk cytogenetic and genetic characteristics. All of them had no response to multiple lines of salvage treatments. After tumor-reduction chemotherapy and lymphodepletion regimens, a median dose of 10 (2–20) × 10^6/kg CD38-CAR-T cells was infused at dose escalation within 4 days.

Results: The day 28 after CD38-CAR-T cells infusion, fourteen patients (70.0%) had a complete remission (CR) or CR with incomplete hematologic recovery. Ten patients (50%) achieved minimal residual disease negative CR. A total of 14 patients (70.0%) occurred cytokine release syndrome, including grade 1 or 2 in 12 patients (60.0%) and grade 3 in 2 patients (10.0%). No case of neurotoxicity was observed. The grade 3–4 hematologic toxic effects were the most common events. Two patients experienced grade 3 hepatotoxicity. All adverse events were manageable. The median overall survival of 20 patients was 10.7 months, the median event-free survival was 5.9 months, and the 2-year cumulative incidence of relapse was 45.6%. The proportion of CD3 + PD-1+ and CD8 + PD-1 + T-cells at 28 days after CAR-T treatment were significant decreased than that of prior treatment (12.93% vs 49.68%, $P = 0.0120$; 3.83% vs 37.72%, $P = 0.0256$, respectively). The CR patients had higher proportion of CD3 + PD-1+ and CD4 + PD-1 + T-cells than that of NR patients before CD38-CAR-T treatment (49.68% vs 12.75%, $P = 0.0238$; 52.49% vs 11.08%, $P = 0.0476$, respectively).

Conclusions: Our prospective study showed that CD38-CAR-T cell therapy was a potential effective and safe treatment option for r/r AML patients (ClinicalTrials. gov number, NCT04351022). This study also described the immunomodulatory effects of CD38-CAR-T through the reduction of CD3 + PD-1 + T-cells immunosuppressive cellular populations.

Clinical Trial Registry: NCT04351022
https://clinicaltrials.gov/ct2/show/NCT04351022

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

O038

ACUTE LYMPHOBLASTIC LEUKEMIA: CD19-CAR-T CELLS ARE AN EFFECTIVE THERAPY FOR POSTTRANSPLANT RELAPSE

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Background: Relapse remains the major cause for treatment failure in patients with ALL who were treated with alloHSCT. Relapse after alloHSCT has l a very poor prognosis, with a probability of event-free survival of only 15-30%. Tisagenlecleucel (Tisa-cel) is a commercial CD19-directed CAR-T cell product licensed for the treatment or post-transplant relapse in CD19 positive ALL.

Methods: We performed a retrospective study between 09/18 and 01/22 in patients with pB-ALL relapse after alloHSCT who received CAR-T cell treatment with Tisa-cel according to approval by the European Medicinal Agency (EMA). The study was approved by the Ethics Committee of the University of Frankfurt/Main (No.: 2021-376).

65 patients with relapse after alloHSCT were included. The median age was 10 years (range: 1.0–25.0 years). Thirty-three patients (52%) had isolated bone marrow (BM) relapse, (8%) patients had CNS involvement. Ten patients (15%) had combined BM and CNS, and in 16 patients (25%) other manifestations, such as testis, skin, kidney, or various combinations, were affected. At the time lymphodepleting chemotherapy (LDC) was started, 33 patients (51%) had <5% leukemia blasts, and 32 patients (49%) had >5% leukemia blasts.

Results: CRS and ICANS

Cytokine release syndrome (CRS) was observed in 37 (57%) patients (grade I-II: $n = 38$ (58%), grade III-IV: $n = 2$ (3%) and grade V: $n = 2$ (3%). Five (7%) patients developed ICANS (grade I: $n = 2$, grade III-IV: $n = 3$).

Response and Survival

The pEFS were 43.4% (±7.1) and 53.2% (±7.7) for pOS. For CAR-T cell responders, the two-year pRFS was 48.6% (±7.7), and the two-year duration of B-cell aplasia (pDBA) was 45.0% (±9.5%). Patients relapsing within 6 months after alloHSCT had a pEFS of 18.4% (±10.1%) (median follow-up of 28.8 months (1.5–38.5) compared with those relapsing beyond 6 months after alloHSCT at 55.5% (±8.8%) ($p < 0.001$) (median follow-up: 20.6 months; range 0.6–44.7).

This corresponded to a pOS of 16.0% (±9.8%) and 74.8% (±8.0%) ($p < 0.001$) and a pRFS of 25.2% (±13.5%) and 56.8% (±8.9%) ($p = 0.019$) for patients relapsing within 6 months and beyond 6 months, respectively.

Cumulative incidence of relapse (CIR) for patients who had relapsed within 6 months of alloHSCT was 68.5% (±14.1%) compared with only 37.1% (±8.6%) for those who had relapsed

beyond 6 months ($p = 0.026$). Patients who relapsed within 6 months after alloHSCT tended to develop CD19-positive relapse (CIR 46.6%) compared with patients who relapsed beyond 6 months (CIR 26.9%) ($P = 0.093$).

We observed that patients who relapsed within 6 months from alloHSCT showed a duration of B-cell aplasia (pDBA) of 19.3% at two years, in contrast to patients who relapsed >6 months from alloHSCT, who had a pDBA of 53.8% at 2 years ($p = 0.008$).

Conclusions: The majority of patients could be rescued with an infusion of CAR-T cells. Patients who relapsed ≥6 months from HSCT have an excellent prognosis with only a single Tisa-cel infusion without further consolidation. Early loss of CAR-T cells allowing B-cells to regenerate may be a reflection of a skewed T-cell repertoire early after alloHSCT. These findings may become relevant for further clinical decision making.

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MH declares no conflict of interest.

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HE declares honoraria from BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, and Novartis; consultancy and advisory board participation with Amgen, BMS/Celgene, Janssen, Takeda, Sanofi, and GSK, Novartis; research funding by BMS/Celgene, Janssen, Amgen, GSK, and Sanofi; and travel support by BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, and Novartis.

UH declares honoraria and consultancies: BMS/Celgene, Kite/Gilead, and Novartis.

CK declares advisory boards: Abbvie, Amgen, BMS, EusaPharm, GSK, Janssen, Kite/Gilead, Medigene, Novartis, Roche, Sanofi, Takeda, Pfizer, and Incyte.

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TF declares no conflict of interest.

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4 - CAR-based Cellular Therapy – Clinical

O039

HIGH SAFETY AND EFFICACY OF ANTI-CD7 CAR-T CELLS IN TREATING RELAPSED OR REFRACTORY CD7 + ACUTE MYELOID LEUKEMIA: FIRST-IN-HUMAN PHASE I STUDY

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Background: The survival rate for patients with relapsed and refractory acute myeloid leukaemia (R/R AML) remains poor, and treatment is challenging. Chimeric antigen receptor T (CAR-T) cells have been widely used for haematologic malignancies. Current CAR-T therapies for AML mostly target myeloid-lineage antigens, such as CD123, CLL1 and CD33, which may be associated with potential haematopoietic toxicity. CD7 is also expressed in 30% of AML patients. Anti-CD7 CAR T-cells had demonstrated encouraging efficacy in xenograft models of AML. We report here on the use of anti-CD7 CAR T-cells in the treatment of R/R AML patients.

Methods: This single-arm phase I dose escalation clinical trial evaluates anti-CD7 CAR-T cells in patients with CD7 + R/R AML. Patients with R/R AML underwent leukapheresis and a lymphodepletion chemotherapy with cyclophosphamide and fludarabine or etoposide before CAR-T cell infusion. Dose escalation are based on 3 + 3 escalation rule, including 2 cohorts: 2×10^6/kg and 4×10^6/kg. The primary endpoint was the incidence of dose-limiting toxicities. The secondary endpoint was the proportion of patients achieving an objective response (i.e., the combined proportion of participants who had a complete response) as per investigator's assessment.

Results: Nine participants received infusions. No DLT was found. Adverse events including cytokine release syndrome grade 1-2 occurred in all patients ($n = 9$) and cytopenia grade 3–4 in 100% ($n = 9$), neurotoxicity grade 1-2 in 11.1% ($n = 1$), and viral activation grade 1-2 in 22.2% ($n = 2$). All adverse events were reversible. 66.7% ($n = 6$) achieved CR/CRi with 3 patients proceeding to stem-cell transplantation. For 3 patients who did not achieve CR/CRi, one patients with FLT3/ITD mutation progressed soon without CAR-T cell expansion. Two patients progressed with CD7 negative AML cells. Anti-CD7 CAR-T cells

expanded dramatically in 8 patients. At a median follow-up of 5.4 months (range 1.0-9.8), 5 remained in remission. We found that the patients' CD7-positive normal T cells were depleted, CD7-negative T cells expanded dramatically.

Conclusions: In this first-in-human study of anti-CD7 CAR-T cells for R/R AML, anti-CD7 CAR-T cells exhibited promising efficacy with manageable toxicity profile. A phase II trial of anti-CD7 CAR-T cells in larger patient cohorts is needed.

Clinical Trial Registry: NCT04599556

Disclosure: Nothing to declare

4 - CAR-based Cellular Therapy – Clinical

O040

CD19 CART-CELL THERAPY FOR ADULTS WITH B-ALL: A LARGE REAL-WORLD SERIES FROM ACUTE LEUKEMIA WORKING PARTY OF THE EBMT

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Background: CD19-directed genetically modified T-cell immunotherapy represents a breakthrough treatment for relapsed and refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) and has been used significantly over the past four years since it was approved by the EMA. Initially, tisagenlecleucel was approved for the treatment of patients up to 25 years of age with B-ALL that is refractory or in second or later relapse. More recently, commercial and academic CD19 CAR-T cells have been used in adult patients. The European Society for Blood and Marrow Transplantation (EBMT) received a regulatory qualification from the European Medicines Agency for using its patient registry to support post-authorization safety studies. The EBMT CAR-T cell Registry was developed to collect long-term safety and efficacy information on recipients of cellular immunotherapies and is used as a post-marketing study in the real-world setting.

Methods: Patients aged 18 years or older who received a first infusion of CD19 CAR-T cells for B-ALL between 2018 and May 2021 were included. Clinical data from the EBMT registry were analyzed for baseline information. Efficacy and safety data were presented for patients with a median of 1 year of follow-up.

Results: Baseline and comprehensive information were available for 118 patients with a median follow-up of 12.4 months (95% CI: 11.6–16.2). The median age was 23.8 years (range, 18.2–67.1). Sixty-for percent were male and 63.9% had a Karnofsky score ≥90. Seventy-one percent received CAR-T cells for Philadelphia chromosome-negative (Ph-) B-ALL and 29% for Ph+ ALL (63 data missing). Most patients (82%) were not in complete remission (CR), 3% were in CR1, 7% were in CR2 and 8% were in ≥CR3. Twenty-seven percent of the patients had not received a previous allogeneic hematopoietic cell transplant (allo-HCT), 58% had received one allo-HCT, and 14% two allo-HCTs. More than 80% of CD19 CAR-T cells were commercial. Lymphodepletion regimen was mostly an association of fludarabine and cyclophosphamide (98%). Almost 88% of the patients developed a cytokine release syndrome (CRS), starting at a median of 3 days post-treatment (range, 0–27) (1/3 data msising). CR was obtained in 91% of patients. Overall survival at 12 months was 88.9% for patients who received CAR-T cells in CR, and 61.9% for non-CR patients. Leukemia-free survival at 12 months was 65.8% for patients in CR, and 38.7% for non-CR patients. Relapse incidence at 12 months was 34.2% in CR patients and 57.2% in non-CR patients. Cumulative incidence of non-relapse mortality at 12 months was 0% in CR patients, and 4% in non-CR patients. Forty-six patients died. Recurrence of the original disease was the main cause of death (79%), while infections represented 4.7% ($n = 2$) of the deaths, and 9.3% ($n = 4$) of deaths were cell therapy related.

Conclusions: The EBMT registry offers access to real-world data, in this analysis focusing on the treatment of adult patients with B-ALL treated with commercial or academic CD19 CAR-T cells. Such large multicenter and multinational real-world evidence demonstrates the feasibility of CAR-T cell therapy at a larger scale. The results were in line with those from registration trials evaluating approved and commercial products.

Disclosure: EB: Research funding, honorarium, speaker's fees and travel expenses from Novartis, Astellas, Alexion, Jazz Pharmaceuticals, Gilead, MSD, Keocyt, Amgen

3 - CAR-based Cellular Therapy – Preclinical

O041

BCMA AND CD229 DUAL-TARGETED CAR T CELL EFFECTIVELY CONTROLS MULTIPLE MYELOMA WITH LOSS OF BCMA EXPRESSION

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Background: Chimeric antigen receptor (CAR) T cells against BCMA have shown promising results in patients with relapsed/refractory multiple myeloma (MM). However, many patients will relapse. MM cells with negative or low BCMA expression are implicated as a reservoir preceding relapse or can appear after the immune pressure exerted by CARTs. Several approaches are being explored to overcome these hurdles, such as targeting novel myeloma antigens or manufacturing CARTs against two antigens simultaneously. At our institution, we have developed an academic BCMA-BBζ CART product (ARI2h; NCT04309981) for relapsed/refractory MM patients with encouraging results. Also, we have developed antibodies against CD229, which is homogenously expressed in MM cells and is essential for myeloma cell survival. The objective of this study is to develop a monospecific CD229 CART cell product with the subsequent generation of a bicistronic BCMA/CD229 CART cell to avoid relapses due to loss of BCMA.

Methods: A monoclonal antibody against the 2nd extracellular domain of CD229 was obtained by hybridoma clone. Two single-chain variable fragments domains were generated with the sequences of the heavy and light variable regions of the antibody. After this, two second-generation CD229 CARs with a 4-1BB costimulatory domain were designed. Both CD229 CART cell products (CD229-VHVL-BBζ and CD229-VLVH-BBζ) were compared with ARI2h (BCMA-BBζ).

Results: Both CD229 CART cells could proliferate, secrete cytokines, and lyse in response to myeloma cell lines that expressed $BCMA^{+}$ and $CD229^{+}$. A xenograft model with NSG mice and $U266^{wt}$ cells was used to verify the in vivo activity. We observed a better tumor control and survival advantage using CD229-VLVH-BBζ instead of CD229-VHVL-BBζ. However, the BCMA CART was still better than both anti-CD229 CARTs. To model the presence of a heterogeneous disease, we mixed bulk $MM1S^{wt}$ cells with 15% MM1S BCMA CRISPR KO ($MM1S^{BCMAKO}$) cells. The CD229-VLVH-BBζ group showed better survival compared to ARI2h.

Subsequently, two dual-targeted bicistronic CAR constructs against BCMA and CD229 were developed (CD229-VLVH-BBζ[2A] ARI2h and ARI2h[2A]CD229-VLVH-BBζ). The expression of both CARs at the surface of the same T cells was confirmed by flow cytometry. Both bicistronic CART cells could proliferate, secrete cytokines, and lyse after the coculture with tumor cell lines that exclusively expressed BCMA, CD229, or both targeted antigens ($BCMA^{+}/CD229^{-}$ [$K562^{BCMAKI}$], $BCMA^{-}/CD229^{+}$ [$MM1S^{BCMAKO}$], and $BCMA^{+}/CD229^{+}$). The xenograft mouse model using a homogenous tumor cell population ($MM1S^{wt}$) showed that both bicistronic CARTs performed effectively and similarly compared with ARI2h. In addition, the mouse model using a heterogeneous disease ($MM1S^{wt}$ 85% + $MM1S^{BCMA\ KO}$ 15%) showed that CD229-VLVH-BBζ[2A]ARI2h group was superior to ARI2h and ARI2h[2A]CD229-VLVH-BBζ in terms of tumor control and survival.

Conclusions: This is the first bispecific BCMA/CD229 CART cell that adequately controls BCMA-expressing and non-expressing myeloma cells. This approach could mitigate disease escape due to biallelic loss of BCMA.

Disclosure: Luis Gerardo Rodríguez-Lobato: Honoraria and travel grants from Janssen, Amgen, GSK and Sanofi.

Lorena Perez-Amill: Current Employment: Gyala Therapeutics S.L.

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Álvaro Urbano-Ispizua: Consultancy: Miltenyi, Celgene, Gilead.

Carlos Fernández de Larrea: Consultancy: BeiGene, Sanofi, GSK, BMS, Janssen; Honoraria: BeiGene, Pfizer, Sanofi, GSK, Takeda, BMS, Janssen; Research Funding: Takeda, Amgen, BMS, Janssen.

3 - CAR-based Cellular Therapy – Preclinical

O042

CRISPR/CAS9 KNOCKOUT OF IMMUNE CHECKPOINT RECEPTOR NKG2A IMPROVES THE ANTI-LEUKEMIC EFFICACY OF PRIMARY CD33-TARGETING CAR-NK CELLS

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Background: Acute Myeloid Leukemia (AML) still represents a severe disease with limited therapeutic options. CD33-targeting chimeric antigen receptor (CAR)-T cells already showed promising efficacy for treatment of AML. However, clinical application of CD33-CAR-T cells remains challenging due to its restriction to autologous cell preparations and potential side effects such as neurotoxicity, graft-versus-host disease and Cytokine Release Syndrom (CRS).

In contrast, natural killer (NK) cells can be safely administered to HLA-mismatched recipients without severe side effects. Recently, we reported on the successful generation of primary CD33-targeting CAR NK cells (CAR33), which are highly effective against AML in vitro as well as in AML-xenograft mouse models (Albinger et al., *Blood Cancer J* 2022). Nevertheless, CAR-NK cell function can be impaired by high levels of the inhibitory immune checkpoint receptor NKG2A (natural killer group 2A) expressed on NK cells (Bexte et al., *Oncoimmunology* 2022).

By applying a CRISPR/Cas9 gene editing for knockout (KO) of the *killer cell lectin like receptor C1* (*KLRC1)* gene, we could significantly reduce NKG2A cell surface expression. The functionality of CRISPR-modified CAR33 NK cells was significantly enhanced in vitro. CITE-Seq analysis revealed a more mature and activated gene regulation

pattern after gene-modification and CRISPR-modified CAR33 NK cells demonstrated complete elimination of AML and leukemia-initiating cells in the bone marrow in vivo.

Methods: CD33-targeting CAR-NK cells were generated by lentiviral transduction of peripheral blood-derived NK cells. KO of the NKG2A-encoding *KLRC1* locus was performed by CRISPR-Cas9 nucleofection. The CAR33- and NKG2A-expression as well as cytotoxicity were analysed using flow cytometry and IncuCyte® after feeder cell-free, IL-15/IL-2-based expansion. The in vivo-efficacy was evaluated in OCI-AML2 (GFP^+, Luc^+) xenografted NSG-SGM3 mouse models.

Results: Transduction of primary NK cells resulted in up to 60% CAR33-positive cells, while *KLRC1* gene disruption resulted in 50% reduction of NKG2A cell surface expression and gene disruption of *KLRC1* was quantified by Insertion/deletion (indel) distribution profiles by Inference of CRISPR Edits (ICE) (>93%). CITE-Seq downstream and qPCR analysis revealed a distinct gene regulation pattern in CAR33- and CAR33-*KLRC1*^{ko}-NK cells with more mature and activated NK cells.

CAR33-*KLRC1*^{ko}-NK cells showed significantly higher elimination of $CD33^+$/HLA-E^+ OCI-AML2 cells in in vitro cytotoxicity assays compared to *KLRC1*^{ko}-NK or CAR33-NK cells. Furthermore, a reduction of leukemic burden was observed in vivo following a single injection of a low dose ($3x10^6$ cells) of CAR33-*KLRC1*^{ko}-NK cells compared to *KLRC1*^{ko}-NK or CAR33-NK cell treatment in an NSG-SGM3 AML-xenograft mouse model. Importantly, two injections of $3x10^6$ CAR33-*KLRC1*^{ko}-NK cells each led to a complete elimination of AML and leukemia-initiating cells in the bone marrow. The complete deletion of bone marrow AML cells was confirmed by bone marrow re-engraftment in vivo survival analysis.

Conclusions: Removing an inhibitory receptor in CAR-NK cells showed a highly beneficial effect for the treatment of AML. This double genetic modification has the potential to enable NK cells to bypass inhibition following contact with malignant cells not only in context of AML, but also in a broad range of other malignant diseases.

Disclosure: N.M. is employee of Miltenyi Biotec. E.U. has a sponsored research project with Gilead and BMS.

N.A and T.B. contributed equally.

5 - Cellular Therapies other than CARs

O043

HLA-MATCHED TREG/TCON ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION ENSURES REMARKABLE CHRONIC GVHD/LEUKEMIA FREE SURVIVAL IN HIGH-RISK LEUKEMIA PATIENTS

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Background: No matter the donor source or conditioning regimen used, leukemia relapse is the leading cause of allogeneic hematopoietic stem cell transplantation (allo-HSCT) failure. An "age-adapted" allo-HSCT clinical protocol consisting of an irradiation-based conditioning regimen and a peripheral blood CD34+ cell graft combined with donor regulatory T cell (Treg) and conventional T cell (Tcon) adoptive immunotherapy allowed for an unprecedented (75%) chronic GvHD (cGvHD)/relapse free survival (CRFS) in patients with acute myeloid leukemia (Pierini, Blood Advances 2021). Such outcomes rivaled results of conventional HLA-matched allo-HSCT. In the present study we report outcomes of "age-adapted" allo-HSCT with Treg/Tcon adoptive immunotherapy in the HLA-matched setting.

Methods: The "age-adapted" allo-HSCT with Treg/Tcon adoptive immunotherapy clinical trial was extended to leukemia patients with an HLA-matched family donor in 2019 (clinicaltrials.gov n. NCT03977103). Acute leukemia patients received a myeloablative conditioning regimen consisting of hyperfractionated total body irradiation (HF-TBI, 13.5 Gy) or total marrow and lymphoid irradiation (TMLI, 13.5 Gy in the marrow and 11.5 Gy in the lymph nodes) according to age or comorbidities. Irradiation was followed by chemotherapy with Thiotepa, Fludarabine, and Cyclophosphamide. Patients also received donor $2x10^6$/kg freshly isolated CD4 + CD25 + FOXP3+ Tregs, $1x10^6$/kg Tcons and purified HLA-matched CD34+ hematopoietic stem cells. No post-transplant pharmacologic GvHD prophylaxis was given.

Results: Twenty-three patients (median age: 52, range: 27–68) with high-risk acute leukemia (18 AML, 4 T-ALL, 1 B-ALL) were enrolled in the study. Five patients had AML with myelodysplasia related changes (MRC, 2 with complex karyotype), 1 therapy-related AML (with NUP98/TOP1 fusion gene). Six/23 patients had active disease at the time of transplant (>5% bone marrow blasts or extramedullary disease). Furthermore, 8/17 (47%) patients who were transplanted in hematological complete remission had minimal residual disease (MRD) detectable by a molecular trackable marker (e.g., FLT3-ITD) and/or cytometry at the time of transplant. Five patients received HF-TBI, while 18 received TMLI.

All patients engrafted. Toxicity was mild as most patients developed no more than grade II oral and intestinal mucositis. Three (13%) developed acute GvHD grade ≥2 (all are alive and off-therapy). No patient developed moderate/severe cGvHD. Post-transplant immune reconstitution was fast and effective as peripheral blood donor CD4 + T cells were 70/uL and CD8 + T cells 200/uL at 1 month after allo-HSCT when pathogen-specific responses were already detectable. Indeed, no patient died because of post-transplant infections or transplant related complications. Despite the high-risk diseases, only two patients relapsed (a FLT3-ITD AML MRD+ at transplant and the only B-ALL). CRFS was 91% with a median follow-up of 21 months (range 3–42).

Conclusions: Treg/Tcon adoptive immunotherapy is safe in the HLA-matched allo-HSCT setting. Indeed, no chronic GvHD and no transplant related mortality occurred allowing for survival with good quality of life of nearly all patients. Moreover, the combination of an age-adapted irradiation based conditioning regimen with Treg/Tcon adoptive immunotherapy in the absence of pharmacologic immune suppression exerted powerful antileukemic activity even in HLA-matched allo-HSCT. Such outcomes make allo-HSCT with Treg/Tcon adoptive immunotherapy ready to be compared to conventional transplantation approaches in multicentric studies.

Clinical Trial Registry: clinicaltrials.gov n. NCT03977103

Disclosure: N/A

29 - Chronic Leukaemia and Other Myeloproliferative Disorders

O044

EXCELLENT OUTCOME OF HEMATOPOIETIC CELL TRANSPLANTATION (HCT) IN PATIENTS WITH SYSTEMIC MASTOCYTOSIS (SM)-WITH ASSOCIATED HEMATOLOGIC NEOPLASM (AHN)

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Background: Mastocytosis is a hematologic neoplasm with complex biology, pathology and a variable clinical course. Among systemic mastocytosis (SM), SM-with Associated Hematologic Neoplasm (SM-AHN) is associated with poor survival ranging from a few months to several years. Clinical risk factors were identified including age (score 1), Hb < 10 g/dl, platelets $<100 \times 10^9$/L and the presence of one S/A/R mutation (SRSF2, ASXL1, and/or RUNX1; score 0.5) or two S/A/R mutations (score 2). Mutation adjusted risk score (MARS) distinguishes low (scores 0–1), intermediate (score 2) and high risk (3-5 scores) with median survival of not reached, 4.3 years and 1.9 years, respectively.

In this analysis we evaluated overall survival (OS) and disease-free survival (DFS) in patients with SM-AHN focusing on non-relapse mortality, relapse and the possibility to measure biomarker or gene alterations during the course of HCT.

Methods: We selected all patients transplanted for SM-AHN at the University Medical Center of Hamburg, UKE, out of a database containing more than 4200 HCT during a period from 2006 to 2022. Mutation analysis was based on amplicon next-generation sequencing performed on DNA from peripheral blood before HCT using myeloid, MDS or PMF next generation sequencing panels and PCR tests.

Results: Twelve predominantly male ($n = 10$) patients [median age 60.5 (range 53–83) years] were diagnosed with SM-AHN with the following associated hematologic malignancies: MDS/MPN ($n = 8$), AML ($n = 1$), PMF ($n = 1$), MDS ($n = 1$) and accelerated phase CML ($n = 1$). Patient had a normal karyotype ($n = 6$), BCR/ABL ($n = 1$), trisomy 8 ($n = 1$), trisomy 11 ($n = 1$) or multiaberrant karyotype ($n = 1$). The majority of patients had a KIT mutation ($n = 9$) with additional aberrations in TET2 ($n = 5$), ASXL1 ($n = 3$), RUNX1 ($n = 4$), SRSF2 ($n = 1$), U2AF1 ($n = 2$) and SF3B1 ($n = 2$). Conditioning regimens were reduced intensity ($n = 7$) or myeloablative ($n = 5$). Donors were predominantly male (n = 10; female donor to male recipient combination n = 2) and related/unrelated with a median age of 31.5 (range 23-62) years. Donors were HLA compatible ($n = 7$), 9/10 matched ($n = 2$), 8/10 matched ($n = 1$) and haploidentical ($n = 2$). Peripheral blood stem cells were used in 11 of 12 cases. The median CD34+ count in the graft resulted in 6.1 (range 1.5–10.5) $x10^6$/kg cells. GVHD prophylaxis was given according to established protocols. All patients reached full donor chimerism and molecular remission of their hematological disease. Tryptase levels were measured longitudinally in six patients showing decrease from high to low level up to 600 days post-transplant. KIT and other molecular markers disappeared early after HCT. Three patients relapsed and two died on hematological relapse. Interestingly, the patient with molecular and hematological relapse did not show an increase in tryptase despite reappearance of molecular alterations (JAK2). After a median follow-up of 878 (103–5677) days, OS amounted to 80% (95% CI: 54–100%) and DFS 68% (95% CI: 37–99%) at 3 years. There was no treatment related mortality.

Conclusions: We conclude that HCT is a very efficient treatment of SM-AHN resulting in impressive OS. Molecular remissions were observed in all patients and correlated with chimerism. Normalization of tryptase levels were seen in all but one patients in the later course post-transplant.

Disclosure: No conflict of interest

29 - Chronic Leukaemia and Other Myeloproliferative Disorders

O045

OUTCOMES OF CMML PATIENTS UNDERGOING ALLOGENEIC HCT IN COMPARISON WITH MDS PATIENTS - A RETROSPECTIVE ANALYSIS ON BEHALF OF THE CMWP OF THE EBMT

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Background: The FAB Group originally classified chronic myelomonocytic leukemia (CMML) as a form of Myelodysplastic Syndromes (MDS). In 2001, the World Health Organization reclassified the disease as part of a newly created MDS/MPN overlap entity. Even though characterized by high mortality and relapse rates, allogeneic hematopoietic cell transplantation (allo-HCT) remains the only curative treatment for both CMML and MDS. Although there are a number of studies investigating the outcomes of CMML and MDS patients after allo-HCT, comparative studies of both diseases including a large number of patients are lacking. In this retrospective registry study, we aimed to identify factors associated with allo-HCT outcomes in CMML, particularly focusing on age, and to compare them with MDS outcomes.

Methods: We compared outcomes of CMML patients who underwent allo-HCT between 2010 and 2018 to MDS population over the same period time. Patients ≥18 years with CMML and MDS undergoing allo-HCT reported to the EBMT registry were included in this retrospective analysis. Those who had transformed to secondary AML were excluded. Overall Survival (OS), Relapse Free Survival (RFS); relapse incidence (REL) and non-relapsed mortality (NRM) were evaluated in univariable and multivariable models using Cox (cause specific) proportional hazard models including age, disease stage and Karnofsky score at allo-HCT, sex, donor type, year of allo-HCT and conditioning intensity.

Results: There were 1499 CMML patients with a median age of 60.4 (18.9–76.3) years and 69.4% were male. 27% had a Karnofsky status ≤80 and 23% of patients had a Sorror HCT-CI ≥3. 28% had HLA-identical sibling donors, 63% unrelated (MUD or MMUD) donors and 8.3% mismatched related donors. A RIC regimen was used in 62%. There were 12,745 MDS patients with a median age of 59.1 (18–79.7) years, 61.1% were male and 47% had blasts above 5%. Regarding Karnofsky scores, Sorror HCT-CI scores, donor types, conditioning regimens and the rates of primary graft failure, there were no clinically meaningful differences between the CMML and MDS patients. OS, RFS and REL rates, were significantly worse in CMML when compared to MDS (all $p < 0.0001$) regardless of the blasts percentage in MDS patients at allo-HCT. For CMML, the HR for each 10-year increase in age, was 1.16 (1.06–1.28), 1.13 (1.04–1.23) 1.06 (0.95–1.19) and 1.21 (1.06–1.37) for OS, RFS, REL and NRM, respectively. Age ≥65 in the adjusted model conferred a negative impact on OS, RFS and NRM in both diseases. There was no significant interaction between disease and age and any of the other variables test and OS and RFS.

Conclusions: We demonstrated that OS, RFS and REL rates after allo-HCT were significantly worse in CMML when compared to MDS. There was no evidence that age was acting differently in CMML or MDS, and advanced age, as expected, was associated with adverse outcomes in both diseases. The worse survival outcomes in CMML seems inherent to the disease itself and significantly higher post-transplant relapse. These results may contribute to future recommendations for allo-HCT indications in CMML patients. Future research should focus on both pre- and post-transplant strategies to improve disease control.

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29 - Chronic Leukaemia and Other Myeloproliferative Disorders

O046

ASCIMINIB AS A BRIDGE - THERAPY BEFORE ALLOGENEIC HEMOPOIETIC STEM CELL TRANSPLANTATION FOR CHRONIC MYELOID LEUKEMIA

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Background: Asciminib is a novel STAMP inhibitor that has shown potential efficacy and a good safety profile according to the results of a phase I and III studies in patients with Ph-positive leukemia failing prior TKIs. While pre-transplant use of 2-nd generation TKIs (nilotinib / dasatinib) does not change the risk associated with allogeneic hemopoietic stem cell transplantation (allo-HSCT) recipients (Niederwieser C.,2021, Masouridi-Levrat S.,2021), there is yet no data available for patients receiving asciminib.

Methods: Asciminib was provided under the Managed Access Program (MAP) by Novartis, 12 pts who received asciminib subsequently underwent allo-HSCT with median (Me) prior duration of asciminib of 194 days (61–377 days). Baseline characteristics: male 58%; Me age 41 years (range 28–59); Me duration of CML before asciminib 2.8 years (range 0.3–15); 3 pts were in chronic phase (CP) CML, 4 and 5 pts had a history of accelerated phase (AP) and blast crisis (BC), respectively. 9 pts (75%) had *BCR::ABL1* mutations, 7 pts (58%) had *BCR:ABL1*^{T315I}. 4pts (33%) had additional chromosomal abnormalities. 9 pts (75%) received ≥3 TKIs, 4pts (33%) had a history of ponatinib treatment. CML status before allo-HSCT: 4 pts achieved CHR, 1 – CCyR, 2 and 1 MMR and MR4, respectively, and 4 pts without CHR. All pts received allo-HSCT with reduced dose intensity conditioning regimen. GVHD prevention with PtCyTxMMF/PtCyCsA or monoCy/monoCsA. 8 pts (67%) have relative donors (5 MRD and 3 Haplo) and 4 pts (33%) – MUD (9/10, 8/10) with transplant source PBSC.

Results: In 5 (41%) pts, the initial dose of asciminib was 40 BID, 7 (59%) pts started with 200 mg BID. On asciminib 11pts (92%) did not develop adverse events (AEs) of any grade and 1 (8%) developed

AEs (neutropenia 3gr, thrombocytopenia 4 gr), but was able to continue treatment at reduced dose 20 mg BID. No unusual toxicity was observed during conditioning. Me engraftment time was D + 20 (range 18–24). Primary and secondary graft failures were recorded in 1 pt each. In the post-transplant period, 4 pts continued to receive asciminib for the treatment of MRD, with the achievement of CMR in 3 cases. One patient developed VOD gr.1 with resolution during therapy. Two pts developed liver aGVHD gr.2, which did not require correction of the underlying immunosuppressive therapy. Two pts developed intestinal aGVHD gr.3 requiring glucocorticosteroids and ruxolitinib treatment. The cumulative incidence of acute GVHD (1-3 gr. up to 100 days) was 18% . 8 pts are alive with median follow-up after allo-HSCT of 135 days.

Conclusions: Asciminib had promising results for the treatment of highly pre-treated CML patients from the Phase 1 data and ASCEMBL study. In our observation asciminib was effective as bridge-therapy before allo-HSCT in highly pretreated pts with low rate of severe toxicity and acceptable rate of aGVHD. It seems that in patients with advanced phases, asciminib is an promising drug to improve the status of the disease before allo-HSCT and with no increase of rate of aGVHD after allo-HSCT. More data obtained on larger cohort is needed in order to assess its impact on long-term survival.

Disclosure: No disclosure

16 - Conditioning Regimens

O047

MATCHED-PAIRED COMPARISON OF 12-GY OR 8-GY TOTAL BODY IRRADIATION FOR ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS IN FIRST COMPLETE REMISSION. ON BEHALF OF THE ALWP OF EBMT

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Background: Whether it is justified to use a lower than the standard 12-Gray (Gy) Total Body Irradiation (TBI) dose as conditioning prior to allogeneic hematopoietic cell transplantation (allo-HCT) for adult patients with acute lymphoblastic leukemia (ALL) in first complete remission (CR-1) is unclear. We recently demonstrated using a registry-based 12-Gy and 8-Gy TBI comparison, that relapse (REL), non-relapse mortality (NRM) and survival outcomes were not influenced by the irradiation dose (*Hemasphere*, in press). Since there was a strong interaction between TBI dose and age, and pre-transplant MRD data were missing, we performed a confirmatory comparison using cohorts matched for these two variables.

Methods: From total 2122 TBI-based (8 or 12-Gy) transplants of ALL-CR1 patients with available MRD data performed in EBMT centers between 2009–2021, we conducted a 1:1 matched-paired analysis using exact matching for ALL-subtype, pre-HCT MRD, donor type (sibling matched/unrelated), and nearest neighbor for age, female-to-male transplant, cell source (PB/BM), Karnofsky, in vivo T-cell depletion (TCD), and CMV status.

Results: 516 patients (median 49 years, 18–69) were included, of which 258 (50%) received 12-Gy and 258 (50%) 8-Gy TBI. In each group, 163 (63%), 60 (23%) and 35 (14%) patients had Ph-positive ALL, B-precursor ALL and T-ALL, respectively, 92 (36%) were MRD-positive, and 172 (67%) had an unrelated donor. Time from diagnosis to HCT (median 5.6 months), Karnofsky (<90% in 31%), HCT-CI (> = 3 in 21%), TCD (in 64%, 98% ATG), use of PTCY (in 5%), and CMV-positivity, did not significantly differ between groups. TBI was delivered in 2-Gy fractions in 80% and in 68% of 8-Gy and 12-Gy treated patients and was given together with fludarabine in 77% of 8-Gy and with cyclophosphamide in 74% of 12-Gy regimens. As 8-Gy patients were transplanted in more recent years (median 2018 vs 2015, $p < 0.0001$), the comparison was adjusted on year of transplant. The use of 8-Gy as compared to 12-Gy was associated with significantly reduced NRM (12.1%, 95% CI: 8.1–16.9 vs 22.6%, 17.4–28.3, HR 1.88, 95% CI 1.1–3.0, $p = 0.008$), without any effect on REL (21.6%, 16.3–27.5 vs 18.4%, 13.6–23.8, HR 0.85, 0.55–1.31, $p = 0.46$). The 12-Gy cohort had a significantly increased rate of acute GVHD II-IV and III-IV (37% vs 24%, $p = 0.0008$ and 12.6% vs 7.2%, $p = 0.047$, respectively), but not of chronic GvHD. Leukemia-free survival (LFS) did not significantly differ between groups (66% vs 59%, $p = 0.22$), but both overall survival (OS) and GRFS were improved for 8-Gy compared to 12-Gy TBI recipients (OS 78.3% vs 66.8%, HR 1.55, 1.06–2.27, $p = 0.024$ and GRFS 54.1% vs 40.7%, HR 1.36, 1.05–1.8, $p = 0.027$, respectively).

Conclusions: We conclude that the use of a reduced 8-Gy compared to the standard 12-Gy TBI dose as conditioning prior to allo-HCT for adult patients with ALL in CR-1 is not associated with increased REL rate. Moreover, 8-Gy TBI regimens are associated with decreased NRM and less acute GVHD, leading to a significantly better OS and GRFS compared to 12-Gy treated patients. This study support 8-Gy as the preferable TBI dose for adult ALL patients transplanted in CR-1.

Clinical Trial Registry: NA

Disclosure: Nothing related to this study

16 - Conditioning Regimens

O048

A RANDOMIZED PHASE 3 STUDY OF ALLOGENEIC HCT WITH IOMAB-B VERSUS CONVENTIONAL CARE IN OLDER PATIENTS WITH ACTIVE, RELAPSED/REFRACTORY AML: PIVOTAL SIERRA TRIAL RESULTS

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Background: Most older patients with relapsed or refractory (R/R) AML cannot tolerate intensive treatment and are not eligible for curative allogeneic hematopoietic cell transplant (HCT). Iomab-B (^{131}I-apamistamab), an anti-CD45 radioimmunoconjugate, delivers high-dose targeted radiation to hematopoietic cells, allowing for myeloablation and eradication of leukemic cells. Iomab-B based conditioning can provide these patients access to allogeneic HCT.

Methods: SIERRA is a prospective, randomized, controlled, Phase 3 trial comparing the rate of durable complete remission (dCR) at 6 months (mos) after complete remission with/without platelet recovery (CR/CRp) and safety between two arms: Iomab-B based conditioning followed by HCT vs physician's choice of conventional care (CC). Patients ≥55 years of age with active, relapsed or refractory AML were randomized (1:1, $N = 153$) to CC or Iomab-B with fludarabine and total body irradiation (2 Gy) followed by HCT. CR/CRp assessment was 28–56 days post-HCT in Iomab-B or 28–42 days from initiation of therapy in the CC arm. Patients not achieving CR could crossover (CO) to Iomab-B-arm and were analyzed separately.

Results: In total 153 patients were randomized (CC $n = 76$, Iomab-B $n = 77$). Baseline characteristics were well balanced between both arms **(Table 1)**. 61% of patients had failed targeted therapies before enrollment, of whom 66% received venetoclax-based therapy. Median time to HCT was 29 days (Iomab-B) vs 66.5 days (CC). All patients who received the therapeutic dose of Iomab-B ($n = 66$) underwent HCT vs 14 (18.2%) in the CC arm. Of evaluable patients 44 (44/59, 74.6%) in the Iomab-B arm achieved initial CR/CRp compared to 4 (4/64, 6.3%) in CC arm. Durable CR

Table 1. Baseline Patient Characteristics

	Iomab-B Arm ($N = 76$)	**Conventional Care Arm ($N = 77$)**	**Randomized to Conventional Care and Crossed Over to Iomab-B ($N = 44$)**
Age, years Median (Range)	**64** (55–77) Pts ≥70 yrs: **14** (18.4%)	**66** (55–76) Pts ≥70 yrs: **16** (20.8%)	**64** (55–76) Pts ≥70 yrs: **12** (27.3%)
Cytogenetic and Molecular Risk* *N* (%)	Favorable: **5** (6.6) Intermediate: **27** (35.5) Adverse: **43** (56.6)	Favorable: **2** (2.6) Intermediate: **31** (40.3) Adverse: **43** (55.8)	Favorable: **1** (2.3) Intermediate: **21** (47.7) Adverse: **21** (47.7)
Disease Status at Randomization *N* (%)	Primary Induction Failure: **43** (56.6) First Early Relapse:**16** (21.1) Relapse/Refractory: **10** (13.2) 2nd + Relapse: **7** (9.2)	Primary Induction Failure: **40** (51.9) First Early Relapse: **22** (28.6) Relapse/Refractory: **10** (13.0) 2nd + Relapse: **5** (6.5)	Primary Induction Failure: **24** (54.5) First Early Relapse: **11** (25.0) Relapse/ Refractory: **7** (15.9) 2nd + Relapse: **2** (4.5)
Prior Lines of Treatment Median (Range)	**3** (1–8)	**3** (1–8)	**3** (1-8)
Received Prior Targeted Therapy *N* (%)	**47** (61.8)	**47** (61.0)	**26** (59.1)
Karnofsky Performance Status *N* (%)	≥90: **31** (40.8) < 90: **45** (59.2)	≥90: **34** (44.2) < 90: **43** (55.8)	≥90: **22** (50.0) <90: **22** (50.0)
% Marrow Blasts at Randomization Median (Range)	**30%** (2–97)**	**20%** (3–97)**	**At Randomization: 24.5%** (3–87)** **At crossover: 35%** (2–89)**

*Per NCCN Guidelines, Version 3, 2020

**Patients with <5% marrow blasts had circulating leukemic blasts

rates at 6 months were 22% vs 0% (95% CI: 12.29, 34.73; $p < 0.0001$) (primary endpoint).

The median overall survival (OS) was 6.4 (Iomab-B) vs 3.2 months (CC arm). Median OS in the CO vs non-CO cohorts in the CC arm was 7.1 vs 3.2 months (HR = 0.51; 95% CI [0.31, 0.85]; $p = 0.0078$). OS in patients achieving dCR in Iomab-B arm ($n = 13$) was 92% at 1 year and 60% at 2 years, longer-term follow-up is ongoing. The 6-months event-free survival was 26% (Iomab-B) vs 0.2% (CC) (HR = 0.22; 95% CI [0.15, 0.34]; $p < 0.0001$).

Iomab-B was well tolerated. The most common (>5%) drug related serious adverse event in Iomab-B was febrile neutropenia (FN; 5.6%). Sepsis incidence was 4 times lower for Iomab-B vs CC (6.1% vs 28.6%). In transplanted patients, the reported incidence of FN, mucositis and acute GVHD (Grades III-IV) in the Iomab-B arm were 43.9%, 15.2% and 9.4% vs 50.0%, 21.4% and 14.3% respectively in CC with HCT.

Conclusions: In patients ≥55 yrs with active R/R AML, Iomab-B based conditioning with allogeneic HCT resulted in rapid engraftment and high initial CR/CRp rates and a favorable toxicity profile. Iomab-B based conditioning and HCT resulted in statistically significant improvement in the pre-specified primary endpoint of dCR. A majority of patients who achieved dCR are long term survivors, in whom OS and EFS was statistically significant. Iomab-B based conditioning was well-tolerated and provided access to HCT with curative potential in a vulnerable patient population traditionally not considered eligible for HCT.

Clinical Trial Registry: NCT02665065
https://clinicaltrials.gov/

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16 - Conditioning Regimens

O049

LONG TERM FOLLOW-UP OF THE MULTICENTRE, RANDOMIZED PHASE 3 TRIAL COMPARING BUSULFAN-FLUDARABINE VERSUS BUSULFAN-CYCLOPHOSPHAMIDE AS CONDITIONING REGIMEN IN ACUTE MYELOID LEUKEMIA PATIENTS UNDERGOING ALLOGENEIC TRANSPLANTATION

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Background: A previous randomized trial performed by the Gruppo Italiano Trapianto di Midollo Osseo (GITMO, AML-R2 study; Rambaldi A et al.: Lancet Oncology, 2015) randomized 252 AML patients (median age 51 years) 1:1 to the conventional combination of busulfan and cyclophosphamide (BuCy2, $n = 125$) and the combination of busulfan and fludarabine (BuFlu, $n = 127$). The 1-year non-relapse mortality (NRM) (primary endpoint of the study) proved significantly lower in BuFlu arm (7.9% in BuFlu arm vs. 17.2% in BuCy2 arm, $p = 0.026$). There was no difference between the two arms in terms of 1- and 2-years cumulative

incidence of relapse (CIR), leukemia free survival (LFS), overall survival (OS). Grade III-IV acute graft versus host disease (GvHD) was significantly higher in BuCy2 group (10%) than BuFlu group (2%). Hereby we present the long-term analysis of this clinical trial.

Methods: We collected data about the last follow up (dead/alive), causes of death (NRM/disease relapse), incidence of chronic GvHD (cGvHD) and current cGVHD therapy, occurrence of disease relapse with the type of subsequent treatment. We also searched for long-term side effects including cardiovascular events, secondary malignancies, other relevant medical events (i.e., infections, neurological or pulmonary events etc.). Endpoints of the current analysis were 4-and 10 years NRM, 10-years CIR, LFS, OS, cumulative incidence of cGvHD and cumulative incidence of moderate/severe cGvHD, 4-and 10-years cGVHD and leukemia-free survival (GLFS).

Results: With a median follow up of 6 years (range 0.03–13), 4-years NRM was 10% in BuFlu arm vs 20% in BuCy2 arm ($P = 0.0388$) and 10-years NRM was 17% in BuFlu vs 24% in BuCy2 ($p = 0.1624$). Stratifying patients according to median age, this difference was much more pronounced in patients older than 51 years old at 4 years (11 %in BuFlu vs 27%in BuCy2, $p = 0.0262$) with a trend in a better outcome even at 10 years (18% in BuFlu vs 33% in BuCy2, $p = 0.0656$). We did not observe any difference in terms of 10-years CIR (39% vs 37% in BuFlu vs BuCy2), LFS (45% vs 38% in BuFlu vs BuCy2), OS (45% in both arms) and cumulative incidence of moderate/severe cGvHD (14% vs 19% in BuFlu vs BuCy2). The 4-years GLFS was 35% in BuFlu arm vs 24% in BuCy2 ($P = 0.0602$). Incidence of secondary malignancies was 7.5% in BuCy2 arm vs 10.2% in BuFlu arm ($p = 0.05$).

Conclusions: BuFlu conditioning is associated with a prolonged improvement in NRM, especially in patients older than 51 years. This advantage was not associated to a higher incidence of late leukemia relapse. We found a better trend in GLFS in BuFlu arm, most likely due to a lower rate of grade III/IV acute GvHD in the experimental arm. CIR was stable and high throughout the observation period (nearly 40% in both arms at 10 years), with no difference between the two arms. AML relapse remains the major concern, urging the development of new therapeutic interventions driven by post-transplant MRD monitoring and pre-emptive therapies in high-risk patients.

Disclosure: Nothing to declare

16 - Conditioning Regimens

O050

LONG-TERM DATA OF THE RANDOMIZED TRIAL COMPARING TBI-CONTAINING CONDITIONING REGIMEN TO A CHEMOTHERAPY-BASED PREPARATION IN CHILDREN WITH ALL. RESULTS OF THE FORUM RANDOMIZED CLINICAL TRIAL

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Background: In a multicenter, international, randomized clinical Trial (FORUM study), we documented (Peters C, et al. J Clin Oncol 2021) that children with ALL given total body irradiation (TBI) in combination with etoposide had a superior probability of 2-year overall (OS) and event-free survival (EFS) in comparison to patients given either one of two myeloablative chemo-conditioning regimens. In this analysis, we assessed whether the benefit deriving from the use of TBI is sustained over time.

Methods: Patients ≤18 years at diagnosis, 4–21 years at HSCT, in CR pre-HSCT, and with an HLA-compatible related or unrelated donor (UD) were randomly assigned 1:1 to a myeloablative conditioning regimen with fractionated TBI and etoposide or fludarabine, thiotepa, and either busulfan (BU) or treosulfan (TREO). Children received homogeneous graft-versus-host disease (GvHD) prophylaxis (see Peters C, et al. J Clin Oncol 2021 for further details).

Results: Between 04/2013 and 12/2018, 413 patients were randomly assigned to receive either TBI/etoposide (212) or a chemotherapy-based conditioning (201). Sixty-five percent of patients were male, 72% had B-cell precursor ALL, 73% were transplanted from a UD, and in 82% of patients bone marrow was the stem cell source employed. Fifty-four percent of patients were in CR1 at time of allograft, while 40% and 4% were transplanted in CR2 and CR3, respectively. Patient's outcomes were updated on February 1st, 2022. With a median follow-up of 3.7 years (range, 0.3–7.9), the 3-year probability of OS of patients allocated to TBI/etoposide or to the chemotherapy-based conditioning regimens was 90 ± 2% and 71 ± 3% ($p < 0.001$), respectively, while that of 3-year EFS was 81 ± 3% and 59 ± 4% ($p < 0.001$). OS and EFS remain comparable in patients receiving BU or TREO in combination with fludarabine and thiotepa. Multivariate analysis confirmed that chemotherapy-based regimens correlated with worse OS [Hazard Ratio, HR, 2.63, 95% CI, (1.61–4.31), $p < 0.001$] and EFS [HR 2.30, 95% CI (1.58–3.35) $p < 0.001$]. Transplantation in >CR1 predicted a worse EFS in multivariate analysis, as well [HR 1.67, 95% CI (1.14–2.45) $p = 0.009$]. Patients given TBI benefited from a lower cumulative incidence of relapse (Fig. 1A), as well as from a lower 3-year cumulative incidence of non-relapse mortality (2 + 1% vs. 10 + 2% in the chemo arm, $p = 0.007$). The 3-year cumulative incidence of chronic GvHD was comparable between the 2 arms (15 + 3% vs. 12 + 2% in the TBI and chemo arm, respectively, $p =$ n.s.). The 3-year probability of GvHD/relapse-free survival (GRFS), considering both relapse and chronic GvHD as events, was better in children prepared with TBI as compared to chemo-prepared patients (Fig. 1B). Five patients (all transplanted from a UD) developed secondary malignancies: 4 of them had received TBI.

Conclusions: With a significantly longer follow-up, we confirm that the use of TBI during the conditioning regimen is associated with better outcomes in children and adolescents with ALL above the age of 4 years transplanted in CR, mainly due to a lower risk of leukemia recurrence. The number of cases of secondary malignancies, particularly in patients offered radiotherapy, underlines the importance of continuous monitoring over time to comprehensively evaluate the long-term sequels.

Clinical Trial Registry: EudraCT: 2012-003032-22; ClinicalTrials.gov: NCT01949129

Disclosure: Franco Locatelli

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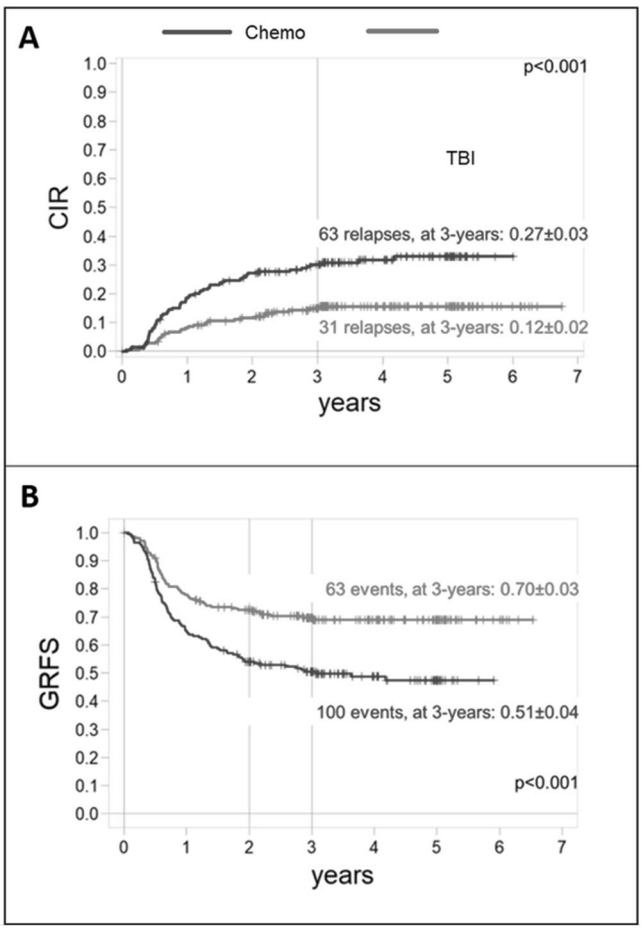
Consulting or Advisory Role: Amgen, Novartis, Pfizer

Peter Bader



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16 - Conditioning Regimens

O051

VALIDATION IN A CONTEMPORARY ELDERLY POPULATION OF THE TRANSPLANT CONDITIONING INTENSITY (TCI) SCORE FOR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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Table 1. Multivariable analysis for early (d100 and d180) NRM, NRM, REL

	NRM day 100		NRM day 180		NRM		REL	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
TCI Low (Ref)	1		1		1		1	
TCI Intermed.	1.95 (1.42–2.69)	<0.0001	1.62 (1.26–2.08)	0.0001	1.44 (1.20–1.74)	0.0001	0.66 (0.57–0.78)	<0.0001
TCI High	4.00 (2.20–7.28)	<0.0001	2.86 (1.76–4.64)	<0.0001	1.87 (1.25–2.80)	0.003	0.79 (0.55–1.13)	0.20

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Background: The intensity of the conditioning regimen given before allogeneic hematopoietic cell transplantation (allo-HCT) can vary substantially. We recently developed the transplant conditioning intensity (TCI) score based on the sum of the intensity weight scores for every component in the pre-transplantation regimen. In the discovery cohort of 8255 patients with AML allografted between 2005–2017, TCI provided finer stratification, better discriminating ability and more standardized assessment than the classical MAC and RIC classification (Bone Marrow Transplantation 2020; 55:1114). A validation conducted in a separate and more contemporary patient population was lacking, hence the current study.

Methods: Using data reported to the EBMT, we included transplant recipients meeting inclusion criteria from the discovery study (AML, first HCT in CR-1, matched sibling or unrelated donor) but who were allografted in a more recent period (2018–2021) and were one decade older (55-75 years), we assigned them to a TCI category (low, intermediate, high) according to the calculated TCI score ([1–2], [2.5–3.5], [4–6], respectively), and examined the validity of the TCI category in predicting early (day 100 and d180) NRM, 2-year NRM and REL.

Results: The validation cohort comprised 4060 adult AML patients (median 63.4 years) who were transplanted in median year 2019. 1934 (48%) and 1948 (48%) patients were assigned to the low, and intermediate TCI-group, respectively, while a high TCI was less prevalent ($n = 178$, 4%). There was an inverse relationship between age, Karnofsky, HCT-CI and TCI group ($p < 0.0001$). The risk of early NRM followed the same pattern as in the discovery cohort, with a monotonic increase in d100 and d180 NRM rate from lower to higher TCI groups. In the unadjusted comparison, the TCI provided a highly significant risk stratification for d100 and d180 NRM, 2-year NRM and REL risk ($p < 0.0001$). In the multivariate analysis adjusted for age, Karnofsky, HCT-CI and other variables, there was a significant increase in risk of d100 and d180 NRM with each TCI group, with near doubling of the HR observed in each TCI group (Table 1). TCI group was found to be also a strong and independent predictor both for overall NRM (HR 1.44, 95% CI: 1.20–1.74, $p < 0.0001$ and 1.87, 95% CI: 1.25–2.80, $p = 0.003$ for intermediate and high TCI, respectively) and for REL (HR 0.79; 95% CI: 0.55–1.13, $p = 0.20$ for intermediate TCI, but only a trend for high TCI group, HR 0.79; 95% CI: 0.55–1.13, $p = 0.20$) (Table 1). Similar results were found when we focused to patients between 55–65 years.

Conclusions: We confirmed in an independent and contemporary validation cohort, the ability of the 3-group TCI index to stratify conditioning regimens according to early NRM, NRM and REL. TCI reflects the preparative regimen related morbidity and anti-leukemic efficacy highly satisfactorily and across other established prognostic factors. Thus, TCI has all the features to be accepted as a valid standard-of-care measure for intensity of the preparative regimen.

Clinical Trial Registry: NA

Disclosure: Nothing related to this study

16 - Conditioning Regimens

O052

DOSE OF IV BUSULFAN IN REDUCED TOXICITY CONDITIONING REGIMEN FOR OLDER AND/OR FRAIL PATIENTS WITH AML OR MDS

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Background: RIC regimen with fludarabine and reduced dose (6.4 mg/kg) of busulfan (FB) is a common option to transplant patients who are unfit for a MAC regimen. However, disease control after RIC remains a challenge, notably for myeloid malignancy. We thus investigated whether FB regimens using higher doses of busulfan (9.6 and 12.4 mg/kg, over 3 and 4 days, respectively) may improve outcome of patients who are unfit for

MAC and who underwent allogeneic transplantation for myeloid malignancies.

Methods: This is a prospective multicenter randomized phase II trial (NCT01985061). Main selection criteria were diagnosis of complete remission AML or MDS; presence of an HLA matched related (MRD) or 10/10 unrelated donor (MUD); ineligibility for MAC due to age from 55 to 65 years, or younger with a HCT-CI $>=3$. All patients received: fludarabine (30 mg/m^2 from day-6 to -2) and iv busulfan at 3.2 mg/kg/day during 2 (Bx2), 3 (Bx3) or 4 (Bx4) days, according to the randomization arm. Graft-versus-host disease (GVHD) prophylaxis was ATG (2.5 mg/kg on day-3 and -2) and cyclosporin A from day-3 to day+180. Graft source was peripheral blood stem cells.

Results: Of the 169 randomized patients, 152 (90%) were transplanted and analyzed according to treatment arm (61 Bx2, 56 Bx3 and 35 Bx4). The Bx4 arm was prematurely closed after 35 treated patients because of an excess of NRM. Median age was 61 years (IQR: 55–63), 98 (64%) and 54 (36%) patients had AML and MDS, respectively, and 53 (35%) and 99 (65%) patients received allo-SCT from a MRD and a MUD, respectively. There was no significant difference in baseline characteristics between the randomization arms.Grade 2-4 acute GVHD at day+100 was 26%, 45% and 51% in Bx2, Bx3 and Bx4 groups, respectively (Bx2 vs. Bx3 $p=0.121$, Bx2 vs. Bx4 $p=0.052$, Bx3 vs. Bx4 $p=0.501$). No significant difference was observed in 2-year extensive chronic GVHD (Bx2 = 34%, Bx3 = 36%, Bx4 = 34%). NRM at 2 years was 7%, 17% and 34% in Bx2, Bx3 and Bx4 groups, respectively (Bx2 vs. Bx3 $p=0.146$, Bx2 vs. Bx4 $p=0.001$, Bx3 vs. Bx4 $p=0.062$), without significant difference in relapse incidence (Bx2 = 20%, Bx3 = 29%, Bx4 = 14%). Overall survival (OS) probability was 81%, 63%, 54% at 2 years in Bx2, Bx3 and Bx4 groups, respectively (Bx2 vs. Bx3 $p=0.060$, Bx2 vs. Bx4 $p=0.008$, Bx3 vs. Bx4 $p=0.412$). Multivariate analysis showed that busulfan dose and the use of an MUD significantly increased the risk of grade 2–4 acute GVHD, while age >60y and Bx4 were significantly associated with higher NRM and worse OS.

Conclusions: In older or unfit patients, the use of 3 or 4 days of busulfan in the FB platform failed to improve outcome of patients compared to the 2-day administration. No benefit in disease control was observed. In addition, the use of 4 days of busulfan is not feasible in this situation due to a high risk of NRM. Finally, Bx2 resulted in better OS with lower NRM and may be considered as a standard RIC regimen in this setting.

Clinical Trial Registry: NCT01985061

Disclosure: Nothing to decalre

16 - Conditioning Regimens

O053

ASSOCIATION OF BUSULFAN PHARMACOKINETICS AND PHARMACOGENETICS WITH ALLOGENEIC STEM CELL TRANSPLANTATION OUTCOMES IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA: RESULTS FROM THE ALL SCTPED-FORUM STUDY

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Background: Previous studies have shown that busulfan (BU) pharmacokinetics (PK) and pharmacogenetics (PG) are correlated with hematopoietic stem cell transplantation (HSCT) outcomes. We evaluated these associations in a homogeneous cohort of pediatric patients with acute lymphoblastic leukemia (ALL) treated with BU – fludarabine (FLU) – thiotepa (THIO) conditioning prior to HSCT.

Methods: Patients prospectively recruited in the ALL SCTped FORUM study (NCT01949129), who received PK-guided BU with FLU and THIO, were included in this analysis. Pharmacokinetic parameters estimation and dose adjustments of BU were performed by the treating centers, either using non-linear mixed-effect models, or non-compartmental analysis. All centers were cross-validated for BU quantification method. Assuming linear pharmacokinetics, the $AUC_{0\text{-}24h}$ and the cumulative $AUC_{0\text{-}\infty}$ were derived from the available PK parameters and the administered doses. A PG subanalysis included *GSTA1* promoter haplotypes and *GSTP1 c.313 (A > G)* genotypes, extracted from whole-genome sequences of the germline DNA of a subset of patients who consented to participate to the pharmacogenomic add-on study of FORUM (NCT02670564). The outcomes of interest were relapse, aGvHD, cGvHD, toxicities (sinusoidal obstructive syndrome (SOS), liver, urinary tract (Hematuria/bladder hemorrhage), and lung toxicities), event-free survival (EFS), overall survival (OS) and non-relapse mortality (NRM). We used Cox-proportional hazard models and Kaplan-Meier method to analyze time-to-event outcomes, and logistic regression models, for binary outcomes. ROC analyses helped to categorize the PK parameters.

Results: 136 patients, who received either once-daily (20.6%), twice daily (0.7%) or four-times daily (78.7%) BU regimen, were included in the PK analysis. The median age was 7.2 years (IQR 2.5–11.4). *GSTA1* and *GSTP1* genotypes were obtained for 67 patients. The median $AUC_{0\text{-}24h}$ was 20.1 mg.h/L (IQR 17.3–24.0) and the median $AUC_{0\text{-}\infty}$ was 80.9 mg.h/L (IQR 71.6–90.8). $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}\infty}$ were significantly correlated ($R=0.80$, $P<0.001$). 38.2% of the patients relapsed. The risk of relapse was increased in patients with $AUC_{0\text{-}24h}$ below 21.6 mg.h/L (HR = 2.04, 95% CI: 1.06–4.12). Stratified Kaplan–Meier analyses showed that the influence of BU PK on relapse incidence was observed in patients in second or third complete remission before transplantation, with 25.9% vs. 60.0% of relapse in patients above and below 21.6 mg.h/L, respectively ($P=0.042$). Patients with $AUC_{0\text{-}24h}$ above 25.3 mg.h/L had a higher risk of NRM (HR = 4.74, 95% CI: 1.23–18.2). Patients with a poor GSTA1 metabolizing capacity, as defined by *GSTA1* promoter polymorphisms, showed a higher, although marginally not significant ($P=0.066$), incidence of NRM. The risks of SOS, pulmonary and urinary tract toxicities correlated also with $AUC_{0\text{-}24h}$ above 25.3 mg.h/L. The risks of grade II-IV aGvHD, and cGvHD were associated with an increasing $AUC_{0\text{-}\infty}$. Poor GSTA1 metabolizing capacity increased the risk of aGvHD II-IV (OR = 6.019, 95% CI: 1.03–35.3). However, BU PK parameters did not significantly influence OS and EFS in this cohort.

Conclusions: Our analyses suggest that pediatric ALL patients conditioned with BU-FLU-THIO would benefit from a daily BU AUC

targeted above 21.6 mg.h/L and below 25.3 mg.h/L, which could limit the risk of relapse, non-relapse mortality and acute treatment-related toxicities. *GSTA1* promoter genotyping could be useful for the prediction of aGvHD II-IV risk.

Clinical Trial Registry: NCT01949129 (clinicaltrials.gov) NCT02670564 (clinicaltrials.gov)

Disclosure: MA received funding from Jazz for covering travel expenses.

16 - Conditioning Regimens

O054

IMPACT OF BUSULFAN, ETOPOSIDE AND HIGH-DOSE ARA-C (BEA) CONDITIONING FOR AUTOLOGOUS STEM CELL TRANSPLANTATION IN AML

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***Background**: High dose myeloablative chemotherapy followed by autologous stem cell transplantation (ASCT) is a clinical option for patients with acute myeloid leukemia (AML) in first complete remission (CR1). However, information on specific conditioning regimens is scarce. The ALWP showed improved outcomes with BuMel conditioning compared to BUCY in high-risk patients. The combination of more AML directed drugs using high dose cytarabine, etoposide and busulfan (BEA) has been the recommended regimen in subsequent PETHEMA studies.*

Methods: In order to analyse the impact of the conditioning regimen we retrospectively compared the outcome of adult patients with AML in CR1 that received ASCT from 2010 to 2021 with either BEA, BUCY or BuMel registered in the EBMT database.

Results: Overall 1560 patients underwent ASCT at a median age of 52 years (range, 18–75). 843 (54%) were male. 267 (23%), 815 (70%) and 75 (7%) had standard, intermediate and high-risk cytogenetics, respectively (data not reported for 403 patients). FLT3 and NPM1 mutations were present in 177 (23%) and 481 (58%) patients. Regarding conditioning, 156, 1143 and 261 received BEA, BUCY and BuMel, respectively. Compared to BUCY and BuMel, BEA patients were younger ($p < 0.001$) and had less frequently NPM1 mutations ($p = 0.03$). Transplant outcomes at 5 years with BEA, BUCY and BuMel were: cumulative incidence of relapse 41.8%, 46.6% and 51.6%; non-relapse mortality 1.5%, 5.2% and 7.3%; probability of leukemia-free survival 56.7%, 48.2% and 41.1% ; and overall survival (OS) 71.3%, 62.3% and 56%. In multivariable analysis BEA regimen showed significant improvement in OS compared to BUCY (HR 0.65; 95% CI: 0.42–0.99, $p = 0.048$) and BuMel (HR 0.59; 95% CI: 0.37–0.94). Favourable cytogenetics and younger age were also associated with improved OS.

Conclusions: High dose myeloablative combination chemotherapy with high dose cytarabine, etoposide and busulfan offered improved outcomes compared to classical BUCY or BuMel in patients with AML in CR1 undergoing ASCT.

Clinical Trial Registry: Not applicable

Disclosure: No COI

16 - Conditioning Regimens

O055

ANTI-CD45 ANTIBODY-DRUG CONJUGATES AS TARGETED CONDITIONING AGENTS FOR TRANSPLANTATION/GENE THERAPY WITH POTENT ANTI-LEUKAEMIC PROPERTIES

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Background: Since CD45 expression is restricted to haemopoietic lineage, including stem cells (HSCs) and almost all haematological malignancies, targeting CD45 could potentially be used for conditioning and as a cytoreduction prior to stem cell transplant (SCT) in patients with refractory leukaemia without the non-haemopoietic toxicity of conventional conditioning agents. We have investigated the potential of anti-huCD45 antibody-drug conjugates (ADCs) to target human HSCs and leukaemia.

Methods: Anti-huCD45 ADCs were generated by conjugating the monoclonal antibody YTH24.5 to SG3249 and SG3376, which share a highly potent pyrrolobenzodiazepine dimer toxin with cleavable/non-cleavable linkers, respectively. In vitro cytotoxicity was assessed in 5-day cell viability and clonogenic assays. To assess depletion of human HSCs in vivo, NSG mice were humanised with huCD34$^+$ cells and treated with anti-huCD45 or isotype-control ADCs. In tumour models, NSG mice were transplanted with an AML cell line (OCIM-1) expressing firefly luciferase. A single dose of 1 mg/kg anti-huCD45 ADC or controls were given before/after established tumour was detected. Tumour progression was monitored by bioluminescence imaging. To determine if anti-huCD45 ADCs enable engraftment in an allogeneic setting, NSG mice were first humanised with huCD34$^+$ cells from a healthy donor (HLA-A3$^+$/HLA-B8$^-$). Following engraftment, mice were conditioned with 1 mg/kg anti-huCD45 ADC or controls. After two weeks, mice received 1×10^6 huCD34$^+$ cells from an HLA mismatched donor (HLA-A3$^-$/HLA-B8$^+$). Seven weeks later, human cells in blood, bone marrow, and spleen were analysed by flow cytometry.

Results: YTH24.5-SG3249 and YTH24.5-SG3376 potently and specifically killed huCD45-expressing leukaemic cell lines in cell viability assays, with EC_{50} values of 0.213 pM and 0.052 pM,

respectively, and showed a wide (>4 log) therapeutic window compared to $CD45^-$ cell lines. In clonogenic assays, both ADCs specifically inhibited colony formation of $huCD34^+$ progenitors with EC_{50} values of 5–10 pM, compared to >17 nM for the isotype-control ADCs.

A single dose of 1 mg/kg of either anti-huCD45 ADC resulted in almost complete depletion of $huCD45^+$ cells and eradicated human HSCs in the bone marrow of humanised mice ($p < 0.05$ vs isotype-control ADC). Moreover, anti-huCD45 ADCs showed potent anti-leukaemic activity preventing the development of AML and prolonging survival in a xenogeneic OCIM-1 model of AML in NSG mice ($p < 0.01$ for both YTH24.5 ADCs vs Isotype-control ADCs and inducing tumour regression and prolonged survival ($p < 0.01$ vs Isotype-control ADCs) in an established tumour model. Similar results were observed with a xenogeneic Jurkat model of T-ALL. Additional studies in a PDX model of AML are ongoing. Finally, in our allogeneic transplant model, anti-huCD45 ADCs as sole conditioning agent enabled high level, multilineage engraftment from the secondary donor ($p < 0.05$ for YTH24.5-SG3249 and $p < 0.0001$ for YTH24.5-SG3376 vs Isotype-control ADCs) with less bystander effect using the non-cleavable linker.

Conclusions: Our anti-huCD45 ADCs showed promise as targeted conditioning agents for allogeneic SCT and gene therapy, potentially avoiding the non-haematopoietic toxicity of conventional conditioning. Additionally, they have potent anti-leukaemic activity suggesting they may also have a role as a cytoreductive bridge to SCT in refractory haematological malignancies.

Disclosure: AL, MS, SS, WV, CB, BG, and AT: no conflict of interests to declare. JY, KC, and PA: patent and royalties from ADC Therapeutics. IK, FZ and PB: current employees and hold stock and/or stock options in ADC Therapeutics.

16 - Conditioning Regimens

O056

RETROSPECTIVE COMPARISON OF CYCLOPHOSPHAMIDE AND HORSE-ANTI-THYMOCYTE-GLOBULIN VERSUS FLUDARABINE, CYCLOPHOSPHAMIDE AND RABBIT-ANTI-THYMOCYTE-GLOBULIN CONDITIONING REGIMEN FOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH ACQUIRED APLASTIC ANEMIA

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative treatment for acquired aplastic anemia (acquired AA).

The objective of the study was to Compare the outcomes of cyclophosphamide and horse anti-thymocyte globulin (Cy-hATG) to fludarabine-cyclophosphamide and rabbit ATG (Flu-Cy-rATG) as part of conditioning regimen in allo-HSCT for acquired AA.

Methods: We retrospectively compared the outcomes of 121 consecutive patients with acquired AA who underwent allo-HSCT from HLA-matched sibling donor (MSD) between January 2008 and April 2022, after conditioning regimen with Cy-hATG ($n = 83$) or Flu-Cy-rATG ($n = 38$). Cy-hATG (Cy: 200 mg/kg, hATG: 90 mg/kg). Flu-Cy-rATG (Flu: 120 mg/m^2, Cy: 120 mg/kg and rATG: 7.5 mg/kg). Graft versus host disease (GVHD) prophylaxis consisted of cyclosporine and short course of methotrexate.

Results: Median age was 19 years (range, 4–39 years) and 26.5 years (range, 5–42 years), in Cy-hATG and Flu-Cy-rATG group, respectively. Patient characteristics of the two groups were not significantly different in terms of severity of AA, pretransplant ferritin level and EBMT score. Pretransplant anti-human leucocyte antigen alloimmunization and infectious complications were significantly higher in Flu-Cy-rATG compared to Cy-hATG group (37% vs 7%, $p = 0.002$ and 84 % vs 58 %, $p = 0.004$). The median interval from diagnosis to transplant was 49 days (range, 15 days–19 months) and 57 days (range, 27 days–80 months), respectively. The graft source was bone marrow in 99% and 95% of patients in Cy-hATG and Flu-Cy-rATG group, respectively. Median time to neutrophil engraftment was 16 days (range, 12–41 days) and 16 days (range, 15–28 days), respectively. Median platelet engraftment was 20 days (range, 12–74 days) and 22 days (range, 14–69 days), respectively. A lower cumulative incidence of graft failure (GF) and grade III-IV acute GVHD was observed in Flu-Cy-rATG group compared to Cy-hATG group without significant differences (6.3% vs 11.2%, $p = 0.4$ and 8.2% vs 17.5%, $p = 0.18$, respectively). There was no significant differences between the two groups in terms of chronic GVHD and transplant related mortality (TRM) (12.3% vs 17.5%, $p = 0.5$ and 8.6% vs 13.7%, $p = 0.37$, in Cy-hATG and Flu-Cy-rATG group, respectively). Death causes were: GF ($n = 6$) and TRM ($n = 12$). Flu-Cy-rATG group was associated with significantly higher CMV reactivation compared to Cy-hATG group (58% vs 32.5%, respectively, $p = 0.008$). There was a trend to higher rate of documented infections with Flu-Cy-rATG group (51.8% vs 68.4%, respectively, $p = 0.09$). After a median follow-up of 58 months (range, 5 days–165 months), estimated overall survival, event-free survival and graft rejection-free survival were not statistically different between the two groups (86.5% vs 83.7%, $p = 0.65$, 81.7% vs 84.2%, $p = 0.9$ and 66% vs 77.2%, $p = 0.24$, in Cy-hATG and Flu-Cy-rATG group, respectively).

Conclusions: In high-risk acquired AA patients Flu-Cy-rATG is associated with comparable outcomes to Cy-hATG in allo-HSCT from MSD, but it seems to be associated with significant risk of CMV reactivation.

Disclosure: Nothing to declare

16 - Conditioning Regimens

O057

ANTITHYMOCYTE GLOBULIN - OR ALEMTUZUMAB-BASED GVHD PROPHYLAXIS IN REDUCED-INTENSITY CONDITIONING ALLO-HCT FOR ACUTE LYMPHOBLASTIC LEUKEMIA IN CR1: A STUDY FROM THE ACUTE LEUKEMIA WORKING PARTY (EBMT)

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Background: For patients with high-risk acute lymphoblastic leukemia (ALL), allogeneic hematopoietic cell transplantation (allo-HCT) in first complete remission (CR1) remains standard of care. Recently, the single arm prospective UKALL14 trial showed a 5-year overall survival (OS) of 55% in patients aged 41–65 years. These patients were uniformly transplanted from a matched sibling or unrelated donor using alemtuzumab for in vivo T cell depletion (TCD) and fludarabine/melphalan reduced-intensity conditioning (RIC). Outside the UK, TCD for this patient population is mostly based on antithymocyte globulin (ATG). We therefore compared outcome of these two transplant strategies.

Methods: This retrospective study from the European Society for Blood and Marrow Transplantation (EBMT) registry included 357 ALL patients aged 40 years or above in CR1 who had received a first allo-HCT from a 10/10 HLA-matched unrelated donor (MUD) in 2010-2021. TCD consisted of ATG ($n = 236$) or alemtuzumab ($n = 121$).

Results: Patients in the ATG group were significantly older (median age 60.4 [range, 40–72] vs 53.6 [range, 40–71] years, $p < 0.0001$). The underlying diagnosis was Philadelphia (Ph)-negative B ALL (23.7% with ATG and 47.1% with alemtuzumab), Ph-positive ALL (60.0% and 34.7%, respectively) or T ALL (15.7% and 18.2%, respectively), $p < 0.0001$. To account for these imbalances, we pair-matched 90 patients in each group according to age (median 56 [range, 40–70] vs 55.7 [range, 41–71] years in the ATG vs alemtuzumab group) and ALL subtype (37.8% Ph-negative B ALL, 46.7% Ph-positive B ALL, 15.6% T ALL in each group).

Median year of allo-HCT was 2016 and time from diagnosis to transplant 6 months in both groups. Patients in the alemtuzumab group received almost exclusively fludarabine/melphalan (Flu/Mel) conditioning (94.4%), while conditioning regimens in the ATG group were fludarabine/busulfan (36.7%), fludarabine/total body irradiation (TBI, 21.1%), Flu/Mel (14.4%) and thiotepa/busulfan/fludarabine (13.3%). GVHD prophylaxis was based primarily on cyclosporine A, either as single agent (74.4% and 11.1% in alemtuzumab and ATG groups, respectively) or combined with methotrexate (12.2% and 34.4%) or mycophenolate mofetil (MMF, 5.6% and 37.8%), whereas 6.7% and 10.0% of patients received tacrolimus +/− methotrexate or MMF, respectively. All but 4 patients engrafted (alemtuzumab: $n = 3$; ATG: $n = 1$).

No difference between groups was observed in terms of leukemia-free survival (LFS) and overall survival (OS) at two years (Alemtuzumab: 56.4% vs ATG: 50.7%, HR 0.82, $p = 0.34$, and 62.7% vs 62.9%, HR 0.91, $p = 0.67$, respectively), Cumulative incidence (CI) of relapse (23.7% vs 23.9%, HR 0.89, $p = 0.69$) and non-relapse mortality (NRM, 19.9% vs 25.4%, HR 0.75, $p = 0.32$), resulting in similar GVHD- and relapse-free survival (GRFS) of 48.9% vs 42.1%, HR 0.8, $p = 0.24$ in alemtuzumab or ATG-treated patients. Leukemia recurrence, GVHD and infection were reported as most frequent reasons for death in both groups. Alemtuzumab and ATG-based TCD was associated with an equally low CI of severe acute GVHD (8.0% vs 6.8%, HR 1.11, $p = 0.84$, respectively) and extensive chronic GVHD (8.4% vs 12.5%, HR 0.5, $p = 0.15$, respectively).

Conclusions: In a well-matched population of ALL patients transplanted in CR1, alemtuzumab and ATG-based immunosuppression, in the context of various RIC regimens, resulted in comparable incidence of acute and chronic GVHD, NRM and survival outcomes.

Disclosure: Gesine Bug received travel grants from Neovii. The other authors had nothing to declare.

16 - Conditioning Regimens

O058

ANTI-CD117 ANTIBODY AND LOW DOSE TOTAL BODY RADIATION ENABLES ALLOGENEIC HEMATOPOIETIC STEM CELL ENGRAFTMENT AND REVERSES AUTOIMMUNE DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) MOUSE MODELS

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Background: Allogeneic hematopoietic stem cell transplant (HSCT) has the potential to cure autoimmune diseases, however the toxicity associated with conditioning limits the use of therapy. Haplomismatched allogeneic HSCT after conditioning with 1000 cGy total body radiation (TBI) with lymphocyte depleting antibody in Lupus (SLE)-prone NZBWF1 mice prevents development of or reverses autoimmune disease (Smith-Berdan et al., 2007). This study evaluated if anti-CD117 antibody can lower the TBI dose required for donor cell engraftment and reversal of autoimmune disease in SLE mouse models.

Methods: NZBWF1 and MRL-lpr mice SLE models were conditioned with a single dose of anti-mouse CD117 antibody (ACK2 clone, 75 mg/kg, day -3 relative to transplant day 0), TBI (650 cGy or 550 cGy, day -2) and anti-CD4 and anti-CD8 antibodies (anti-CD4/8) for three days (-2, -1, and 0). Haplomismatched donor lineage-cKit+Sca+ (LSK) cells isolated from B6D2F1 mice and MHC matched donor lineage-cKit+ (LK) cells isolated from C3H/HeJ mice were transplanted into conditioned NZBWF1 and MRL-lpr mice, respectively. Overall survival, donor cell chimerism in blood and marrow (BM), autoimmune features including splenomegaly, arthritis, lymphocyte expansion in spleen and thymus, and autoantibody titers were assessed following conditioning and transplant.

Results: While 650 cGy TBI and anti-CD4/8 without HSCT in NZBWF1 mice increased overall survival rate compared to unmanipulated age-matched controls, suggesting that 650 cGy TBI is a non-myeloablative conditioning regimen, >90% of mice conditioned with ACK2/TBI died within two weeks after conditioning, indicating effective myeloablation by ACK2/TBI conditioning. HSCT following conditioning increased survival compared to age-matched controls. While TBI alone yielded around 60% haplomismatched donor chimerism in total, myeloid, B-, T-cells in blood, ACK2 synergized with 650 cGy TBI resulting in >90% stable and sustained donor chimerism in NZBWF1 mice at 18 weeks post-HSCT. MHC matched allogeneic HSCT in MRL-lpr mice conditioned with ACK2 and 650 cGy TBI yielded >95% in blood lineage cells. Lowering TBI dose to 550 cGy resulted in 90% total blood donor chimerism. Both 650 cGy and 550 cGy TBI alone conditioning resulted in lower donor cell chimerism than treatment with ACK2/TBI. Autoimmune features were assessed in MRL-lpr mice transplanted with MHC matched LK cells. All assessed autoimmune features were significantly

	Age-matched control ($n = 5$)	TBI + anti-CD4/8 ($n = 5$)	ACK2 + TBI + anti-CD4/8 ($n = 3$)
Spleen			
Weight (mg)	0.73 ± 0.46	0.20 ± 0.08	0.15 ± 0.03
Length (mm)	29.4 ± 6.2	23.2 ± 5.3	18.0 ± 4.4
CD3 + CD4 + T cells (% in live cells)	29.6 ± 12.5	18.6 ± 11.2	12.5 ± 3.8
Thymus			
CD138 + B220+ cells (% in live cells)	0.89 ± 0.73	0.10 ± 0.10	0.05 ± 0.04
Arthritis			
Paw thickness (mm)	2.51 ± 0.28	2.45 ± 0.29	2.18 ± 0.21
Autoantibodies			
Total IgG ($\times 10^7$ ng/mL)	5.16 ± 1.70	2.34 ± 1.55	1.51 ± 0.07
dsDNA ($\times 10^7$ U/mL)	0.99 ± 1.3	1.51 ± 2.08	0.03 ± 0.00
Anti-nuclear antibody ($\times 10^5$ U/mL)	2.14 ± 1.04	2.61 ± 2.89	0.58 ± 0.14

decreased in all transplanted mice compared to age-matched controls, with the most significant improvement observed in mice conditioned with ACK2/TBI prior to HSCT (Table 1), suggesting higher donor cell chimerism may effectively reverse autoimmune disease. Histopathological analysis of kidney and spleen is ongoing.

Conclusions: Anti-CD117 antibody enables the use of reduced TBI in conditioning for successful allogeneic HSCT, leading to reversal of autoimmune disease in SLE mouse models. We provide nonclinical proof of concept that allogeneic HSCT could be a potentially curative treatment for SLE and supports the use of anti-CD117 antibody and low dose TBI as a safe and effective conditioning regime for transplant.

Disclosure: A Wells, C Chang, C Ardoin, A Ji, W pang, H-S Kwon are current employees of Jasper Therapeutics and current holders of *stock options* in a privately-held company. K Martell has nothing to declare.

16 - Conditioning Regimens

O059

LIMITATIONS OF BUSULFAN/FLUDARABINE-BASED PREPARATIVE REGIMEN IN CTLA-4 HAPLOINSUFFICIENCY TO ACHIEVING DISEASE PHENOTYPE CORRECTION

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Background: CTLA-4 haploinsufficiency (CTLA4-HI) is a broad immune dysregulation disorder characterized by multisystem autoimmunity and immune deficiency. HSCT is increasingly offered as a definitive intervention. In this report, we highlight the limitations of myeloablative Busulfan-Fludarabine (Bu-Flu)-based regimens in patients with CTLA4-HI.

Methods: Three patients with CTLA4-HI underwent HSCT between 2018 and 2019 from three centers. Nine patients with nonmalignant disorders without T cell (TC) dysregulation, who underwent allo-HSCT with a similar Bu-Flu-based regimen, constituted the comparison cohort. To gain further insights, we performed TC subset chimerism studies in CD4 recent thymic emigrants (RTE), CD4 and CD8 naïve T cells, T regulatory cells (Tregs), circulating T follicular helper cells (cTfh), and CD4 and CD8 effector memory (EM) cells.

Results: Two patients (P1, P2) underwent MSD and one MUD (P3) HSCT with BM grafts at a median age of 15 years (13-19 years). The cumlative busulfan AUC was 66-95 mg*h/L; fludarabine dose was 160 mg/m2. Alemtuzumab 0.3-0.48 mg/kg was used in two patients (P1, P3), with the final patient receiving no serotherapy. Neutrophil (Day +18) and platelet (Day +24) engraftment was achieved in all patients with complete donor myeloid chimerism. None had aGVHD. Mean TC chimerisms at engraftment, 3 and 6 months, 1 year, 2 years, and last follow-up in the CTLA4-HI group was 20%, 26%, 25%, 45%, 46%, and 49%, respectively; lower than the comparison cohort – 59%, 52%, 70%, 87%, 93%, and 97%, respectively. Corresponding to low TC chimerism post-HSCT, all three patients had a relapse of autoimmune manifestations with GI enteropathy in P1 (7.5 months post-HSCT) and multilineage immune cytopenia in P2 (3 months, 15 months post-HSCT) and P3 (7 months post-HSCT), necessitating initiation of immune-modulatory therapy. No obvious advantage of donor TC in T reg, cTfh, or CD4 or CD8 EM compartments was noted. P1 died at home unexpectedly at 25 months post-HSCT while still on sirolimus. P2 continues on medications for cytopenias. P3 came off sirolimus 3 years post-HSCT without autoimmune manifestations. CD4 RTE remains mixed donor (69%) >3 years post-HSCT (P2), suggesting incomplete thymic niche clearance, and chimerisms were only 54% in Tregs and 52% in cTfh. Correspondingly, P2 immune phenotype showed both CD4 and CD8 activation with an expansion of cTfh and decreased Treg frequency, which suggests ongoing immune dysregulation.

Conclusions: In our CTLA4-HI cohort, Bu-Flu-based conditioning resulted in inadequate immune ablation, low TC chimerisms, and incomplete or delayed disease phenotype correction. Additionally, unlike classical IPEX where there is an appreciable advantage to donor T regs, no such donor advantage is noted in CTLA4-HI. In addition to enhancing immunoablation, strategies to enhance graft vs. immune dysregulation must be explored.

Disclosure: 1. Jennifer Whangbo: Vor Biopharma (Employee)

2. Rachael Grace: Agios Pharmaceuticals (Consultant, Grants/Research Support Recipient), Novartis (Grants/Research Support Recipient), Sanofi (Consultant), and Sobi (Board of directors)

3. Shanmuganathan Chandrakasan: SOBI (Scientific Advisory Board)

16 - Conditioning Regimens

O060

A PROSPECTIVE STUDY OF ALLOGENEIC STEM CELL TRANSPLANTATION OF A/B T-LYMPHOCYTE DEPLETED GRAFT CONDITIONED WITH A REDUCED INTENSITY REGIMEN IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HCT) is a curative therapy for patients with advanced hematologic malignancies. Despite improvements in transplant outcomes, non-relapse mortality (NRM) secondary to graft versus host disease (GVHD), toxicities related to the conditioning regimen and infectious complications hinder the success of this curative treatment. A very effective method to prevent GVHD is by depletion of T lymphocytes from the allograft (T cell depleted transplant, TCD). However, this type of transplant is done mostly with the use of a high intensity myeloablative conditioning regimens. Identifying a reduced intensity conditioning regimen that allows engraftment of a TCD graft has the potential to improve transplant outcomes. This is particularly relevant in elderly patients and those with significant co-morbidities.

Methods: This is a prospective pilot study with a primary end point of ability to achieve sustained donor stem cell engraftment of a T cell depleted (TCD) graft following a reduced intensity conditioning regimen (RIC). Patients were conditioned with Fludarabine 30 mg/m2 daily x 5, anti-thymocyte globulin (ATG) 2 mg/kg/daily x 3 and TBI 2GY daily x 2 and received post-transplant cyclophosphamide (PT-Cy) 50 mg/kg/daily x 2 with aim to further reduce host T cells as well as one dose of Rituxan 200 mg/m2 to reduce risk of EBV PTLD. The TCD graft was composed of a TCR-α/β^+ lymphocyte depleted and CD34+ selected peripheral blood stem cells (PBSC) graft from HLA-matched (related and unrelated) donors.

Results: Between May 2018 and March 2022, 18 patients were screened, 14 were enrolled, 2 are not evaluable and total of 12 are evaluable on study. All patients were treated for MDS or AML. Patient's characteristics and main outcomes are summarized. The median CD34 dose was 7.39X10(6) cells/kg (5.8–12.5) and the median dose of the TCR-α/β^+ depleted product was 17.21 x 10(3) cells/kg (0–164.7). All patients engrafted with median time of 15 days for both neutrophils and platelets engraftment, ranging between 13–24 and 10–22 days, respectively. There was one late graft rejection, and the patient underwent a successful 2nd transplant. The OS and RFS at 2 years post-transplant were 86% (95% CI 63–100%) and 76% (95% CI 51–100%), respectively. Among the 4 relapses, 2 occurred within 6 months, 1 at 1-year and the other, more than 2 years post-transplant. Six patients suffered from acute GVHD, all were grade II (skin and/or upper gut) and only one with lower gut GVHD requiring systemic steroids. There were no cases of chronic GVHD. Median CD4 and CD8 counts at 3 months post-transplant were 37 cells/uL (4–258) and 60 cells/uL (2–727) and at 6 months 118 cells/uL (51–538) and 254 cells/uL (30–833), there was no evidence of B cell recovery at these time points.

Conclusions: In this study we demonstrated that using a strong lymphodepleting conditioning regimen is sufficient to allow consistent engraftment of a T cell depleted graft. Moreover, the lack of NRM, severe acute GVHD and chronic GVHD in this elderly patient population is encouraging and requires further evaluation.

Disclosure: I have no COI to disclose

6 - Experimental Transplantation and Gene Therapy

O061

LENTIVIRAL-MEDIATED EX-VIVO GENE THERAPY FOR PEDIATRIC PATIENTS WITH SEVERE LEUKOCYTE ADHESION DEFICIENCY-I (LAD-I): INTERIM RESULTS FROM AN ONGOING PHASE 1/2 STUDY

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Background: Severe leukocyte adhesion deficiency-I (LAD-I) is an autosomal recessive inborn error of immunity due to mutations in the ITGB2 gene that encodes the common CD18 subunit of β2-integrins, essential for neutrophil adhesion to the inflamed endothelium and transmigration into tissues. Severe LAD-I, defined as <2% of normal CD18 polymorphonucleocyte [PMN] expression, is characterized by frequent and often refractory bacterial and fungal infections, impaired wound healing, and significant pediatric mortality in the absence of allogeneic hematopoietic stem cell transplant (alloHSCT). AlloHSCT is potentially curative but limited by donor availability, graft-versus-host disease, and graft failure. The gene therapy RP-L201-0318 (NCT03812263) employs autologous CD34+ cells transduced with a lentiviral vector carrying ITGB2 to restore CD18 expression.

Methods: Patients ≥3 months old with severe LAD-I were enrolled. Hematopoietic stem cells (HSCs) were collected via apheresis after mobilization with granulocyte-colony stimulating factor and plerixafor and transduced ex-vivo with Chim-CD18-WPRE-LV. Myeloablative therapeutic drug monitoring (TDM) busulfan conditioning preceded RP-L201 infusion. Patients were followed for safety and efficacy measures, including survival to age two and ≥1-year post-infusion, peripheral blood (PB) PMN CD18 expression, PB vector copy number (VCN), neutrophilia improvement, decrease in infections/hospitalizations, and resolution of skin/periodontal abnormalities.

Results: Nine patients (age 5 months to 9 years) received RP-L201 with follow-up of 12 to 24 months. RP-L201 cell doses ranged from 2.8x106 to 10x106 CD34+ cells/kg with a drug product VCN of 1.8 to 3.8. All nine patients demonstrated PMN CD18 restoration (median expression of 56.3%) with sustained, stable genetic markings (median PB mononuclear cell VCN of 1.53). At one year, the overall survival (OS) rate was 100% per Kaplan–Meier estimate. Pre-treatment leukocytosis improved uniformly. Hospitalizations and severe infections were significantly reduced following therapy. No RP-L201-related serious adverse events (SAEs) were reported. Insertion site analyses indicate highly polyclonal integration patterns across the entire cohort.

Conclusions: RP-L201 has a favorable safety profile and confers durable correction of the severe LAD-I phenotype with improved

clinical course in all nine pediatric patients treated as demonstrated via all laboratory and clinical parameters.

Clinical Trial Registry: NCT03812263

Disclosure: Booth: SOBI: Consultancy, Honoraria; Orchard Therapeutics: Consultancy, Honoraria; Takeda: Honoraria; Rocket Pharmaceuticals, Inc.: Consultancy; GSK: Honoraria. Sevilla: Inventor on patents on lentiviral vectors filed by CIEMAT, CIBERER and Fundación Jiménez Díaz, and may be entitled to receive financial benefits from the licensing of such patents. Rocket Pharmaceuticals, Inc.: Consultant, Patents & Royalties, Licensed Medical Products. Consultant/ Advisor/Honorarium for the following: Amgen, Novartis, Miltenyi, Sobi. Rao: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Lopez: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Almarza: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Terrazas: There are no relationships to disclose. Zubicaray: Novartis: Consultancy. González-Vicent: There are no relationships to disclose. Chetty: There are no relationships to disclose. G O'Toole: There are no relationships to disclose. J Xu-Bayford: There are no relationships to disclose. E Nicoletti: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. A Fernandes: There are no relationships to disclose. C Kuo: There are no relationships to disclose. De Oliveira: Bluebird Bio: Research Funding; Orchard Therapeutics: Research Funding. Moore: There are no relationships to disclose. Choi: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. M Zeini: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. C Mesa-Núñez: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Thrasher: Orchard Therapeutics: Consultancy and Equity Ownership; Rocket Pharmaceuticals, Inc.: Consultancy; 4Bio Capital: Consultancy; Generation Bio: Consultancy and Equity Ownership. Schwartz: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Bueren: Rocket Pharmaceuticals, Inc.: Consultancy; Other: Inventor on patents on lentiviral vectors filed by CIEMAT, CIBERER and Fundación Jiménez Díaz, and may be entitled to receive financial benefits from the licensing of such patents and receives funding for research. Kohn: Consultancy and Scientific Advisory Board Member: Allogene Therapeutics, Pluto Therapeutics, ImmunoVec, MyoGeneBio.

6 - Experimental Transplantation and Gene Therapy

O062

BIOCHEMICAL ENGRAFTMENT AND CLINICAL OUTCOMES OF EX-VIVO AUTOLOGOUS STEM CELL GENE THERAPY FOR MUCOPOLYSACCHARIDOSIS TYPE IIIA

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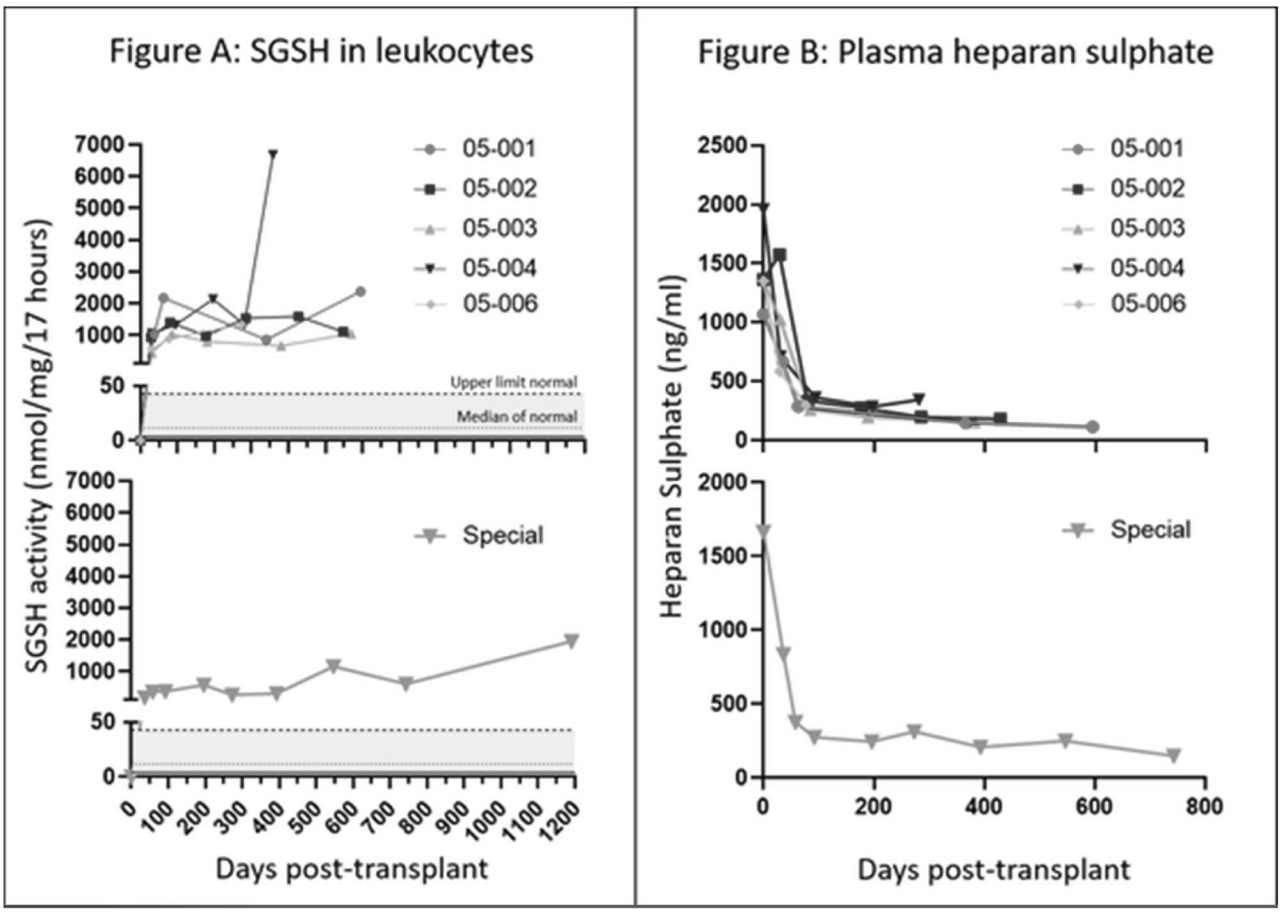

Background: Mucopolysaccharidosis type IIIA (MPSIIIA, Sanfilippo syndrome) is a lysosomal storage disease caused by a gene defect in the SGSH gene, producing the defective enzyme N-sulfoglucosamine sulfohydrolase. Children with MPSIIIA, accumulate the substrate of SGSH, heparan sulphate, in all cells in the body, causing developmental delay, regression of previously acquired skills, hyperactivity, seizures and progressive cognitive decline. The disease is life-limiting, with death occurring typically within the second decade of life. MPSIIIA is unresponsive to allogeneic stem cell transplant.

Autologous ex vivo hematopoietic stem cell gene therapy (HSC-GT) is an experimental treatment for MPSIIIA, with the insertion of a functional copy of the SGSH gene into the patient's own CD34+ stem cells prior to transplant, to allow overexpression of the missing SGSH enzyme.

Methods: This is a phase I/II open label study (NCT04201405/EudraCT#2019-002051-42) with primary outcomes of safety and tolerability and peripheral expression of SGSH activity in total leukocytes at 12 months. Secondary endpoints include neurocognition with measures including the Bayley Scales of Infant and Toddler Development. Patients will be followed for a minimum of 3 years.

Five patients with severe MPSIIIA, aged 6 to 24 months, have been treated with HSC-GT as part of this trial, completing enrolment. All children underwent stem cell mobilization and peripheral collection of CD34+ cells, followed by transduction with the lentiviral vector and cryopreservation. Patients received myeloablative busulfan condition before infusion of the drug product.

Results: Three trial patients have >18 months follow-up post-transplant, one patient has >12 months and one patient has >9 months. Vector copy number of the IMP ranged from 1.19 to 8.91 copies/cell, with a cell dose between 4.3 to 22.7x106 CD34 + / kg. Engraftment was rapid with median time to neutrophil, platelet and red cell engraftment of 19, 28 and 25 days, respectively. In all patients, engraftment is sustained to date, with supra-physiological levels of SGSH enzyme measurable in leukocytes (38-91-fold above median normal range at one-month post-transplant; see Fig. A). Supra-physiological SGSH levels were also rapidly detected in CD15+ lineages, plasma and bone marrow. CSF SGSH levels were within or above normal range by 6-months post-transplant. Abnormal heparan sulfate levels at baseline were rapidly reduced in both urine (>90%) and plasma (82%, see Fig. B), and CSF.

Neurocognitive assessments of trial patients continue and early outcomes will be presented suggesting an alteration in the neurologic phenotype of the disease in one patient, whilst three patients are currently within the normal DQ range but require longer follow-up.

Conclusions: Treatment with ex-vivo autologous HSC-GT is well tolerated and delivers supra-physiological levels of enzyme throughout the body, and early data suggest a clinically significant modification of the neurologic phenotype.

Clinical Trial Registry: NCT04201405

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

O063

EFFICACY AND SAFETY OF RUXOLITINIB IN PATIENTS WITH STEROID-REFRACTORY CHRONIC GRAFT VERSUS HOST DISEASE AFTER CROSSOVER IN THE PHASE 3 REACH-3 STUDY

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Background: Chronic graft-versus-host disease (cGvHD) is a serious complication experienced by 30–70% of allogeneic stem cell transplant recipients. Standard first-line therapy is glucocorticoids; however, approximately 50% of patients become steroid-refractory or dependent (SR/D), both conditions being associated with worse outcomes. Ruxolitinib, a JAK1/2 selective inhibitor, was recently approved in the US and Europe for the treatment of adult/adolescent patients with SR/D cGvHD based on the results from the REACH-3 randomized clinical trial (NCT03112603).[1] In REACH-3, ruxolitinib demonstrated, among several endpoints, a significantly higher overall response rate (ORR) at week 24, best overall response (BOR) at any time, and a longer duration of response (DOR) compared with best available therapy (BAT).[1] Here, we evaluated the efficacy and safety of ruxolitinib in patients who crossed over from BAT.

Methods: Patients aged ≥12 years diagnosed with SR/D cGVHD were randomized to receive either ruxolitinib ($n = 165$) or investigator-selected BAT ($n = 164$). Patients receiving BAT could crossover to ruxolitinib on or after cycle 7 day 1 (week 24) if they did not achieve or maintain response, had a cGVHD flare, or developed toxicity to BAT.

Results: Overall, 69 patients (42.1%) crossed over to ruxolitinib. At data cutoff (June 25, 2021), two patients had completed the crossover treatment period, and 34 patients (49.3%) were still receiving ruxolitinib. Patients who stopped ruxolitinib before 24 weeks were considered non-responders. Thirty-three crossover patients (47.8%) discontinued ruxolitinib treatment, the most common reasons for discontinuation were physician decision ($n = 10$), lack of efficacy ($n = 8$) and subject/guardian decision ($n = 6$). A total of 22 crossover patients (31.9%) entered long-term survival follow-up.

The ORR at week 24 after crossover was 47.8% (95% CI: 35.6–60.2%). Complete response (CR) was observed in three (4.3%) patients, while 30 (43.5%) patients achieved a partial response (PR). The BOR during crossover was 79.7% (95% CI: 68.3–88.4%), including CR, 5.8% and PR, 73.9%. These response rates are consistent with observations in the primary analysis.[1]

After crossover, the median duration of exposure with ruxolitinib was 75.7 weeks (range, 2.6–135 weeks). Even with longer exposure, the safety profile of ruxolitinib after crossover from BAT was consistent with that observed for ruxolitinib in the primary analysis (Table 1). The most common AEs were anemia (20.3%; grade ≥3, 8.7%), upper respiratory tract infection (18.8%; grade ≥3, 4.3%), cough (15.9%; grade ≥3, 0%) and pyrexia (14.5%; grade ≥3, 1.4%). There were 6 deaths (8.7%), mainly due to infection ($n = 3$), while 1 patient died due to cGVHD.

Table 1. Overview of AEs

	BAT→RUX ($n = 69$)[a]	RUX ($n = 165$)[b]
Duration of exposure, median (range), weeks	75.7 (2.6–135.0)	41.3 (0.7–127.3)
AEs (any grade), *n* (%)	65 (94.2)	161 (97.6)
AEs Grade ≥3, *n* (%)	39 (56.6)	94 (57.0)
Serious AEs (any grade), *n* (%)	25 (36.2)	55 (33.3)

	BAT→RUX ($n = 69$)[a]	RUX ($n = 165$)[b]
Serious AEs (Grade ≥3), *n* (%)	23 (33.3)	49 (29.7)
AE leading to discontinuation, *n* (%)	5 (7.2)	27 (16.4)?

AE adverse event, *BAT* best available therapy, *RUX* ruxolitinib
[a]Crossover analysis data cut-off date: 25-June-2021
[b]Primary analysis data cut-off date: 08-May-2020

Conclusions: Ruxolitinib led to high response rates in patients who crossed over from BAT to ruxolitinib. ORR and BOR were consistent with those seen with ruxolitinib during the randomized period.[1] No new safety signals were observed in crossover patients. These findings support the use of ruxolitinib in patients with SR/D cGVHD who have not responded to other systemic therapies.

Reference:
1 Zeiser R, et al. N Engl J Med 2021;385:228–238

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT03112603

Disclosure: D. Russo has received honoraria from Medac and MSD, meeting/travel support from Medac, and has been a member of advisory boards for Janssen, Jazz, Medac, and Novartis. F. Locatelli 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. T. Teshima has received research 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 MSD, Novartis, and Takeda. S J. Lee has received research funding from Amgen, AstraZeneca, Incyte, Kadmon, Pfizer, and Syndax, is a member of a steering committee at Novartis, has been provided with study medication by Janssen, and has consulted for Equillium, Kadmon, and Mallinckrodt. M. Gowda, X.Li, and T.Stefanelli are employed by Novartis. R.Zeiser has received honoraria from Incyte, Mallinckrodt, Sanofi and Novartis.

12 - Graft-versus-host Disease – Clinical

O064

POST-TRANSPLANT CYCLOPHOSPHAMIDE (PTCY) *VERSUS* ANTI-THYMOCYTE GLOBULIN (ATG) *VERSUS* COMBINATION FOR GRAFT-*VERSUS*-HOST DISEASE PREVENTION IN HAPLOIDENTICAL TRANSPLANTATION FOR ADULT ACUTE MYELOID LEUKEMIA: A REPORT FROM THE EBMT

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Background: Different strategies are employed for graft-versus-host disease (GVHD) prevention in allogeneic stem cell transplantation (allo-SCT), with increasing popularity of post-transplant cyclophosphamide (PTCy) particularly in haploidentical transplants (haplo-SCT). Using the European Society for Blood and Marrow Transplantation (EBMT) registry, we compared PTCy-based GVHD prophylaxis *versus* anti-thymocyte globulin (ATG) as well as their combination in haplo-SCT for adult patients with acute myeloid leukemia (AML).

Methods: In this retrospective registry-based analysis, we identified 3649 adult patients (43.3% females; median age: 53.6 years [range, 18–76]) with AML undergoing haplo-SCT in complete remission between 2007 and 2021 at 260 participating EBMT centers. Cord blood transplants, combined bone marrow and peripheral grafts, and transplants with ex-vivo graft manipulation were excluded. Patients were divided into 3 groups, those receiving PTCy only ($n = 2999$), those receiving ATG only ($n = 358$), and those receiving combination prophylaxis ($n = 292$). Median follow-up was 31.8 months.

Results: The 3 groups mostly had similar characteristics, however notable differences included higher rates of non-adverse cytogenetics in the ATG only group (86.6% vs 80.7% in PTCy only and 79.8% in combination, $p = 0.022$), lower percentage of NPM1 mutations (29.7% vs 40.8% in PTCy only and 34.9% in combination, $p = 0.01$), higher rate of myeloablative conditioning (MAC) (57.3% vs 48.3% in PTCy only and 47.6% in combination, $p = 0.005$), and higher proportion of stem cells collected from the bone marrow (43.9% vs 30.9% in PTCy only and 18.8% in combination, $p < 0.0001$).

In multivariate analysis, after adjusting for patient age and performance status, disease status at transplant and cytogenetics risk, conditioning intensity and stem cell source as well as sex matching and patient and donor cytomegalovirus positivity, we found significant differences between the 3 groups. Compared to PTCy alone, ATG alone had higher risk of non-relapse mortality (NRM) (HR = 1.55, $p = 0.004$), worse leukemia-free survival (LFS) (HR = 1.35, $p = 0.005$), overall survival (OS) (HR = 1.46, $p = 0.001$), and GVHD-free and relapse-free survival (GRFS) (HR = 1.25, $p = 0.025$). Furthermore, the PTCy and ATG combination was superior to either one alone in terms of both grade II-IV (combination vs PTCy only HR 0.51, $p = 0.0003$; combination vs ATG only HR 0.5, $p = 0.002$) and grade III-IV acute GVHD (aGVHD) incidence (combination vs PTCy only HR 0.5, $p = 0.018$; combination vs ATG only HR 0.44, $p = 0.019$). No difference was observed between the 3 groups in terms of chronic GVHD (cGVHD).

Conclusions: We conclude that compared to PTCy, ATG is associated with a higher NRM, lower LFS, OS, and GRFS, however when added to PTCY, the combination can lead to lower incidence of aGVHD without otherwise affecting outcome. Our results are in line with other reports comparing PTCy and ATG in haploidentical transplants in other settings, and we propose the routine use of either PTCy alone or in combination with ATG over the standalone use of ATG in haploidentical transplants in AML.

Disclosure: Abdul-Hamid Bazarbachi received research funding from the American Society of Hematology (ASH).

12 - Graft-versus-host Disease – Clinical

O065

THIRD-PARTY FECAL MICROBIOTA TRANSPLANTATION FOR THE TREATMENT OF HIGH-RISK TREATMENT-NAIVE ACUTE GRAFT-VERSUS-HOST DISEASE OF THE LOWER GASTROINTESTINAL TRACT

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Background: Disruption of the intestinal microbiome has been implicated in the development of acute graft-versus-host disease (GVHD) following allogeneic hematopoietic cell transplantation (allo-HCT). Previous studies have demonstrated the potential of fecal microbiota transplantation (FMT) as a treatment for refractory acute GVHD. We hypothesized that the administration of third-party FMT via oral capsules is feasible and safe to treat high-risk treatment-naïve lower GI GVHD.

Methods: In this open-label single-arm pilot study, adult allo-HCT recipients who developed high-risk acute GVHD were enrolled and treated. Subjects had either treatment-naïve (<3 days of corticosteroids ≥1 mg/kg/day) high-risk GVHD as defined by Refined Minnesota Criteria or steroid-refractory (SR) GVHD. All subjects had lower GI involvement. FMT treatment was scheduled as a standard dose (15 capsules/day for 2 consecutive days) followed by 3 maintenance doses (15 capsules/day, once weekly). For subjects with treatment-naïve GVHD, FMT was given in combination with standard systemic corticosteroids. All FMT capsules were prepared from a single donor, following initial donor evaluation and serial screening procedures. The primary endpoint of this study was feasibility of FMT capsules for lower GI acute GVHD. Donor FMT capsules and serial subject stool samples were subjected to metagenomic shotgun sequencing for microbiome characterization. 3-indoxyl sulfate levels were measure on serial urine samples.

Results: 10 subjects were enrolled on the study, with treatment-naïve ($n = 9$) or SR ($n = 1$) GVHD. 9 participants were able to complete all eligible doses, meeting the primary study endpoint of feasibility. There were no treatment-related significant adverse events observed. There were 2 cases of bacteremia in the first 28 days after FMT (MRSA, Lactobacillus), both unrelated to FMT. At day 28, the ORR was 80% (60% CR, 20% PR). Initial clinical response was observed within 1 week for all responders. The lower GI CR rate at Day 28 was 70%. Clinical responses have been durable, without recurrent lower GI GVHD in subjects achieving CR. Among responders, the median duration of response was 152 days and 7 subjects had an ongoing GI response at data cutoff. Median follow-up among survivors was 311 days (range, 69, 443). NRM and OS at 6 months were 21% and 79%, respectively. There have been 2 deaths, both due to GVHD in non-responders.

At baseline, all subjects had dysbiotic microbiomes with low richness and high abundance of taxa, notwithstanding heterogenous microbial composition. Microbial richness increased significantly among responders. Increasing 3-IS levels were observed, correlating with improved diversity. Microbial community structures trended away from baseline composition and approximating donor composition 28 days following FMT, but without achieving high degree of donor similarity. Seven days following FMT, we observed a significant increase in *Alistipes finegoldii*, *Bacteroides uniformis*, *Eggerthella lenta* among all CRs but not in the single NR.

Conclusions: Administration of third-party FMT via oral capsules is feasible and safe in the treatment of high-risk lower GI GVHD. High clinical response rates and durable responses were observed. Continued investigation is needed to optimize microbiome-targeted interventions in the treatment for LGI acute GVHD.

Clinical Trial Registry: NCT04139577

Disclosure: Nothing to declare.

12 - Graft-versus-host Disease – Clinical

O066

SYSTEMIC COMPLEMENT ACTIVATION INFLUENCES OUTCOMES AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION: A PROSPECTIVE FRENCH MULTICENTER TRIAL

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Background: Complement activation (CA) has shown a role in murine models of graft-versus-host-disease (GvHD) and in endothelial complications after allogeneic hematopoietic cell transplantation (allo-HCT). However, its impact on post-transplant outcomes has not been so far fully elucidated.

Methods: Here, we conducted a prospective multicentric trial to explore the activation of complement cascade, performing serial measurements of complement proteins (C3, C4, Factor B) and regulators (C1 esterase inhibitor -C1i-, CD46, CD55, CD59, CD88, Factor H, Factor I) along with CH50 activity, for 12 weeks after allo-HCT in 85 patients receiving a MAC for hematological malignancies. We correlated composite metrics of complement activity with clinical outcomes and histologically characterized complement deposition on targeted acute GvHD organs.

Results: Based on the kinetics of C3, C4 plasma levels and CH50 activity, 26 patients showed a complement "activated" profile defined as a post-transplant decline of these components as compared to pre-HCT concentrations. In this group we did not observed significant dysregulation of Factor B or altered levels of complement regulators C1i, Factor I, CD46 and CD55, indicating that neither alternative pathway activation nor impaired complement inhibition contributed to this profile. In contrast the remaining

79 patients were characterized by a sustained or increased plasma levels of C3, C4 and of CH50 activity ("non-activated" group. Patients in both groups had comparable pre-transplant characteristics, except for a higher frequency of advanced diseases in activated group ($p = 0.01$). Median time of CA was 21 days (range 10–70) post-HCT. Univariable and multivariable time-dependent COX regression models demonstrated that CA was associated with increased non relapse mortality (HR: 3.69: 95% CI: 1.55–8.78, $p = 0.003$), poor overall survival (HR: 2.72 (95% CI: 1.37–5.39), $p = 0.004$) and progression free survival (HR: 2.69; 95% CI: 1.39–5.20, $p = 0.003$), and increased incidence of grade II–IV acute GvHD (HR: 4.24, 95%CI: 2.12–8.49, $p < 0.001$), with a striking correlation with gastro-intestinal (GI) GvHD (HR: 36.8, 95% CI 12.4–109.1, $p < 0.001$). Interestingly, in these patients CA was always observed before onset of GI symptoms (median of 3.5 days, IQR 2-6.5). Through immune-staining techniques we demonstrated the exposition of C1q and C5b9 components on endothelial vascular cells in gut biopsies of patients developing this complication. The number of stained vessels was correlated with the histological grade of GvHD, while no complement deposition was shown in control biopsies. CA was also associated with higher incidences of thrombotic microangiopathy (HR: 8.58, 95% CI 2.6–34.08, $p = 0.0022$), capillary leak syndrome (HR:7.36, 95% CI: 2.51–21.66, $p = 0.00028$), bacterial infections after engraftment (HR: 2.37, 95% CI: 1.22–4.63, $p = 0.01$) and EBV reactivation (HR: 3.33, 95% CI: 1.31–8.45, $p = 0.0112$).

Conclusions: Altogether these findings, powered by the force of a prospective trial, demonstrate that classical complement activation after allo-HCT is associated with poor survival, acute GvHD, endothelial complications and infections and may have a pathophysiological role in severe GI GvHD. These results support the prognostic role of post-transplant complement monitoring and pave the way for assessing the use of complement inhibition strategies in patients with alloreactive complications.

Clinical Trial Registry: NCT01520623

Disclosure: No COI

12 - Graft-versus-host Disease – Clinical

O067

MACHINE LEARNING-BASED IDENTIFICATION OF THREE DISTINCT PATHWAYS IN PRIMARY AND SECONDARY OPERATIONAL TOLERANCE AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) USING THE PROSPECTIVE ABLE1.0 PEDIATRIC STUDY COHORT

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Background: Understanding the mechanisms underlying primary operational tolerance (no aGvHD or cGvHD) and secondary operational tolerance (with aGvHD that resolved by day 100 and developed no cGvHD) after HSCT is important for designing chronic graft-versus-host-disease (cGvHD) preventions. We hypothesized that multiple pathways exist for achieving operational tolerance.

Methods: The ABLE pediatric cohort ($N = 241$) was prospectively evaluated at 3, 6, and 12 months after HSCT. Fifteen clinical factors, 75 cell populations by whole blood phenotyping, 10 cytokines and chemokines, and 132 metabolites were measured with clinical adjudication for late aGvHD and cGvHD. We clustered primary tolerance ($N = 73$) and both primary and secondary operational tolerance ($N = 109$) into subgroups based on their marker patterns at 3, 6, and 12 months post-HSCT. We first identified markers that separate immune tolerant patients from cGvHD and late aGvHD using linear mixed models with clinical factors as fixed effect confounds and subject-specific intercepts and number of days post-HCT to blood collection as random effects. Markers meeting all three of the following criteria were used for clustering tolerant patients into subgroups: $p < 0.05$, ROC AUC > 0.6, and effect ratio ≥ 1.3 or ≤ 0.75. Clustering was performed by applying the Girvan-Newman algorithm with marker values from all three time points jointly used as features. To determine markers that distinguish the subgroups for each time point, we applied multiple regression to contrast the marker values of each subgroup against all other subgroups, with the 15 clinical factors as confounds. Markers were considered relevant based on the same criteria above except we stricten the p-value threshold to $p < 0.05/217$ tested markers.

Results: Evaluation of primary tolerant patients found three distinctive subgroups. Subgroup A was Naïve T cell predominant with an increase in Th, Tc and Treg at 3 months post HSCT. This pattern persisted when evaluated at both 6 and 12 months post HSCT and was associated with a sibling donor HSCT. Subgroup B was characterized by a metabolome predominant pattern with high biogenic amines and an increase in long, medium, and short chain fatty acids. This subgroup also showed a decrease in the organic acids, lactic acid, succinic acid, and an increase in methylmalonic and homovanillic acid. Unlike subgroup A, the subgroup B pattern did not persist at 6 and 12 months but was characterized by an increase in Naïve T cell populations. Subgroup B associated most closely with a PBSC donor source. Subgroup C was characterized by high Memory Th, Tc, and lysophosphatidylcholines at 3 months. While the lysophosphatidylcholines elevation diminished at the 6 and 12 months, the memory cell population predominance persisted until 12 months. Subgroup C associated most clsely with an unrelated donor. Evaluation of the primary plus secondary tolerant group together also found 3 clusters with patterns similar to primary tolerance.

Conclusions: These marker patterns represent testable hypotheses of operational immune tolerance after HSCT, suggesting that both primary and secondary tolerance develop along similar pathways. Strategies for induction of tolerance after HSCT may need to adjust to different clinical settings.

Disclosure: There are no conflicts to disclose.

12 - Graft-versus-host Disease – Clinical

O068

GVHD PROPHYLAXIS INCORPORATING METHOTREXATE IN ALLO-HCT FOR CHRONIC MYELOID MALIGNANCIES AND SAML: A RETROSPECTIVE ANALYSIS FROM THE CMWP OF THE EBMT

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Background: Methotrexate (MTX) given on days 1, 3, 6 (and 11) after allogeneic haematopoietic cell transplantation (allo-HCT) along with calcineurin inhibitors (CNI) was established as effective GVHD prophylaxis decades ago when myeloablative conditioning was standard. Although MMF was associated with more severe GVHD in some reports, similar survival outcomes were reported for both regimens in most randomized trials and in meta-analyses. Taking advantage of a very large sample size within the EBMT registry, the aim of this retrospective study was to determine outcome differences after allo-HCT between MTX- and MMF-based GVHD prophylaxis regimens considering subgroup heterogeneity.

Methods: Eligible were patients from the EBMT registry with select chronic myeloid malignancies (CML, CMML, MDS, myelofibrosis, secondary AML) who were transplanted from matched related, matched unrelated and mismatched unrelated donors between 2007 and 2017 and received either MTX or MMF prophylaxis in combination with a CNI. Endpoints were overall (OS) and relapse-free survival (RFS), relapse incidence, non-relapse mortality (NRM), and cumulative incidence of grade 2-4 acute GVHD. Cause specific hazards models were fitted for relapse and NRM. We tested whether the association between the type of prophylaxis and the outcome was different in patient subgroups by including interaction terms in multivariable analyses between prophylaxis type (MTX/MMF) and ATG, age, Tacrolimus, conditioning intensity, use of TBI, diagnosis, disease stage and recipient CMV status. Finally, we studied the association between the same set of variables and OS, relapse and NRM in patients after aGvHD and separately in a landmark analysis at 3 months in patients without aGvHD.

Results: Overall, 13699 patients from 321 centers were included. CNI prophylaxis was Tacrolimus ($n = 1248$), ciclosporin ($n = 12286$), both ($n = 165$). Median follow up was 42.8 months (IQR 19.8–74.5 months).

Unadjusted analyses demonstrated significantly better outcomes with MTX in all subgroups of patients (TBI/no TBI, RIC/MAC, diagnoses except myelofibrosis, ATG/no ATG, age at allo-HCT < or ≥60 years). The cumulative incidence of acute GVHD grade 2-4 was lower in in particular RIC patients.

MTX was associated with significantly reduced overall mortality (HR 0.88, 95% CI 0.81–0.95, $p < 0.001$) and NRM (HR 0.87, 95% CI 0.78–0.96, $p = 0.008$) in multivariable analyses in the whole cohort.

Notably, there was no significant interaction effect between prophylaxis type and any of the eight variables (ATG, age, tacrolimus, conditioning intensity, use of TBI, diagnosis, disease stage and CMV status in recipients) tested for OS and NRM, except that the beneficial association of MTX on OS was weaker for patients with Myelofibrosis.

OS after acute GVHD was significantly lower with MTX prophylaxis and this was similar in RIC and MAC. MTX did not significantly associate with improved outcome in a landmark analysis in patients without aGvHD at 3 months after allo-HCT.

Conclusions: Compared to MMF, MTX-complemented calcineurin inhibitor prophylaxis was associated with favorable early OS and NRM, and in particular with favorable OS after aGVHD. These results may have future impact on clinical practice and trial design.

Clinical Trial Registry: None

Disclosure: Nothing to disclose

11 - Graft-versus-host Disease – Preclinical and Animal Models

O069

HUMAN MICROBIOTA-REACTIVE DP8A REGULATORY T CELLS EXPRESSING CD73 ARE LACKING IN ACUTE GVHD PATIENTS AND PREVENT DISEASE DEVELOPMENT IN A PRE-CLINICAL HUMANIZED MOUSE MODEL

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Background: Allogeneic stem cell transplantation (allo-HSCT) to treat hematological malignancies can induce life-threatening complications, such as graft-*versus*-host disease (GvHD). Increasing evidences strongly suggest that gut microbiota composition and the activity of regulatory T cells (Tregs) could be involved in GvHD prevention.

We have identified a novel FoxP3-negative IL-10-secreting Treg subset, named DP8a, which displays a TCR-specificity for the gut *Clostridium IV* bacterium *Faecalibacterium prausnitzii*. Sizable fractions of these cells also expressed the membrane-bound ectonucleotidases CD39 and CD73, which are directly involved in their suppressive activity in vitro.

Altogether, these data prompted us to hypothesize that *F. prausnitzii*-reactive DP8a Tregs could bridge microbiota dysbiosis and GvHD incidence in allo-HSCT patients.

Methods: We first used flow cytometry to study the DP8a Treg subset in 63 patients (*Table I*) with hematological malignancies, who received allo-HSCT, among whom a third developed aGvHD. Next, we evaluated the therapeutic efficacy of DP8a Tregs in a pre-clinical model of acute xeno-GvHD induced through human PBMC i.v. injection in irradiated NSG mice. Immunohistochemistry and flow cytometry were also used to analyze mouse samples.

Results: We quantified circulating DP8a Tregs and their CD39 and CD73 expression pre- and post-allo-HSCT. A strikingly deficiency of CD73-expressing DP8a Tregs was strongly associated with aGvHD development ($p < 0.001$) at 1-month post-transplant, as compared to aGvHD-free patients or patients before transplantation. Importantly, CD73 expression was not affected on any other T cell subset analyzed and did not result from corticotherapy. Altogether, these data strongly suggest that a CD73-dependent functional alteration of DP8a Tregs could, at least in part, be involved in aGvHD occurrence and/or development.

We next evaluated the therapeutic efficacy of $CD73^+$ DP8a Tregs in a pre-clinical model of acute xeno-GvHD induced through human PBMC injection in irradiated NSG recipient mice. In vitro-expanded $CD73^+$ DP8a Treg injected i.v. drastically protected mice against xeno-GvHD (Log-rank, $p < 0.0001$; without preventing the development of human chimerism. Moreover, these in vivo experiments, repeated 4 times using different PBMC donors, all confirmed the potent protective role of $CD73^+$ DP8a Tegs in this

		Healthy Donors ($n = 38$)	Patients ($n = 63$)
Gender	Female: *n* (%)	20 (47.6%)	28 (44.4%)
Age	Years: Median (min, max)	54 (36, 72)	60 (22, 71)
Disease	AML	N/A	24 (38.1%)
	ALL		8 (12.7%)
	MDS		14 (22.2%)
	Lymphoma		9 (14.3%)
	Myelofibrosis		6 (9.5%)
	Others		2 (3.2%)
Donor Type	Haplo-identical	N/A	27 (42.9%)
	Matched 10/10 : - Familial		10 (15.9%)
	- Unrelated		26 (41.2%)
Conditioning	MAC	N/A	9 (14.3%)
	RIC		54 (85.7%)
GvHD Prophylaxis	Ciclosporin	N/A	2 (3.2%)
	Ciclosporin / ATG		3 (4.8%)
	Ciclosporin / MMF / ATG		21 (33.3%)
	Ciclosporin / Methotrexate		1 (1.6%)
	PTCy		7 (11.1%)
	PTCy / Ciclosporin / MMF		19 (30.2%)
	PTCy / Ciclosporin / MMF / ATG		10 (15.9%)
Complication	No GvHD	N/A	27 (42.9%)
	Grade II aGvHD		18 (28.6%)
	Grade III, IV aGvHD		3 (4.8%)
	cGv38HD		5 (7.9%)
	Death by GvHD		4 (6.3%)
	Relapse		13 (20.6%)
	Death by Relapse		5 (7.9%)
	Other Deaths		6 (9.5%)
Organ targeted by aGvHD	Skin	N/A	10 (45%)
	Intestine		9 (41%)

model. Accordingly, serum inflammatory human cytokines and tissue infiltration by human cells were significantly lower in mice treated with $CD73^+$ DP8a Tregs, as compared to untreated mice. In addition, the colon was rapidly populated with the injected DP8a Tregs and well-preserved in treated mice, while clearly damaged in untreated mice.

Conclusions: Altogether, these results strongly support a role for $CD73^+$ DP8a Tregs in aGVHD prevention and advocate for the use of these cells to both predict aGvHD risks and give rise to the development of innovative therapeutic strategies to preclude GvHD-related inflammation. Such therapeutic approaches would be based on the infusion of DP8a Tregs and/or their in vivo stimulation, e.g., with *F. prausnitzii*-derived antigens or probiotics. Of note, DP8a Tregs display an uniquely high proliferating potential and stable immunosuppressive functions in vitro, a key feature to implement such therapeutics.

Disclosure: Nothing to declare

11 - Graft-versus-host Disease – Preclinical and Animal Models

O070

MOCRAVIMOD AMELIORATES CHRONIC GRAFT-VERSUS-HOST DISEASE AFTER MOUSE ALLOGENEIC HSCT

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Background: Sphingosine-1-phosphate receptor (S1PR) modulators are a new drug class that sequesters T cells in the lymph nodes (LNs) by downregulating S1PR1. We have previously shown that short-term administration of the S1PR1-specific modulator mocravimod (KRP203) ameliorated mouse acute graft-versus-host disease (GVHD), while significant graft-versus-leukemia (GVL) effects were maintained even after prolonged administration of mocravimod (Yokoyama, BMT 2020). In the current study, we tested whether long-term administration of mocravimod could ameliorate chronic GVHD, using a mouse model of allogeneic bone marrow transplantation (allo-BMT).

Methods: BALB/c (H-2^d) mice were irradiated (5.5 Gy) and intravenously injected with 8×10^6 bone marrow cells combined with 15×10^6 splenocytes from minor histocompatibility antigen-mismatched allogeneic B10.D2 (H-2^d) donors on day 0. Recipients were orally administered with 3 mg/kg/day mocravimod or diluent from day -1 to day +42 after allo-BMT. To evaluate graft-versus-leukemia (GVL) effects, B6D2F1 recipients were injected with luciferase-expressing P815 leukemia cells on day 0 of allo-BMT.

Results: We found chronic GVHD skin scores were significantly reduced by mocravimod, and lachrymal secretion volume was significantly preserved in mocravimod-treated recipients. Pathological skin chronic GVHD scores and the fibrotic area in the liver and salivary glands were significantly decreased in mocravimod-treated recipients compared to vehicle-treated controls. Flowcytometric analysis on day +42 demonstrated that prolonged administration of mocravimod significantly reduced both $CD4^+$ and $CD8^+$ donor T cells in the mesenteric LNs, suggesting that mocravimod induced activation-induced cell death of donor T cells as expected (Hashimoto Eur J Haematol 2007, Yokoyama BMT 2019). Importantly, mocravimod significantly reduced donor $CD4^+$ T cells while sparing $CD8^+$ T cells in other organs, such as spleen, bone marrow, and liver. Mocravimod significantly increased absolute numbers of $CD62L^-PD\text{-}1^+TOX^+$ exhausted T cells in the mesenteric LNs, while it did not affect the numbers of exhausted T cells in other organs, further confirming that mocravimod strengthens donor T-cell activation specifically in the LNs. It was expected that $CD8^+$ T cells persisting after mocravimod-treatment could contribute to GVL. Thus, we evaluated GVL effects using another mouse GVHD model in which B6D2F1 recipients were transplanted from C57BL/c donors and injected with recipient-type luciferase-expressing leukemia. Leukemia-injected recipients were treated with mocravimod (day 0–42) alone or in combination with short-term (day 0–14) or long-term (day 0–42) cyclosporine (CSP). In vivo bioluminescence imaging demonstrated that leukemia was rejected in the recipients treated with vehicle or mocravimod alone. In sharp contrast, CSP significantly increased leukemia expansion, while CSP cessation on day +14 blunted leukemia growth, suggesting that mocravimod spared potent GVL effects after allo-BMT.

Conclusions: Mocravimod primarily reduced $CD4^+$ donor T-cell expansion while sparing $CD8^+$ T cells after allo-BMT, which ameliorated chronic GVHD and contributed to persisted GVL effects after mocravimod-treatment.

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S.D. is an employee of Priothera.

11 - Graft-versus-host Disease – Preclinical and Animal Models

O071

THE DNA-SENSOR AIM2 PROMOTES BCR-ACTIVATED B CELLS IN CHRONIC GRAFT-VERSUS-HOST-DISEASE

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Background: Chronic graft-versus-host-disease (cGVHD) remains a common cause of late non-relapse morbidity/mortality after allogeneic hematopoietic stem cell transplantation (allo-HCT). T cells and IgG-producing B cells mediate cGVHD development and perpetuation. New treatments have shown encouraging success, but molecular mechanisms driving immune pathology require further study to develop new drugs. We studied B cells from the peripheral blood (PB) of allo-HCT patients with single cell RNA-sequencing and we identified *AIM2* as a prime candidate for further investigations (*Poe, bioRxiv 2022*). AIM2 senses double-stranded DNA (dsDNA) to incite inflammasome-mediated pyroptosis in macrophages, but AIM2 function in B cells is largely unknown. AIM2 is expressed by CD27+ antigen-experienced B cells in healthy individuals (HI) (*Svensson, PlosOne 2017)* and emerging evidence suggests that AIM2 promotes IgG production *(Yang, Signal Transduct Target Ther 2021)*. We hypothesize that AIM2 promotes pathological B cells and anti-host IgG production in cGVHD.

Methods: We used intracellular flow cytometry and PB samples from HI and allo-HCT patients to study AIM2 protein expression. We performed dsDNA lipofection to study the pyroptotic function of AIM2 in human B cells. We assessed the effects of AIM2 on the humoral response by immunizing AIM2-KO and WT mice with NP-KLH+alum. We studied the amount of *AIM2* transcripts in B cells in our mouse model of bone-marrow transplantation (BMT) with cGVHD manifestations (*Jia, Blood 2021*), using WT donors. We also used $AIM2^{fl/fl}Mb1^{Cre/+}$ conditional KO mice (AIM2-CKO), deficient in AIM2 only in B cells, to be compared with $AIM2^{fl/fl}Mb1^{+/+}$ control littermates as BMT donors.

Results: The AIM2 protein was expressed by antigen-experienced B cells in the PB from HI (CD27+ and CD27- IgD-). After allo-HCT, we found a higher proportion of AIM2+ cells in the CD27+ IgD- post-germinal center (GC) B cells from cGVHD patients ($n = 13$) vs. no cGVHD patients ($n = 8$, $p = 0.04$). In our BMT mouse model, we found significant overexpression of *AIM2* transcripts in B cells from cGVHD+ mice ($p = 0.03$, Fig. 1A). In HI, CD27 + B cells had nuclear localization of AIM2 and did not undergo pyroptosis after stimulation with dsDNA. This was not due to a deficiency of inflammasome components in B cells which readily died after nigericin stimulation that activates the NLRP1/3 inflammasome sensors. AIM2-KO mice had larger splenic GC vs. WT controls ($p < 0.0001$) at day 8 after NP-KLH immunization. GC enlargement paradoxically associated with lower anti-NP IgG levels ($p = 0.03$) from day 28. In our BMT model, cGVHD+ mice have a higher proportion of GL7 + BCR-activated blood B cells (*Jia et al., Blood 2021*). We then asked whether AIM2 promoted GL7 + B cells. At day 24 post-BMT, cGVHD+ recipients from AIM2-CKO mice had a significantly lower percentage of GL7 + B cells vs. cGVHD+ recipients from the AIM2-sufficient littermates ($p = 0.004$, Fig. 1B).

Conclusions: Our data show that AIM2 promotes IgG-producing B cells and circulating GL7 + B cells in cGVHD mice. AIM2 may play

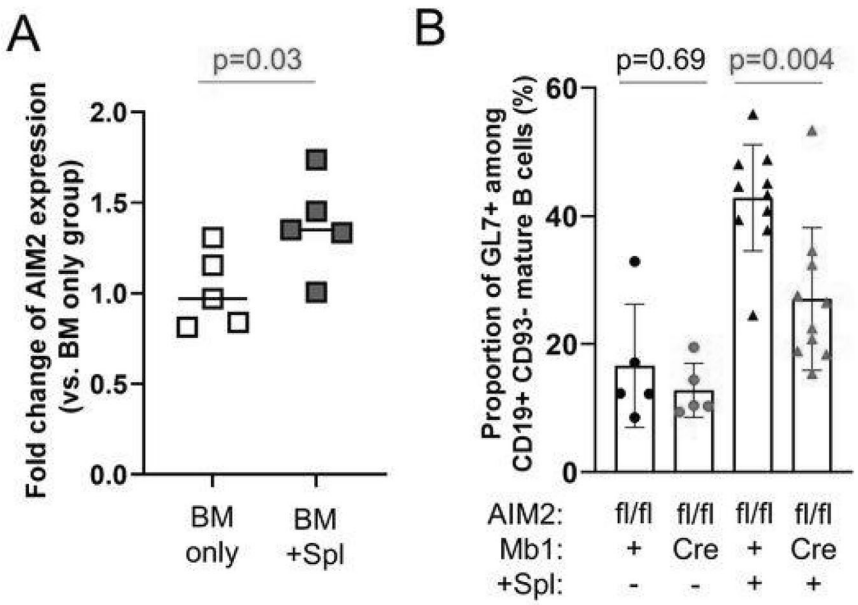

Figure 1 - AIM2 is increased in total B cells and promotes GL7+ BCR-activated B cells in mouse cGVHD. **A**: Comparison of AIM2 transcript levels in splenic B cells purified on Day +83 post BMT from mice +/- cGVHD manifestations. cGVHD BALB/c mice were lethally irradiated and received T-cell depleted bone marrow (BM) +/- low dose T cell splenocytes (Spl) from wild-type C57BL/6 donors (*Wu et al., J Immunol 2013*). Because there is no anti-mouse AIM2 antibody available for intracellular flow cytometry, we performed qPCR after RNA extraction and cDNA synthesis to measure *AIM2* mRNA. We compared the 2 groups with the ΔΔCt method, the BM only group being used as the reference. N=5/group, Mann-Whitney U-test. **B**: Comparison of GL7+ B cells in mice +/- cGVHD after BMT with B-cell AIM2 knockout or AIM2-sufficient donors. BALB/c mice were lethally irradiated and received BM +/- Spl from C57BL/6 donors sufficient ($AIM2^{fl/fl}$ $Mb1^{+/+}$) or deficient ($AIM2^{fl/fl}$ $Mb1^{Cre/+}$) for AIM2 in B cells. At day 24 post-transplant, the mice were bled and the percentage of GL7+ BCR-activated B cells among CD19+ CD93- mature B cells was determined by flow cytometry. N=5 for BM only groups, N=10 for BM+Spl groups, Mann-Whitney U-test.

a novel non-canonical inflammasome-independent role in cGVHD B cell pathology. We are actively investigating how AIM2 effects alloantibody production and cGVHD development, so that therapeutic targets can be identified.

Disclosure: Vincent Ho: Consultancy for Alexion, Allovir and Omeros, Research Funding from Jazz

11 - Graft-versus-host Disease – Preclinical and Animal Models

O072

MEMORY $CD4^+$ T CELLS EFFICIENTLY RECOGNIZE DIVERGENT HLA-DP IMMUNOPEPTIDOMES RELEVANT IN ALLOGENEIC HCT

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Background: Naïve T-cell (TN) responses are considered the main mediators of alloreactivity involved in graft-versus-host disease after hematopoietic cell transplantation (HCT), prompting clinical trials using TN-depleted grafts composed of CD34-selected peripheral blood stem cells supplemented with enriched memory T cells (TM) from HLA-matched related or unrelated donors (Bleakley et al. *J Clin Oncol* 2022). In the matched unrelated donor setting, the potential targets of alloreactive $CD4^+$ T cells are either minor histocompatibility antigens (mHAg), i.e., genetic variant-bearing peptides presented by matched HLA molecules, or permissive or non-permissive HLA-DP mismatches. We have previously demonstrated that the immunopeptidome divergence between mismatched HLA-DP allotypes determines the strength and T-cell receptor (TCR)-diversity of the alloreactive $CD4^+$ T-cell response and is regulated by the peptide editor HLA-DM (Meurer et al. *Blood* 2021). Here, we hypothesized that divergent immunopeptidomes generated by structural differences or HLA-DM deregulation could impact the relative role of TN vs TM cells in alloreactive responses against HLA-DP.

Methods: We used an established in vitro model of HCT to stimulate isolated TN ($CD45RA^+CD45RO^-$) and TM ($CD45RA^-CD45RO^+$) cells from healthy individuals with HeLa cells expressing costimulatory molecules and single HLA-DP allotypes (HeLa-DP), either matched or permissively or non-permissively mismatched to the responder, in the presence or absence of HLA-DM. Alloreactive T-cell responses were quantified by CD137 upregulation, and the TCR alpha (TRA) and beta (TRB) repertoires of responding cultures were investigated by next-generation sequencing. HLA-DP immunopeptidomes were characterized by tandem mass spectrometry, and probed for candidate mHAg by comparative whole-exome sequencing of responders and HeLa-DP stimulators in the presence or absence of HLA-DM.

Results: In the presence of HLA-DM, alloreactive $CD4^+$ TN responses against mHAg presented by matched HLA-DP, and against permissive HLA-DP mismatches with low immunopeptidome divergence were significantly stronger than those from the TM subset ($14.4 \pm 13.9\%$ vs $5.9 \pm 7.7\%$, $p = 0.0041$ and $16.7 \pm 14.3\%$ vs $3.0 \pm 3.3\%$, $p = 0.005$, respectively). In contrast, $CD4^+$ TM responses against non-permissive HLA-DP mismatches with high immunopeptidome divergence were strong and not significantly different from TN responses ($40.0 \pm 18.1\%$ vs $33.4 \pm 22.3\%$, $p = 0.08$). 133 SNP-bearing peptides from 50 genes were identified in the immunopeptidomes of HeLa-DP. Absence of the peptide editor HLA-DM significantly increased the number of candidate mHAg presented in the HeLa-DP immunopeptidomes (7.9 ± 5.1 to 18.9 ± 7.2; $p = 0.016$). Presentation of these novel mHAg by self-HLA-DP in the absence of HLA-DM was associated with a significant increase in the $CD4^+$ alloresponse to comparable levels in the TN and TM subsets ($33.9 \pm 14.6\%$ vs $36.3 \pm 15.7\%$, $p =$ n.s.).

Conclusions: TM cells contribute substantially to the alloresponse against divergent immunopeptidomes presented by structurally diverse, non-permissive HLA-DP mismatches, as well as against deregulated mHAg presented by matched HLA-DP in the absence of HLA-DM immunopeptidome editing. Our findings bear implications for the efficacy of naïve T-cell depletion strategies to prevent graft-versus-host disease after HCT, in particular with unrelated donors where HLA-DP disparity is common.

Disclosure: Nothing to declare

11 - Graft-versus-host Disease – Preclinical and Animal Models

O073

CIRCULATING EXTRACELLULAR VESICLES RELEASED BY ANTI-HUMAN THYMOCYTE GLOBULINS (ATG)-EXPOSED MONONUCLEAR CELLS CAN CONTRIBUTE TO IMMUNE MODULATION IN ALLOGENEIC STEM CELL TRANSPLANTATION

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Background: Polyclonal anti-human thymocyte globulins (ATG) significantly reduce the incidence of graft versus host disease (GVHD) post allogeneic stem cell transplantation (HSCT), while inducing regulatory T cells. Exosomes were previously demonstrated to be a therapeutically active component of immunoregulatory cells. Here we explored the potential tolerogenic role of exosomes derived from peripheral blood (PB) or cord blood (CB) mononuclear cells exposed to ATG assessing their ability to attenuate immune responses.

Methods: Purification and functional analysis of ex vivo generated exosomes and circulating exosomes from the peripheral blood of patients undergoing allo-HSCT with ATG conditioning were utilized.

Results: In vitro analyses revealed that ATG-produced exosomes suppressed the stimulation and proliferation of CD3/CD28 activated CD3 + T cells and inhibited IFNγ secretion, both in a purified T cell fraction as well as in the PBMCs co-culture.Proteomic characterization identified 196 proteins being up-regulated and 55 proteins being down-regulated in ATG-generated exosomes (Exo-ATG) compared to control IgG-treated vesicles. Among others, we identified immunomodulatory molecules NAMPT and GZMB being up-regulated in exosomes upon ATG pre-treatment and confirmed their functional role in the suppression of T cell activation.Furthermore, we characterized the incorporation ability of generated exosomes into different immune cell populations. Notably, ATG treatment significantly improved the uptake of exosomes by more differentiated memory (both central and effector) CD4+ and CD8 + T cells. Moreover, CD8 + T cells with the activated phenotype (PD1-positive and CD25-positive) exerted the enhanced uptake of ATG-generated exosomes. Accordingly, IL-2 stimulation similarly increased the ability of CD25-expressing T cells to incorporate ATG-generated exosomes. These results strengthen the ability of ATG-generated exosomes to preferentially target activated effector T cells. Additionally, Exo-ATG effectively incorporated into myeloid cells, promoting immunomodulatory M2 phenotype acquisition. Furthermore, Exo-ATG suppressed lipopolysaccharide (LPS)-activated human macrophages and reduced their LPS-stimulated cytokine and chemokine production including IL-1β, IL-6, IL-8, CCL5, and TNFα. Taking into account the role of LPS-activated M1 macrophages in GVHD development, this exosome ability can be a relevant approach in the settings of GVHD treatment. Notably, our results demonstrate that ATG antibodies present on the generated exosomes, and can be transferred to recipient cells upon exosome uptake, possibly contributing to immune modulation. Finally, ATG was detected in the circulating exosomes from the peripheral blood of patients undergoing allo-HSCT with ATG conditioning. Moreover, patient-derived purified exosomes demonstrated strong immunosuppressive activity, inhibiting T cell proliferation and activation ex vivo.

Conclusions: Our findings suggest that in patients receiving ATG pre-HSCT as anti-GVHD prophylaxis, ATG can be present and transferred with the exosomes to different target organs, therefore exhibiting different pharmacokinetic characteristics. Ex vivo generated ATG-loaded immunosuppressive exosomes provide a novel therapeutic tool for GVHD.

Disclosure: Nothing to declare

1 - Haematopoietic Stem Cells

O074

OUTCOME OF SECOND ALLOGENEIC HSCT IN NON-SCID INBORN ERRORS OF IMMUNITY (IEI): AN INTERNATIONAL COHORT ANALYSIS (EBMT IEWP SECOND ALLO STUDY GROUP)

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Background: Graft failure (GF) is a serious complication after HSCT. This multicentre study compared the outcomes of second HSCT in 160 children with non-SCID IEI between 2009 and 2020.

Methods: Primary endpoints were overall survival (OS) and event-free survival (EFS; survival without GF, grade III-IV acute GvHD (aGvHD), extensive chronic GVHD (cGVHD) and third transplant). Variables included for predictor analysis were Karnofsky score (KS), active infection at HSCT, conditioning, donor, use of same donor, stem cell (SC) source. Subgroup differences in OS and EFS were evaluated by log-rank test. Competing risks methods were used for the cumulative incidence (CI) of aGvHD and cGVHD, with competing events being represented by death, graft failure, and a subsequent transplant. Subgroup differences in GvHD were evaluated by Gray's test.

Results: Diagnoses were CGD ($n = 45$, 28%), combined immunodeficiency ($n = 16$, 10%), neutrophil disorders ($n = 16$, 10%), WAS ($n = 15$, 9%), MHC class II deficiency ($n = 11$, 7%) and others ($n = 57$, 36%). Median age at first transplant was 2.4 years (1–18 years) and donors were MFD ($n = 23$; 14%), MUD ($n = 100$, 63%), MMFD ($n = 36$, 23%) and MMUD ($n = 1$).

Median age at second HSCT was 4.1 years (0.5–25 years). Median interval between first and second transplant was 6.2 months (0.7–189 months). At second HSCT, 40 (28%) had KS ≤70, 46 (30%) had infection and 26 (17%) had autoimmunity. 45 (37%) had the same donor. Donor were MFD ($n = 27$; 17%), MUD ($n = 83$; 52%), MMFD ($n = 49$; 31%) and MMUD ($n = 1$). SC source was BM ($n = 72$; 46%), PBSC ($n = 69$; 44%) and CB ($n = 11$;7%). Conditioning were myeloablative (MAC, $n = 74$; 52%), reduced intensity (RIC, $n = 53$; 37%) and reduced toxicity (RTC, $n = 15$; 11%). 5-year OS and EFS for the entire cohort 76% (68–83%; 95% CI) and 60% (52–68%), respectively. OS was inferior in patients with KS ≤70 at 64% (49–79%) compared to 85% (78–93%) in KS >70 ($p = 0.001$). Infection was associated with inferior OS at 66% (50–81%) compared to patients without infection (83%, 75-90%) ($p = 0.03$). OS was inferior in CB 36% (8–65%) compared to BM 78% (67–88%) and PBSC 82% (73–92%) ($p < 0.001$). Donor type ($p = 0.08$), use of the same donor ($p = 0.46$) and conditioning ($p = 0.54$) had no impact on OS.

The significant predictors for EFS was KS (<70, 39%, 24–55% versus >70, 70%, 61–79%, $p < 0.001$), infection (43%, 27–59% versus no infection, 69%, 60–78%, $p = 0.009$), conditioning (MAC 66%, 55–77% versus RTC 52%, 27-78% versus RIC 48%, 34–62%, $p = 0.049$) and SC source (BM 64%, 52–76%; PBSC 64%, 52–75%; CB 27%, 1–54%, $p = 0.017$). Donor type ($p = 0.89$) and use of same donor ($p = 0.36$) had no impact on EFS. Day-100 cumulative incidence of grade III-IV aGVHD was 7% (3-11%; 95% CI). One-year CI of extensive cGVHD was 5% (1–8%). Of 35 (22%) deaths, the causes were infection ($n = 14$, 52%), GVHD ($n = 2$, 7%), other transplant complications ($n = 9$, 34%) and disease related complications ($n = 2$, 7%).

Conclusions: Second HSCT for non-SCID IEI is a safe strategy for GF and associated with low risk of severe GVHD. Optimization of pre-transplant status, conditioning and stem cell source potentially improve the EFS for second transplant.

Clinical Trial Registry: None

Disclosure: None

23 - Haemoglobinopathy

O075

IMPROVED T-CELL CHIMERISM AND SUCCESSFUL WITHDRAWAL OF IMMUNOSUPPRESSION AFTER NON-MYELOABLATIVE STEM CELL TRANSPLANTATION FOR SICKLE CELL DISEASE WITH AZATHIOPRINE/HYDROXYUREA PRECONDITIONING ADDED TO ALEMTUZUMAB/TBI CONDITIONING

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only established curative treatment option for sickle cell disease (SCD). In adult SCD patients, myeloablative conditioning is associated with significant toxicity, primarily because of cumulative organ damage. Recently, matched sibling donor (MSD) transplantation with non-myeloablative conditioning (alemtuzumab/3 Gy total body irradiation (TBI)) showed promising outcomes in adult SCD patients. This chemotherapy-free regimen, typically resulting in mixed chimerism, is associated with mild toxicity with no reports of graft-versus-host disease (GvHD). Despite mixed chimerism, the red blood cell (RBC) phenotype is completely donor-derived. However, in a large series, 13% of patients experienced graft failure. Another 8.2% of patients could not stop their immunosuppression (sirolimus) after one year, because of low donor T-cell chimerism (<50%). Reported mean donor T-cell chimerism at 12-months post-transplantation was 48%. (Br J Haematol. 2021 Feb;192(4):761–768).

We hypothesized, that the addition of azathioprine and hydroxyurea as preconditioning to the alemtuzumab/TBI conditioning regimen will reduce the risk of graft failure and improve donor T-cell chimerism, enabling successful withdrawal of sirolimus in all patients.

Methods: Adult SCD patients with an available HLA-identical sibling donor were eligible for this treatment. All patients received three months of azathioprine 150 mg qd and hydroxyurea 25 mg/kg qd preconditioning. After exchange transfusion (target HbS <30%), conditioning with alemtuzumab 1 mg/kg total dose and 3Gy TBI started on day -7, followed by unmanipulated peripheral hematopoietic stem cell infusion on day 0. Sirolimus as GvHD and rejection prophylaxis started on day -1.

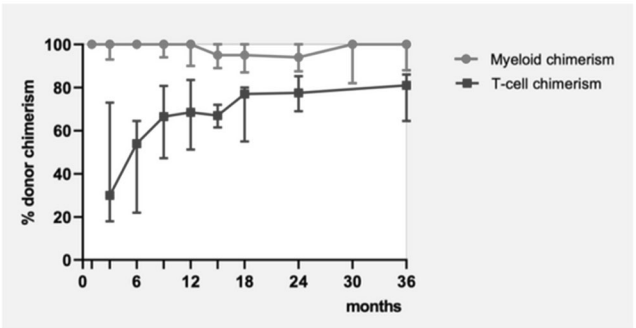
Results: Twenty SCD patients (median age 26 (range 19–49) years) were transplanted with a median follow-up of 26.0 months (range 3.3-55 months). Patient and transplant characteristics are shown in Table 1. Median donor myeloid and T-cell chimerism of engrafted patients was 100% (range 87–100%) and 68.5% (range 37–89%) at 12-months post-transplantation and 94% (range 86–100%) and 78.5% (range 68–88%) at 18-months post-

transplantation, respectively (Fig. 1). These donor T-cell chimerism percentages are higher than previously reported with alemtuzumab/TBI conditioning only. All engrafted patients had a corrected SCD phenotype with normalized hemoglobin levels. Importantly, all patients with a follow-up of ≥12 months ($n = 12$) could successfully taper and stop sirolimus without decreases in donor chimerism. One year estimated disease-free survival and overall survival were 94.7%. and 93.3%, respectively. One patient (5%) experienced graft failure without autologous regeneration and subsequently died after a series of complications, including EBV reactivation, post-transplantation lymphoproliferative disease, and systemic aspergillosis. Acute gastrointestinal GvHD grade 2 occurred in one patient (5%) and resolved quickly after treatment with prednisolone.

Table 1. Patient and transplant characteristics

	Patients ($n = 20$)		
Age at transplant, median years (range)	26 (19–49)	Medical management before HSCT, ***n* (%)**	
Male/Female gender, *n*	7/13	Hydroxyurea	16 (80.0%)
SCD genotype, *n* (%)		Chronic RBC exchange transfusions	7 (35.0%)
HbSS	16 (80.0%)	Patient/donor gender mismatch, *n* (%)	11 (55.0%)
HbSß+	2 (10.0%)	ABO mismatch, *n* (%)	
HbSß0	2 (10.0%)	Major	5 (25.0%)
Coexisting conditions and indications for HSCT, *n* (%)		Minor	4 (20.0%)
VOC	17 (85.0%)	Bidirectional	1 (5.0%)
ACS	12 (60.0%)	None	10 (50.0%)
AVN	6 (30.0%)	Composition of infused graft, median (range)	
PH, elevated TRV	5 (25.0%)	CD34+ cells, x10^6/kg	9.7 (7–11.3)
Retinopathy	4 (20.0%)	CD3+ cells, x10^7/kg	20.7 (7.3–89.6)
Nephropathy	3 (15.0%)		
Stroke	1 (5.0%)		
Priapism	1 (5.0%)		
Hepatopathy	1 (5.0%)		
Splenic sequestration	1 (5.0%)		
Septic arthritis	1 (5.0%)		

Figure 1. Median (IQR) donor myeloid and T-cell chimerism after HSCT



Conclusions: Azathioprine/hydroxyurea preconditioning prior to alemtuzumab/TBI resulted in improved donor T-cell chimerism, potentially reducing the risk of graft failure after non-myeloablatieve MSD transplantation in SCD patients. Importantly, all engrafted patients reached donor T-cell chimerism >50% and were able to stop immunosuppressives as scheduled.

Clinical Trial Registry: ClinicalTrials.gov number: NCT05249452

Disclosure: Nothing to declare.

23 - Haemoglobinopathy

O076

PRE-TRANSPLANT IMMUNE SUPPRESSION AND POST-TRANSPLANT CYCLOPHOSPHAMIDE (APOLLO PROTOCOL) BEYOND HAPLOIDENTICAL FAMILY DONOR HEMATOPOIETIC STEM CELL TRANSPLANT FOR HEMOGLOBINOPATHIES: DOES IT HELP CONSOLIDATE OUR GAINS?

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Background: Awaiting gene therapy, hematopoietic stem cell transplant (HSCT) is only curative treatment for Transfusion Dependent Thalassemia (TDT)/Sickle Cell Disease (SCD). Although conventional myeloablative conditioning (MAB) with calcineurin inhibitor (CNI) based graft-versus-host-disease (GvHD) prophylaxis in HLA identical donors (related/unrelated) (MSD/MRD/MUD) have shown good outcomes but are associated with increased regimen related toxicity (RRT), acute and chronic GvHD especially with use of peripheral blood stem cells (PBSC). We hereby report our experience of using (APOLLO protocol) for HLA identical donor HSCT for TDT/SCD.

Methods: Patients from 1 year to 20 years with TDT or SCD presenting at our center for blood and marrow transplant between November 2019 to November 2022 were enrolled in the study. It was single arm prospective study approved by institutional ethics committee (IAH-BMR-021/07-20). Patients received 1–2 course of Pre transplant Immune-suppression (PTIS) with Flu-Cy-Dex. Conditioning regime included rATG (SanofiGenzyme) 1.5 mg/kg/d (Day-7 to −5) or recombinant ATG Fresenius 5 mg/kg/day (Day-7 to -5), Thiotepa (TT) 10 mg/kg (D-7) in two divided doses, Flu 30 mg/m2/d (Day −7 to −3), Cy 14.5 mg/kg/d (Day −3, −2), total body irradiation (TBI) 2/4 Gy (Day −1). GVHD prophylaxis included Cy 50 mg/kg/day (Day +3, +4), mTOR inhibitor (Sirolimus) 2 mg/m^2/day once and mycophenolate mofetil sodium 10 mg/kg/dose thrice daily.

Results: Thirty-two consecutive patients (TDT-16/SCD-16) were enrolled. Fourteen underwent MUD-HSCT whereas 18 received MSD/MRD. All tolerated PTIS well and proceeded to HSCT. No significant RRT was seen in any of our patients. One patient developed acute grade II/IV GvHD (skin/liver) whereas none of the evaluable patients had chGvHD. CMV reactivation was seen in 7 (21.88%) patients and BK induced hemorrhagic cystitis was seen in 3 (9.38%) patients. Engraftment fever was noticed in 25 (78.13%) patients whereas 2 (6.25%) had Engraftment syndrome. Median CD4+ counts at day +100 was 329 cells/mm3 (range 34–959); CD8+ was 803 cells/mm3 (range 13–2983); CD19+ was 107 cells/mm3 (range 0–1514) and that of CD56+ was 165 cells/mm3 (range 32–1223). Five out of thirty-two patients showed drop in chimerism warranting the need of initiation of

DLI. Post DLI at the last follow-up, all the patients have >95% donor chimerism barring one which has mixed stable chimerism. Out of 32 evaluable patients at a median follow-up of 249.5 days (range 18–1074), 31 are alive and disease free, making an overall survival (OS) and disease-free survival (DFS) of 96.88 %.

Conclusions: APOLLO protocol including PTIS, augmented John Hopkins conditioning and PTCY can safely be extended to HLA identical donors with minimal RRT, acute or chronic GvHD.

Clinical Trial Registry: IAH-BMR-021/07-20

Disclosure: Nothing to declare.

23 - Haemoglobinopathy

O077

IMPROVED CEREBRAL PERFUSION AND OXYGEN METABOLISM AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH SICKLE CELL DISEASE

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Background: Hematopoietic stem cell transplantation (HSCT) is currently the only curative treatment for patients with sickle cell disease (SCD). Whereas several studies have shown that the markers of anemia and hemolysis normalize after HSCT, little is known about the effects of HSCT on the parameters of cerebral perfusion and oxygen metabolism in adult SCD patients. In SCD patients, cerebral blood flow (CBF) is increased to compensate for anemia in order to maintain adequate oxygen delivery. However, despite this, oxygen extraction and consumption have been found to be lower compared to controls. So far only a single study in four SCD patients reported that the CBF and oxygen extraction fraction (OEF) normalized after HSCT. In this work, we analyzed the effect of HSCT on CBF, cerebrovascular reactivity (CVR), OEF and cerebral metabolic rate of oxygen ($CMRO_2$) in adult SCD patients before and after HSCT.

Methods: We included 10 patients (7 HbSS, 2 $HbS\beta^0$ and 1 $HbS\beta^+$; mean age: 28.3 years (19–45), 3 female) who were studied 15–246 days before HSCT and 6–34 months after non-myeloablative matched sibling donor ($n = 8$) or haploidentical HSCT ($n = 2$). Gray matter (GM) and whole brain (WB) CBF were measured using time-encoded pseudo-continuous arterial spin labeling (te-ASL). Venous blood T_2 in the superior sagittal sinus was measured using T_2-Relaxation-Under-Spin-Tagging. Te-ASL was performed before and after a vasodilatory stimulus using acetazolamide (ACZ). OEF was calculated from arterial saturation measured by pulse oximetry and venous saturation calculated from blood T_2 using a SCD-specific calibration model before HSCT and a healthy control model after HSCT. $CMRO_2$ was calculated using the following equation:

$CMRO_2 = WB\ CBF \times OEF \times$ oxygen content where oxygen content was calculated from hemoglobin and arterial saturation.

CVR reflects the capacity of the blood vessels to dilate in response to a vasoactive stimulus and was calculated using the following equation: $CVR = (GM\ CBF_{post\text{-}ACZ} - GM\ CBF_{pre\text{-}ACZ}) / GM\ CBF_{pre\text{-}ACZ} \times 100\%$.where $CBF_{pre\text{-}ACZ}$ and $CBF_{post\text{-}ACZ}$ are the CBF measured before and after ACZ respectively.

A Wilcoxon signed-rank test was used to test the significant differences in parameters before and after HSCT.

Results: Data of one patient were excluded because of severe motion during the te-ASL scan. Hemoglobin levels were significantly higher ($Z = -2.8$; $p < 0.01$) and markers of hemolysis (LDH ($Z = -2.7$; $p < 0.01$), reticulocytes ($Z = -2.8$; $p < 0.01$) and total bilirubin ($Z = -2.8$; $p < 0.01$)) were significantly lower after transplantation. GM CBF significantly decreased after HSCT while GM CVR increased in all patients ($Z = -2.7$; $p < 0.01$). OEF ($Z = -2.2$; $p = 0.03$) and $CMRO_2$, parameters of cerebral oxygen metabolism, significantly increased after transplantation.

Conclusions: Cerebral blood flow normalized after HSCT in adult SCD patients. In addition, we found increased GM CVR after HSCT suggesting an increase in the vasodilatory capacity of the cerebral vessels after HSCT. Cerebral oxygen metabolism, reflected by OEF and $CMRO_2$, was also restored to values reported in healthy controls, indicating improved cerebral oxygen utilization in these patients following HSCT. Looking ahead, follow-up scans need to be performed to determine whether this improved cerebral oxygen metabolism will prevent future cerebral (silent) infarctions.

Disclosure: Nothing to declare.

23 - Haemoglobinopathy

O078

OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THALASSEMIA MAJOR PATIENTS: A 30-YEAR EXPERIENCE FROM A SPECIALIZED CENTER IN TEHRAN, IRAN

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Background: Hematopoietic stem cell transplantation [HSCT] has revolutionized the landscape of thalassemia treatment with anticipated prolonged survival and potential longtime risks, thus long-term real-life data are appreciated.

Methods: We conducted a retrospective study, evaluating data from our registry in a specialized HSCT center. We included all consecutive thalassemia major patients undergoing allogeneic HSCT at Shariati hospital in Tehran, Iran from October 1991 to December 2022.

Results: In total, 812 patients were enrolled (male/female, 1.32:1). The median age of patients at the time of transplantation was 104 months or 8.6 years (range, 24–370 months). Donors were matched related [MRD] (98.5%; other related 9.9%, sibling 90.1%) and matched unrelated [MUD] (1.5%). Myeloablative and non-myeloablative conditioning regimens were employed in 89.3% and 10.7%, respectively. Umbilical cord blood was the source of stem cells for 12 patients (1.5%) and bone marrow was used for 67%. 138 patients developed chronic graft versus host disease [cGVHD] and cGVHD was persistent in 46 during last follow up. Acute GVHD was observed in (33.6%) patients, with one fifth of them being grade III or IV. The 5-year overall survival [OS] and thalassemia-free survival [TFS] were $84.2 \pm 1.3\%$ and $83.5 \pm 1.9\%$, respectively. After the median follow up of 122 months (95% confidence interval [CI], 115–127), the median OS, TFS, and GVHD-

free relapse-free survival probabilities were 89.7%, 86.5%, and 84% respectively. The optimal age cut-off for best OS was nearly 7 years, with an OS of 84.7 ± 2% vs. 89.2 ± 2% and an TFS of 85 ± 1.7% vs. 89.6 ± 2% favoring transplants done before this age ($P = 0.017$ and 0.15, respectively). OS and TFS were also higher for transplants performed after 2000 ($P < 0.001$).

Conclusions: Our large and long-term data carefully collected over three decades in a country with abundant thalassemia cases, confirm that allogeneic HSCT for thalassemia specially before the age of 7, is a curative approach with presumably excellent lifelong results.

Disclosure: Nothing to declare.

23 - Haemoglobinopathy

O079

OUTCOMES OF MATCHED SIBLING DONOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH SICKLE CELL DISEASE – DOES DONOR SICKLE CELL TRAIT STATUS MATTER?

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Background: Allogeneic Hematopoietic Stem cell transplantation (HSCT) remains curative therapy for Sickle Cell Disease (SCD), however lack of suitable donor may be a barrier for its widespread application. Healthy siblings with Sickle Cell (SC) trait could be a suitable donor with no evidence to affect transplant-related outcome. Graft-versus-Host-Disease (GVHD), Transplant-related toxicities, rejection and mortality are complications that may occur.

Methods: Retrospective-chart review of 59 children who underwent HSCT from matched-sibling donors from 2014 to 2022 for SCD (HbSS) was conducted. Primary end-point were Overall Survival (OS) comparing donors with and without SC trait, while secondary endpoints included transplant outcomes and transplant-related complications. Study was approved by the IRB at King Faisal Specialist Hospital & Research Centre, Jeddah, Saudi Arabia.

Results: Median age at transplant was 11.3 years with male (30) to female (29) ratio of 1:1. Transplant indication involved central-nervous-system insult in 68% (40), recurrent Veno-Occlusive pain crisis (VOC) in 17% (10) and VOC pain crisis with acute chest syndrome (ACS) in 15% (9). All donors were HLA-identical siblings with a median age of 15.0 years at donation. Amongst donors, 66% (39) has SC trait, while 34% (20) with normal hemoglobin (Hgb) electrophoresis pattern. All patients received busulfan (16 mg/kg), cyclophosphamide (200mg/kg) and rabbit antithymocyte globulin (7.5mg/kg) as conditioning regimen. Bone marrow was the frequent source of stem cells in 98% (58) with median TNC dose of 3.40 x 10^8/kg (1.65–8.22) and CD34 dose of 11.32 x 10^6/kg (1.68–15.72). The median time of neutrophil engraftment was 19 (10–33) days and platelet engraftment was 22 (12–43) days. Acute (a) GVHD developed in 18 patients (30%) with a median time from product-infusion of 34 days. Grade I-II aGVHD observed in 13 and 5 patients developed grade-III aGVHD. Skin was the major site of involvement, 74% followed by Gut and Liver at 13% each. Chronic GVHD occurred in 4 patients (7%). Post-transplant complications included CMV re-activation in 32 patients (54%), Posterior Reversible Encephalopathy syndrome (PRES) in 7 patients (12%) and Veno-Occlusive disease (VOD) in 4 patients (7%). At a median follow-up of 3.14 years, no patient showed signs/symptoms of SCD and maintaining full (85%) to mixed (15%) chimerism at last contact. Three-year OS of the cohort was 98.3%; when the OS compared for donors with vs. without SC trait, it was 97.4% vs. 100%, it was statistically insignificant. Similarly, when cell dose, cell recovery, chimerism, GVHD and transplant-related complications compared, there was no statistical significance observed (Table-1). One-patient died within 100 days of transplant due to transplant-related complications.

Transplant-related variables	Sickle Cell trait	Free of Sickle Cell trait	*P*-Value
Number of patients	$n = 39$	$n = 20$	
CD34 dose (10^6/kg)	7.71	4.91	0.484
TNC dose (10^8/kg)	3.96	3.33	0.439
Platelet recovery	22	22	0.534
ANC recovery	20	20	0.831
Mixed Chimerism	32	18	0.354
CMV reactivation	23	9	0.308
PRES	4	3	0.594
VOD	3	1	0.350
aGVHD	20	39	0.795
3-year OS	97.4%	100%	0.474

Conclusions: Our results are comparable to internationally reported post-transplant outcomes in SCD. Findings from this analysis documents no statistical difference in product cell-count dose (CD34 and TNC), post-HSCT cell recovery, chimerism, GVHD, transplant-related complications and overall survival when donors with/without SC trait compared. We recommend allogeneic HSCT to be offered as an effective therapy from a healthy HLA-matched sibling donor irrespective of the SC trait status.

Disclosure: Nothing to Declare

23 - Haemoglobinopathy

O080

EXCELLENT GVHD-FREE, DISEASE-FREE SURVIVAL AFTER HAPLOIDENTICAL HSCT WITH PTCY FOR SICKLE CELL DISEASE

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Background: Mismatched family donor (haplo) HSCT for sickle-cell disease (SCD) is increasingly performed as only a minority of patients have matched sibling or unrelated donors. An optimal conditioning and T-cell depletion approach for haplo HSCT remains to be identified. We present the results of pediatric and young adult patients who received an institutional protocol based on post-transplant cyclophosphamide (PTCY).

Methods: Patients with severe SCD undergoing HSCT from 2014 to 2022 with unmanipulated bone marrow from parental HLA-haploidentical donors received conditioning with alemtuzumab 0,4mg/kg, fludarabine 150mg/m^2, thiotepa 10mg/kg, cyclophosphamide 29mg/kg, and treosulfan 42g/m^2. After the initial five patients, treosulfan was replaced by submyeloablative busulfan (target AUC 65-75mg*h/ml) over concerns of insufficient myeloablation with treosulfan. GVHD prophylaxis comprised PTCY (d3 + 4), MMF (until d35) and tacrolimus.

Results: Ten patients were transplanted at a median age of 7 years (range 3-22) with grafts containing a median of 5.1*10^8 TNC/kg (range 2.6-7.9). All had severe SCD with recurrent vaso-occlusive crises (10/10), prior acute chest syndrome (4/10), stroke (2/10), red blood cell allo-immunization (3/10) and anti-donor HLA antibodies (2/10). Total AUC of busulfan ranged from 58 to 70mg*h/ml.

After a median follow-up of 14 months (2–98), all patients are alive. Two experienced secondary graft failure with autologous reconstitution and recurrence of SCD symptoms at 6 and 78 months post HSCT, both after treosulfan-based conditioning. At last follow-up, the remaining eight patients exhibit 100% donor chimerism and a median HbS of 37% (31–41%) reflecting the level of their carrier donors.

Neutrophil (>0.5G/l) and platelet (>50G/l) engraftment occurred at a median of 18 (12–22) and 25 (13-180) days after HSCT. Tacrolimus was stopped at median day 124 (61–146). Early immune reconstitution was encouraging with median CD3 counts of 401/µl (17-2200), CD4 118/µl (4–623), CD8 261/µl (4–1786), and CD19 255/µl (29–1632) at 100 days and 1239/µl (754–2267), 348/µl (182–506), 882/µl (340–1754), and 278/µl (0–1313) at 180 days post HSCT, respectively. Virus reactivation was frequent with CMV viremia - but not CMV disease - requiring treatment in 8/10 patients at risk, and EBV and VZV reactivation occurred in one patient each. Acute toxicity was manageable with hepatic toxicity CTCAE °3 in five patients (ALT >5x ULN), no renal impairment > CTCAE °2, and moderate VOD in one patient. Temporary acute GVHD °II was observed in 2/10 patients. However, neither acute GVHD >°II nor any chronic GVHD occurred.

In summary, we observed overall survival, event-free survival and GVHD-and-relapse-free survival rates of 100%, 80%, and 78%, respectively. All five patients with busulfan-based conditioning are alive, as well as disease and GVHD free at last follow-up.

Conclusions: This protocol with reduced toxicity myeloablative conditioning and haplo PTCY resulted in excellent survival, negligible GVHD and low toxicity in ten pediatric and young adult patients with SCD. Intensifying myeloablation with busulfan may lead to higher rates of disease correction, but further exploration is required.

Clinical Trial Registry: n/a

Disclosure: No potential conflict of interest.

23 - Haemoglobinopathy

O081

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN SICKLE CELL DISEASE: RETROSPECTIVE STUDY ON BEHALF OF THE BRAZILIAN BONE MARROW TRANSPLANTATION AND CELL THERAPY SOCIETY (SBTMO)

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Background: Sickle cell disease (SCD) is a severe genetic disorder affecting approximately 300,000 newborns worldwide, annually. Although few symptomatic treatments are available (i.e., hydroxyurea and blood transfusions), patients with SCD have reduced life expectancy and poor quality of life. Since the first report, in 1984, several authors have described successful hematopoietic stem cell transplants (HSCT) for patients with SCD. However, these reports are limited to developed countries. Experience in HSCT for SCD in developing countries, where most patients with SCD live, is unknown. Here we report the outcomes of 124 patients with SCD from different centers in Brazil transplanted in the past two decades.

Methods: Between 2003 and 2022, 124 patients were transplanted in 21 HSCT centers. One hundred patients (80.6%) were transplanted from matched related donors (MRD) and twenty-four (19.4%) from Haploidentical (HAPLO) donors, most of them following the Vanderbilt Global Haploidentical Transplant Learning Collaborative (VGC2) guidelines. Among patients with MRD donors, bone marrow was the main graft source (93%), followed by peripheral stem cells (3%) and cord blood (4%). All patients undergoing HAPLO transplants had bone marrow grafts. Baseline patients characteristics are reported as median and range (continuous variables) or as numbers and percentages (categorical variables). Demographics and clinical characteristics are shown in Table 1.

	MRD ***N* = 100**	**Haploidentical** ***N* = 24**
Age median (range)	13 (3–39)	13,5(3–37)
Conditioning regimen		
Fludarabine, Busulfan + ATG	80/100 (80%)	-
Busulfan, Cyclophosphamide +ATG	16/100 (16%)	-
Fludarabine, Cyclophosphamide, Thiotepa, TBI + ATG	-	14/24 (57%)
Fludarabine, Cyclophosphamide, TBI + ATG	-	8/24 (33%)
Other	4/100 (4%)	2 (10%)
GVHD prophylaxis		
CsA and short Mtx	95/100 (95%)	-
CsA	3 (3%)	-
CsA and MMF	1 (1%)	-

	MRD $N = 100$	Haploidentical $N = 24$
TACRO and short Mtx	1 (1%)	-
PT-Cy + Sirolimus + MMF	-	21 (87.5%)
PT-Cy +CsA+MMF	-	3 (12.5%)
Graft failure	6/100 (6%)	7/24 (29%)
Median Follow-Up (range)	58 months (2–228)	13.5 months (1–37)
Overall Survival	95%	75%

MRD matched related donors, *ATG* anti-thymocyte globulin, *TBI* total body irradiation, *GVHD* graft versus host disease, *CsA* cyclosporine, *Mtx* methotrexate, *MMF* mycophenolate mofetil, *TACRO* tacrolimus, *PT-Cy* post-transplant cyclophosphamide.

Results: One hundred and nine patients are alive at a median follow-up of 40.5 months (range:1–228). The 4-year overall survival (OS) is 87.5%: 95% in MRD and 75% in HAPLO transplants. One hundred and twenty-one patients (97.5%) engrafted successfully; two died of intracranial hemorrhage on day 8 and sepsis on day 17 and are not evaluable for engraftment. One patient had primary graft failure (PGF) and 13 had secondary graft failure, 7 of 24 undergoing HAPLO, and 6 of 100 undergoing HSCT from MRD. Acute graft versus host disease (GvHD) was reported in 43 patients (34.6%), 4 of them grades III/IV. Thirteen patients have chronic GvHD, moderate/severe in only two of them. Fifteen patients died at a median of 360 days (range 8–6840 days) after HSCT, and the main causes of death were infections and hemorrhage.

Conclusions: Our data showed an OS of 87.5%, and better with MRD donors, compared with HAPLO HSCT, as expected. Although the numbers are small, our results in the MRD setting are similar to what was published in Europe or USA. The high rate of secondary graft failure in HAPLO should be addressed in future studies. Considering the high prevalence of SCD in the Brazilian population and in other low and middle-income countries, a better understanding of the difficulties and challenges of HSCT in this setting is desirable.

Disclosure: Nothing to declare

23 - Haemoglobinopathy

O082

MATCHED SIBLING AND HAPLO-IDENTICAL ALLOGENEIC STEM CELL TRANSPLANTATION OUTCOME OF SICKLE CELL DISEASE: EXPERIENCE OF 104 PATIENTS

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Background: Allogeneic stem cell transplantation (SCT) is the only approved curative option for sickle cell disease (SCD). SCT with HLA-identical sibling donor is associated with an excellent outcome ranging from 90%-100% overall and event-free survival. There is extension to the pool of potential donors to include unrelated and haploidentical donors with different conditioning regimens and GVHD prophylaxis in use.

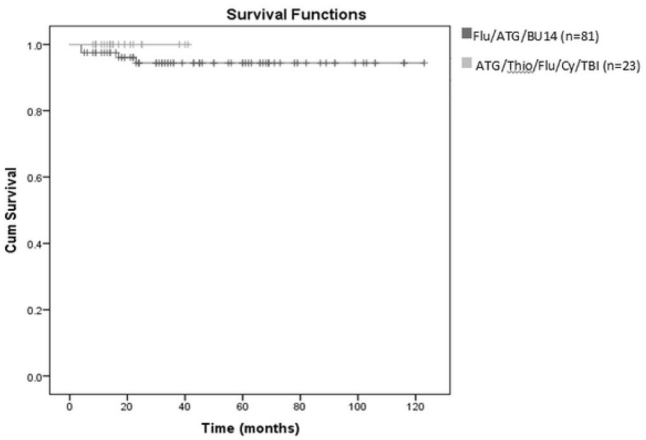
Methods: Patients aged ≥14 years old who underwent SCT for SCD between March 2013 and December 2021 at Adult Hematology, HSCT and cellular therapy section, Oncology center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia were initially reviewed. Two used conditioning regimens were identified, FLU/ATG/BU14 group mainly for matched identical donors and ATG/Thio/Flu/Cy/TBI 200 cGy used for haploidentical donors as part of phase-II trial (ClinicalTrials.gov identifier NCT01850108) and in maternal identical donors. Graft versus host disease (GvHD) prophylaxis in matched identical group were Methotrexate with cyclosporine or tacrolimus (MTX/CSA) in 63 patients and (MTX/FK) in 18 patients, for the haploidentical (haplo-SCT) group PTCy/MMF/Sirolimus was the GvHD prophylaxis ($n = 23$). Here, we report transplantation outcomes for both groups for acute and chronic GvHD, CMV reactivation and survival rates.

Results: The whole cohort included 104 patients with median age was 21.5 (range: 14–43), 55.8% of them were females. Donors were matched identical for 85 patients, and haploidentical for 19 patients. The mean follow-up of surviving patients was 117 months.

FLU/ATG/BU14 group with matched identical donor had a median age 21, a median CD34 cell dose of 5.4×10^6/kg. Acute GvHD occurred in 21(26.6%), G3-4 acute GvHD in 3(3.7%), chronic GvHD 13 (17.3%), CMV reactivation 57 (71.3%). Four deaths happened due to sepsis, severe acute GvHD with multiorgan failure, fungal pulmonary infection with respiratory failure.

ATG/Thio/Flu/Cy/TBI 200 group for haploidentical (19 patients) and maternal identical donors (4 patients) group had median age 24, median CD34 cell dose 4.9×10^6/kg. Acute GvHD occurred in 2(2.9%), G3-4 acute GvHD in 1(4.3%), chronic GvHD 2(2.9%), CMV reactivation 14 (60%). No deaths were reported.

The overall survival in the matched related donor SCT using FLU/ATG/BU14 conditioning is 95.1% and 100% in haplo-SCT group, Figure-1.



Conclusions: ATG/Thio/Flu/Cy/TBI 200 conditioning mainly for haploidentical donors showed favorable outcomes. Alternative donors for SCT in SCD represent potential option for patients lacking matched identical donors.

Clinical Trial Registry: Not applicable

Disclosure: No conflict of interest to disclose

25 - Immunodeficiency Diseases and Macrophages

O083

TEN-YEAR SINGLE-CENTER EXPERIENCE OF TCRAB/CD19 DEPLETION FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN INBORN ERRORS OF IMMUNITY

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Background: Hematopoietic stem cell transplantation (HSCT) is curative for many inborn errors of immunity (IEI). TCRαβ/CD19 depletion is an effective method to prevent graft-versus-host disease (GVHD) and reduce transplant-related morbidity. Here we present an experience of ten-year use of TCRαβ/CD19 depletion for IEI in our center.

Methods: From 2012 to January 2022, 299 primary HSCTs with TCRαβ/CD19 depletion were performed in IEI. 39 patients had severe combined immunodeficiency (SCID), 119 other combined immunodeficiency, 57 immune dysregulation, 51 phagocyte disorders, and 33 other IEI. 147 patients received transplants from mismatched related donors (MMRD), 139 from matched unrelated donors (MUD), 13 from matched siblings (MSD). Median age at HSCT was 4.9 years (range 0.2–17.6).

Conditioning regimen with 1 alkylator (treosulfan 36–42g/m^2) was used in 47 patients, 2 alkylators (treosulfan+melphalan 140mg/m^2 or thiotepa 10mg/kg) in 147, 2 alkylators and plerixafor 240 μg/kg in 66 (mostly Wiskott-Aldrich syndrome and chronic granulomatous disease), reduced doses of alkylators in 39 patients (mostly DNA repair defects). Serotherapy was used in 293 patients: thymoglobulin 5-10mg/kg in 252, ATGAM 80–160mg/kg in 30, campath 1mg/kg in 10; 272 additionally received rituximab 100–375mg/m^2.

Graft composition was (medians, ranges): NC 7,6 (3.85–31.3) x10^8/kg, CD34 + 10,48 (5.8–15)x10^6/kg, CD3 + TCRαβ + 15.69 (1–275.9)x10^3/kg. Post-transplant immunosuppression was used in 190 patients, and 109 received no immunosuppression.

Results: The median follow-up time in 223 survivors was 4.9 years (range 0.8–10.2). Engraftment was reached in 275 patients, 19 had non-engraftment, 7 died before engraftment. The median time of neutrophil/platelet engraftment was 14/12.5 days.

Cumulative incidence of graft failure (GF, rejection/non-engraftment) was 0.16 (95%CI 0.13–0.21). Rate of GF varied between different conditioning: 0,32 (95% CI 0.21–0.49) after 1 alkylator, 0.319 (95% CI 0.21–0.49) after 2 alkylators, 0,05 (95% CI 0.02–0.14) after 2 alkylators and plerixafor, and 0.16 (95% CI 0.08–0.33) after reduced doses of alkylators, $p = 0.002$.

Cumulative incidence of acute GVHD grade II-IV was 0,25 (95% CI: 0.24–0.34) after thymoglobulin and 0.47 (95% CI 0.35–0.64) after other serotherapy regimens; GVHD grade IV was seen in 2 patients after thymoglobulin and 6 after other regimens. Cumulative incidence of chronic GVHD in all patients was 0,09 (95% CI 0.06–0,13). Use of different donors (MUD, MMRD and MSD) and post-HSCT immunosuppression did not influence risks of GF and acute GVHD. 44.5% of the patients developed CMV infection, and 33.1% other significant viral infections, requiring therapy.

Overall survival (OS) in 299 patients was 0.73 (95% CI 0.68–0.78). OS was 0.45 (95% CI 0.29–0.61) in SCID and 0.78 (95% CI 0.72–0.83) in other IEI, $p < 0.0001$. 68 patients died of transplant-related mortality (84% infection), 8 patients of other causes.

Conclusions: TCRαβ/CD19 depletion is an effective method of severe GVHD prevention, decreasing transplant morbidity in all types of donors. Pre-HSCT conditioning and serotherapy regimens may significantly influence transplant outcomes, whilst post-HSCT immunosuppression does not. Increased risk of GF after TCRαβ/CD19 depletion may require stronger myeloablation, and non-toxic agents, enhancing myeloablation effects, such as plerixafor, are of particular interest. Infections remain a serious problem, which is important for IEI who often develop severe infections pre-HSCT, and high transplant-related mortality in SCID is related to severe pre-HSCT infections in most of them.

Disclosure: Nothing to declare.

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

O084

OUTCOMES OF HLA-MISMATCHED HSCT WITH TCRAB/CD19 DEPLETION OR POST-TRANSPLANT CYCLOPHOSPHAMIDE FOR INBORN ERRORS OF IMMUNITY: ANALYSIS BY EBMT IEWP HAPLOHSCT IN IEI STUDY GROUP

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Background: HLA-mismatched donor HSCT is increasingly used for inborn errors of immunity (IEI) who lack a matched donor. This multicentre study compared the outcomes of first HLA-mismatched donor HSCT in 296 children, using either in-vitro TCRαβ/CD19 depletion (TCRαβ, $n = 157$, 53%) or in-vivo T-cell depletion with post-transplant cyclophosphamide (PTCY, $n = 139$, 47%) from 2011 to 2019.

Methods: Primary endpoints were overall survival (OS) and event-free survival (EFS; survival without graft failure and extensive chronic GVHD [cGVHD]). Secondary endpoints were GvHD, toxicities, immune reconstitution and long-term graft function. Variables included for predictor analysis were age at HSCT, T cell depletion (TCD) method (TCRαβ vs PTCY), diagnosis (SCID vs non-SCID IEI), conditioning (Bu-based vs Treo-based vs others), organ damage, infection, autoimmunity, malignancy, and number of pre-HSCT morbidities. Competing risks methods were used for the cumulative incidence (CI) of aGvHD and cGVHD, with competing events being represented by death and graft failure.

Results: Median age at HSCT was 1.4 years (range, 0.1–19.6). Ninety-nine (33%) were SCID and 197 (67%) were non-SCID IEI. Donors were haploidentical family donors ($n = 282$, 95%) and mismatched unrelated donors 14 (5%). A significantly larger proportion of PTCY recipients had pre-HSCT infection ($n = 118$, 85% vs TCRαβ, $n = 108$, 69%, $p = 0.002$), organ damage ($n = 74$, 54% vs TCRαβ, $n = 48$, 31%, $p < 0.001$), and significantly more comorbidities ($p < 0.001$). Bu-based conditioning ($n = 91$, 66%), serotherapy (ATG, 62, 45%; Alemtuzumab, 46, 33%; none, 31, 22%)

and marrow ($n = 114$, 82%) were predominantly used in PTCY while Treo-based conditioning ($n = 99$, 63%), serotherapy (ATG, 113, 72%; alemtuzumab, 6, 4%; ATG+alemtuzumab, 1; none, 37, 24%) and PBSC ($n = 152$, 97%) were used in TCRαβ.

The 3-year OS was 81% (95% confidence interval 75–88%) after TCRαβ and 65% (56–74%) after PTCY ($p < 0.001$) while EFS was 70% (62–77%) after TCRαβ and 60% (52–69%) after PTCY ($p = 0.08$). Upon univariate analysis, TCD method ($p < 0.001$), conditioning ($p < 0.001$), organ failure ($p < 0.001$), infection ($p = 0.006$) and number of pre-transplant comorbidities ($p = 0.002$) were significant predictors for OS. Upon multivariate Cox analysis, TCD method ($p = 0.01$) and organ damage ($p = 0.001$) were independent predictors of OS, while organ damage ($p = 0.007$) was the only significant predictor for EFS.

CI of grade III-IV aGvHD was significantly higher, 14% (9–20%) after PTCY compared to TCRαβ (6%, 3–10%) ($p = 0.02$). There was no significant difference in cGvHD between TCRαβ (6%, 2–10%) and PCTY (10%, 5–16%) ($p = 0.08$). Nine (6%; CD34+ boost, 5; DLI, 4) TCRαβ patients and 4 (3%; CD34+ boost, 3; DLI, 1) PTCY patients received second procedures ($p = 0.36$). No significant difference in proportion of patients receiving second HSCT between TCRαβ ($n = 17$, 11%) and PTCY ($n = 9$. 7%) ($p = 0.27$). PTCY had significantly higher rates of VOD (14% vs TCRαβ 5%, $p = 0.02$) and acute kidney injury (13% vs TCRαβ 5%, $p = 0.03$). Adenoviraemia rate was significantly higher in TCRαβ, 19 % compared to PTCY (11%) ($p = 0.01$). Post-HSCT CMV viraemia was 44% after TCRαβ and 41% after PTCY ($p = 0.97$).

Conclusions: This study demonstrated that both TCRαβ and PTCY are safe and effective alternative donor transplant strategies for IEI. Optimisation of both approaches is required to improve transplant outcomes to be fully equivalent to HLA-matched donor HSCT.

Clinical Trial Registry: None

Disclosure: None

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

O085

CLINICAL AND NEUROLOGICAL OUTCOME IN PURINE NUCLEOSIDE PHOSPHORYLASE DEFICIENT CHILDREN AFTER ALLOGENEIC HSCT - A MULTI-CENTER STUDY

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Background: PNP-deficiency is a rare AR-inherited disorder of purine metabolism leading to CID, autoimmunity and neurological damage. Comprehensive data on long-term clinical and neurological outcomes is currently lacking.

Methods: In a retrospective multi-center study, initial clinical presentation (infectious (I+), neurological (N+), autoimmune (A+), or none) and clinical outcome after HSCT were investigated. Besides OS, EFS, DC, neurological CHIMO-outcome-score (0–17) based on cognition (0–3), hearing (0–3), communication (0–4), movement (0–4) and occupation 0–3) and Karnofsky/Lansky scores at latest follow-up were analyzed.

Results: From 2000 to 2021, $n = 42$ patients (21 male, 21 female) patients from 20 centers were enrolled. Median age at initial clinical presentation/PNP-diagnosis was 11.5 (1–48) and 15 (0–108) mo, respectively. $N = 18$ patients presented initially with infectious/no neurological (I+/N-) (med. age 8.5 mo), $n = 14$ with neurological/no infections (N+/I-) (med. age 8.5 mo), $n = 5$ (med. age 18 mo) with combined I+/N+ and n = 1 with autoimmunity/no infectious/no neurological symptoms (A+/I-/N-) (age 6 mo). $N = 4$ asymptomatic patients were diagnosed ante-/perinatally.

I+-symptoms were bacterial ($n = 30$), Candida ($n = 8$), and viral/parasitic infections ($n = 23$), comprising VZV, CMV/EBV, intractable respiratory, Rota-/Noro-/Sapo/ADV viruses and Lamblia. A+-symptoms comprised of Evans, AIHA, ITP, MGOS, AIN, myocarditis, GBS (total $n = 10$); and N+ symptoms presented with developmental/motor delay ($n = 28$), ataxia ($n = 8$), tremor/chorea ($n = 2$), spasticity ($n = 8$), muscular hypotonia ($n = 11$), speech delay ($n = 4$), and miscellaneous symptoms, i.e., micro-/brachycephaly, encephalitis/meningitis, cerebral polymicrogyria, corpus callosum atrophy, hemiplegia, delayed myelinization, lower motor neuron signs, and sensorineural hearing loss.

All 42 patients received a total of 46 transplants (med. age at HSCT: 26 mo; 2-205 mo). Donors were MFD ($n = 13$), haploidentical family ($n = 6$), MUD ($n = 19$; $n = 16$ HLA-10/10, $n = 3$ HLA-9/10) and UCB ($n = 3$ HLA-6/6, n = 3 HLA-5/6; $n = 2$ HLA-4/6). Patients received Melphalan-($n = 12$), Busulfan- ($n = 24$), and Treosulfan-based ($n = 5$), TBI/TT ($n = 2$) or no conditioning (n = 3). Four patients needed consecutive transplants and 6 needed DLI and/or HSC boosts (total $n = 46$ transplants; $n = 21$ BM, $n = 16$ PBSC, $n = 9$ CB).

At a median follow-up (FU) period of 7.365 years (0.5–22), n = 36 patients are alive (OS 86%, EFS 71%). Five developed aGvHD stage ≥2 and seven cGvHD. Six patients died due to infections ($n = 3$), GvHD ($n = 2$) or neurological ($n = 1$) complications. Pre-existing autoimmunity resolved in all patients. Donor chimerism on WBC was 90-100% in $n = 26$, 50–90% in $n = 5$ and 10–50% in $n = 5$ patients. N = 28 with T-cell DC of 90–100%, $n = 8$ with 44-85%. $N = 27$ with B-cell DC of 90–100%, $n = 5$ with 45–70%, $n = 4$ with 0–11%. $N = 31$ are off IvIG.

Median scores for cognition were 3 (0–3), for hearing 3 (1–3), for interaction 3.5 (1–4), for movement 3 (1–4) and for occupation 3 (1–3) resulting in a median CHIMO-score of 15 (6–17). Median Karnofsky/Lansky scores were 90 (40–100%) and 100% (40–100%), respectively. $N = 28$ of survivors showed amelioration, $n = 6$ stabilization and $n = 2$ deterioration of neurological symptoms.

Conclusions: PNP-deficiency presents with a variable sequence of infectious, neurological and autoimmune symptoms usually in late infancy. HSCT providing sufficient myeloid DC ensures detoxification, cure of immunodeficiency and stabilization of neurological disease.

Neurological outcome varied between satisfactory and severely neurologically disabled. Factors (age at diagnose/transplant, type of neurological/infectious compromise before HSCT, etc.) potentially influencing neurological outcome are currently being analysed.

Clinical Trial Registry: Trial of the Working Party Inborn Errors of the EBMT

Disclosure: No conflicts of interest

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

O086

OUTCOME OF FLUDARABINE AND TREOSULFAN CONDITIONING FOR HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN 415 CHILDREN WITH NON-SCID IEI: A MULTICENTRE RETROSPECTIVE COHORT ANALYSIS

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Background: Treosulfan has been increasingly used in children with inborn errors of immunity (IEI). This multicentre study compared transplant outcomes in 415 chilldren with non-SCID IEI who received fludarabine-treosulfan for first haematopoietic stem cell transplantation (HSCT) between 2006–2021 at 6 transplant centres in the UK.

Methods: Primary endpoints were overall survival (OS), event-free survival (EFS; survival without graft failure and second procedures). Secondary endpoints were grade II-IV aGvHD, cGvHD and toxicities. Subgroup differences in OS and EFS were evaluated by log-rank test. Competing risks methods were used for the cumulative incidence of aGvHD, cGvHD and VOD with death as the competing event, subgroup differences were evaluated by Gray's test.

Results: Median age at transplant was 3.2 years (range 0.2–19.0 years). Diagnoses were CGD ($n = 62$), HLH ($n = 51$), WAS ($n = 36$), MHC class II deficiency ($n = 33$), CID ($n = 18$), CD40L deficiency ($n = 17$), autoimmune enteropathy ($n = 17$), congenital neutropenia (n = 13), DOCK8 deficiency ($n = 12$), LAD ($n = 11$), APDS ($n = 9$), JIA ($n = 9$), IPEX ($n = 9$), STAT3 GOF ($n = 8$) and others ($n = 110$). Donors were MFD ($n = 73$, 18%), MUD ($n = 211$, 37%), MMFD/MMUD (n = 62, 15%) and haploidentical donor (HID, $n = 69$, 17%). Stem cell sources were marrow ($n = 96$, 23%), unmanipulated PBSC ($n = 220$, 20%), T cell depleted PBSC ($n = 72$, 17%; 64 TCRab/CD19 depletion; 2 CD3/CD19 depletion; 6 CD34 selection) and cord blood (CB) ($n = 27$, 32%). 273 (66%) received treosulfan–fludarabine and 141 (34%) received fludarabine-treosulfan-thiotepa. Treosulfan dose was 30g/m^2 in 27 (7%), 36g/m^2 in 99 (24%) and 42g/m^2 in 289 ($n = 70$%). Alemtuzumab was used in 302 (73%), ATG in 74 (18%) and 39 (9%) received no serotherapy. GvHD prophylaxis were CSA + MMF ($n = 323$, 76%), CSA ($n = 53$, 13%), none ($n = 32$, 7%) and others ($n = 6$, 1.3%).

Median duration of follow-up was 3.6 years (range, 0.09 to 13.2 years). 3-year OS and EFS for the entire cohort was 86% (95% CI, 82–89%) and 82% (77–85%) respectively. OS was inferior in cord blood recipients 70% (48–83%) compared to marrow (89%, 78–93%), PBSC (90%, 84–93%) and TCD PBSC (79%, 48–83%) ($p = 0.03$). Age at transplant ($p = 0.89$), donor ($p = 0.11$), add-on thiotepa ($p = 0.31$), Treosulfan dose ($p = 0.14$) and serotherapy ($p = 0.09$) were not associated with OS. TRM at 1 year was 7% (5–10%). EFS was significantly lower after Treo 30g/m^2 (63%, 40–79%) compared to Treo 36g/m^2 (83%, 72–89%) and Treo 42g/m^2 (82%, 78–87%) in the entire cohort ($p = 0.03$), similar observation was seen in patients aged >1 years of age ($p < 0.001$).

Day-90 cumulative incidence (CI) of grade II-IV and grade III-IV aGvHD was 22% (18–27%) and 5% (3–8%) respectively. CI of cGvHD at 1 year was 8% (5–12%). CI of VOD was 1.5% (1–3%) for entire cohort.

Table 1: Treosulfan dose according to age and BSA

Treosulfan dose	Age < 1 ($n = 81$)	Age > 1	Age > 1	Age > 1
	BSA <0.5 ($n = 81$)	BSA <0.5 ($n = 58$)	BSA >0.5 to <1.0	BSA >1.0 ($n = 97$)
30 g/m^2	20	7	0	0
36 g/m^2	46	10	43	0
42 g/m^2	15	41	136	97

Conclusions: Treosulfan-based conditioning is associated with low TRM and VOD rates, but optimal dosing needs further PK study in children with non-SCID IEI.

Clinical Trial Registry: None

Disclosure: None

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

O087

NEWBORN SCREENING FOR HURLER SYNDROME LEADS TO EARLY TREATMENT AND EXCELLENT OUTCOMES WITH UNRELATED UMBILICAL CORD BLOOD TRANSPLANT

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Background: Hematopoietic cell transplantation (HCT) including unrelated umbilical cord blood transplant (UCBT) provides durable neurocognitive improvement, longevity and better quality of life in patients with MPS-1 (Hurler syndrome; HS). Multiple studies have shown that early HCT is an important predictor of better short- and long-term outcomes in HS patients. Addition of HS to newborn screening (NBS) in several states in the USA allows the possibility of early HCT. Here we present the outcomes of UCBT performed at our center in HS patients diagnosed by NBS.

Methods: This retrospective study includes all HS patients ($N = 7$; female = 4; Caucasian = 5) diagnosed through NBS and referred to Duke between 2017 to 2022. Diagnosis was confirmed by genetic testing, blood alpha-L-iduronidase (IDUA) enzyme and urine glycosaminoglycans (GAGs). Comprehensive pre-transplant evaluation included organ involvement and functional status, infection screening, and neurocognitive functional assessment. Cord blood units (CBU) were from unrelated donors and the selection criteria included HLA matching, cell dose and IDUA enzyme level. Patients underwent conditioning with busulfan (1 mg/kg every 6hr for 16, doses adjusted based on PK), cyclophosphamide (50 mg/kg/dose every 24 h for 4 doses) and equine antithymocyte globulin (30 mg/kg/dose every 24 h for 3 doses). In one patient, Fludarabine instead of cyclophosphamide was used due to cardiomyopathy. GVHD

prophylaxis was cyclosporine and mycophenolate in all. CBU were 4/6 ($n = 2$) or 5/6 ($n = 5$) matched by low resolution for HLA-A and B and high resolution DRB1.

Results: Children were first seen at Duke at a median age of 2 months (range, 1.1–5.2) and transplanted at a median age of 5.4 months (range, 3.4–13.6) with a median weight of 7.8 kg (range, 5.6–10.4). Median transplant age is significantly younger from the historical cohort. Median (range)/Kg of cryopreserved total nucleated cell (TNC) and reinfused TNC were 26.0(21.2–37.4) x10e7 and 16.8(7.2–22)x10e7. All patients engrafted. The median (range) time to neutrophil and platelet engraftment was 17 days (13–36) and 63 days (22–76), respectively. One patient had grade I acute GvHD and one patient had limited chronic GvHD. Two patients developed VOD that resolved with defibrotide and one patient developed microangiopathy that resolved with eculizumab. Three patients developed auto-immune hemolytic anemia (AIHA) requiring transfusion support, steroids and monoclonal antibody therapy. At a median follow-up of 27.3 months (range 18.6–68.7), 6 of 7 patients are alive with normal IDUA levels, Lansky scores of 90–100% and developing milestones. One patient died due to AIHA at an outside institution on day +139. This subject had normal IDUA level and >98% donor chimerism at day +100. All surviving patients had >98% myeloid donor chimerism. Cardiomyopathy improved after UCBT in one patient who had it at diagnosis.

Conclusions: UCBT for HS patients diagnosed through NBS corrects IDUA enzyme deficiency, results in sustainable high-level donor chimerism and excellent survival outcomes. This early diagnostic approach allows for intervention with HCT at a younger age before development of significant neurocognitive damage and organomegaly and should be considered in patients with HS. Follow up studies are ongoing to ascertain the long-term benefits of this approach.

Disclosure: Nothing to declare

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

O088

EXTENDED CLINICAL PHENOTYPE AND TREATMENT MODALITIES IN 23 JAGN1 DEFICIENT PATIENTS - AN EBMT IEWP MULTI-CENTER STUDY

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Background: Autosomal recessively inherited mutations in the *JAGN1* (Jagunal-homolog1) gene lead to congenital neutropenia, early onset bacterial infections, aphthosis and skin abscesses due to aberrant differentiation and maturation of neutrophils. In addition, syndromic features like facial dysmorphisms, short stature and neurodevelopmental delay have been reported. In a retrospective multicenter study supported by the Inborn Errors Working Party (IEWP) we collected data on patients with JAGN1-deficiency. We aimed to perform a phenotype-genotype analysis.

Methods: Patient data were gathered via case report forms with added data from the published literature if the patient was previously reported. Data on clinical manifestations and hematopoietic stem cell transplantation (HSCT) were collected and analyzed.

Results: We were able to summarize a cohort of 26 patients with JAGN1-deficiency from 15 centers. Patients showed eight distinct homozygous mutations in *JAGN1*. All patients showed early onset infectious complications including pneumonia, otitis, aphthosis, mastoiditis and skin abscesses. Moreover, 12 patients presented syndromic features with short stature and facial dysmorphisms. In four patients of three families neurodevelopmental delay was found. Two patients received allogeneic stem cell transplantation due to therapy-refractory neutropenia, and one because of secondary acute myeloid leukemia (AML). One patient had to undergo a second transplantation because of autologous reconstitution. One patient died at the age of five years due to pancolitis and septicemia. All other patients were reported alive and well at last follow-up. All except one non-transplanted patients receive G-CSF treatment with three being non responsive to the treatment.

Conclusions: In this retrospective study, we present the extended phenotype of a cohort of severe neutropenia due to JAGN1-deficiency. Besides early onset infectious complications one patient developed secondary AML. It is recommended to carefully monitor affected patients for the occurrence of malignancies. The indication for transplantation was available in four patients due to severity of the disease.

Disclosure: Nothing to declare.

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

O089

WHAT WE HAVE DONE AND WHAT WE HAVE FAILED TO DO: THE STORY OF LIBMELDY AS A NOW LICENSED STEM CELL GENE THERAPY FOR MLD

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Background: Metachromatic leukodystrophy (MLD) is a rare, inherited, lysosomal storage disease caused by mutations in the ARSA gene and deficiency of its enzyme arylsulfatase A. Affected individuals meet early developmental milestones, before motor and cognitive deterioration ensues, with early death.

Atidarsagene autotemcel (Libmeldy), an autologous haematopoietic stem cell gene therapy (HSC-GT) product of autologous CD34+ stem cells transduced ex-vivo with a lentiviral vector encoding the human ARSA gene, has demonstrated sustained clinically relevant benefits in children with MLD, preserving cognitive and motor function, and slowing demyelination and brain atrophy. Libmeldy received EU marketing authorisation for treatment of MLD in December 2020 and was subsequently approved for NHS treatment in the UK in February 2022. These licensing criteria, however, have strict limitations in that treatment is only approved for patients who have either asymptomatic late infantile or early symptomatic early juvenile MLD, with early clinical manifestations of the disease, and who maintain the ability to walk independently before the onset of cognitive decline.

We evaluate the impact Libmeldy approval has had on patients with MLD in the largest real-world dataset of MLD HCT-GT outside of clinical trial.

Methods: Hospital records were reviewed for the 19 patients with MLD referred to Royal Manchester Children's Hospital (RMCH) since Libmeldy was approved for NHS treatment in February 2022. Information was gathered about disease phenotype and clinical presentation along with demographics, eligibility for HCT-GT treatment and whether any siblings were affected.

Results: In the 10-month period since Libmeldy received UK marketing approval, 19 patients with MLD have been referred for HCT-GT treatment at RMCH. 4 patients (21%) met eligibility criteria and have undergone successful mobilisation, leukapheresis, product manufacture, and transplant of this product, including 1 infant who weighed 5 kg at time of leukapheresis.

15 patients failed screening (Table 1), including 12 with late infantile disease who were symptomatic on assessment, 1 with early juvenile disease and cognitive decline (FSIQ70), 1 with late juvenile disease and cognitive regression (FSIQ51), and a further symptomatic patient with adult-onset disease. 3 of the 4 patients treated at RMCH were diagnosed by screening of an apparently unaffected younger sibling after MLD was diagnosed in a symptomatic older sibling.

In summary, we have treated 4 patients but reviewed 15 other children with MLD, who could not be treated because their disease was too advanced. We are therefore treating just over 20% of children with MLD that have been referred to our centre.

Table 1: Characteristics of the MLD screen patients

	Characteristics of the 18 screened patients
Age	Mean 4.5 years, median 3 years- Range 0-23 years
Screen failure patientsphenotype and reason for ineligibility	•11x late infantile- all symptomatic •1x early juvenile- walking independently but cognitive regression (FSIQ 70) •1x late juvenile- cognitive regression (FSIQ 51) •1x adult onset- symptomatic
Treated patients	•2x asymptomatic late infantile- both screened because of affected siblings •1 x asymptomatic early juvenile- screened following diagnosis of affected sibling •1x early symptomatic early juvenile- no sibling, motor deterioration with ataxic gait and lower limb spasticity, maintains the ability to walk independently and normal cognitive ability (FSIQ 1010)

Conclusions: The success of HCT-GT for MLD and its ability to deliver lifesaving treatment for this devastating disease has heralded a new era of hope for families affected by this condition. Our real-world experience highlights that most patients with MLD present with disease features and are ineligible for treatment at diagnosis. The feasibility of apheresis in very young and low weight infants together with the availability of a licensed and effective HCT-GT product indicate the urgent need for newborn screening for MLD to ensure that patients can be diagnosed and treated before the onset of symptomatic clinical disease.

Disclosure: none of the authors have any conflicts of interest related to this abstract

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

O090

ALLOGENEIC HCT RESOLVES INFLAMMATORY AND INFECTIOUS MANIFESTATIONS OF CHRONIC GRANULOMATOUS DISEASE IN AFFECTED FEMALE X-LINKED CARRIERS

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Background: Female carriers of X-linked chronic granulomatous disease (XL-CGD) with impaired neutrophil oxidative burst due to lyonisation experience lupus-like autoimmunity and infective and inflammatory manifestations leading to morbidity[1,2] and poor quality of life[3]. Haematopoietic cell transplantation (HCT) is curative for XL-CGD, but there are few published reports in affected carriers[4,5].

Methods: Retrospective study of symptomatic XL-CGD carrier patients undergoing HCT. Clinical, laboratory, and transplant characteristics were collected. Neutrophil oxidative burst (%NOB) activity expressed as percentage of leucocytes able to oxidise 123-dihydrorhodamine following stimulation with phorbol 12-myristate 13-acetate. The small sample size precluded statistical analysis.

Results: Seven patients were identified: six with heterozygous pathogenic mutations or deletions in *CYBB* and one with a large deletion incorporating *CYBB*. Pre-HCT %NOB ranged 1.2–30%. Manifestations included: severe, recurrent, or life-threatening infection typical of CGD (including by *Nocardia*, *Burkholderia cepacia*, and *Staphylococcus aureus*) in 6/7; colitis in 5/7, requiring multiple monoclonal antibodies in 3 patients; lupus-like phenomena including photosensitivity and discoid rash in 3/7, and autoimmune cytopenia in 2/7.

Median age at HCT was 18 years (range: 1–56), and survivors were followed for 1.5–7.5 years post-HCT. Patients received grafts from 2 matched sibling donors, 4 matched unrelated donors, and one haploidentical donor following conditioning with area-under-curve-adjusted busulfan- or treosulfan-based regimens, 6/7 with alemtuzumab serotherapy. One HLA 9/10 unrelated graft underwent TCRαβ/CD19-depletion prior to infusion, and prophylaxis against graft-versus-host disease (GvHD) was ciclosporin A and mycophenolate mofetil in 5/7, and sirolimus and post-HCT cyclophosphamide in 2/7. Four patients received corticosteroids peri-HCT.

Five patients survived: one died at D + 30 post-HCT from multi-organ failure and encephalopathy from an idiosyncratic reaction to chemotherapy, and one at D + 131 from disseminated adenoviral infection following acute grade III gastrointestinal and hepatic GvHD. Two other patients had limited cutaneous GvHD requiring topical therapy only.

Post-HCT, median donor myeloid chimerism and %NOB are 100% (60–100%). All survivors have remission of colitis and are free from infections outside of the immediate post-transplant period. One patient had autoimmune haemolysis whilst fully donor chimeric, which remitted following intravenous immunoglobulin and sirolimus.

Table 1. Patient and transplant characteristics and outcome at latest follow-up.

Patient	Pre-HCT morbidity	% NOB	Age at HCT (years)	Stem cell source and HLA match	Conditioning regimen Serotherapy	Peri-HCT morbidity	Latest follow-up	%NOB	Outcome
P1	Recurrent pneumonia, lymphadenitis, discoid rash, colitis, polyarthralgia	25%	15	10/10 MUD PBSC	Treosulfan Fludarabine Thiotepa Alemtuzumab	HHV6 viraemia Inflammatory pneumonitis AIHA	3.5 years	100%	Premature ovarian failure Colitis in remission No infection
P2	Staphylococcal liver abscess, recurrent skin infection, oral ulcers	10%	18	10/10 MUD PBSC	Treosulfan Fludarabine Thiotepa Alemtuzumab	Encephalopathy Anuric renal failure	-	100% (D + 30)	Death at D + 30 from encephalopathy
P3	Severe colitis despite infliximab, methotrexate, certolizumab	30%	20	10/10 MUD BM	Busulfan Fludarabine Alemtuzumab	Grade I acute skin GvHD	7.5 years	100%	Remission of colitis
P4	Pulmonary nocardiosis necessitating extracorporeal membrane oxygenation, discoid lupus	6.7%	56	10/10 MSD PBSC	Busulfan Alemtuzumab PTCy	Grade I acute skin GvHD Klebsiella bacteraemia	3.0 years	60%	Autoimmunity in remission No infection
P5	Pulmonary nocardiosis, extensive colitis with rectovaginal fistulae	3.5%	22	5/10 parental PBSC	Busulfan Fludarabine PTCy	Grade III liver/ gastrointestinal GvHD Disseminated adenovirus infection	-	98% (D + 100)	Death at D + 131 from multi-organ failure
P6	Pneumonia, *Burkholderia gladioli* abscess Hypogammaglobulinaemia	15%	7	10/10 MSD BM	Busulfan Fludarabine Alemtuzumab	CMV viraemia	2.0 years	100%	Infection free
P7	Bilateral pneumonia, colitis	1.2%	1	9/10 TCRαβ/ CD19-deplete PBSC	Busulfan Fludarabine Alemtuzumab	Uncomplicated	3.0 years	100%	Colitis in remission Infection free

MUD matched unrelated donor, *MSD* matched sibling donor, *PBSC* peripheral blood stem cell, *HHV6* human herpesvirus-6, *AIHA* autoimmune haemolytic anaemia, *GvHD* graft-versus-host disease, *PTCy* post-HCT cyclophosphamide.

Conclusions: Restoration of %NOB in symptomatic XL-CGD carriers by HCT may reverse inflammatory and infective manifestations and offers cure in severely affected patients. The multimorbidity of this cohort is reflected in transplant-related mortality of two out of seven patients.

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Disclosure: Nothing to declare.

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

O091

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH MUCOPOLYSACCHARIDOSIS-IVA: *A PRELIMINARY REPORT*

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Background: Mucopolysaccharidosis IVA (MPS IVA; Morquio syndrome) is a lysosomal storage disorder and features systemic skeletal dysplasia that is caused by defective Nacetylgalactosamine-6-sulfate sulfatase (GALNS). GALNS deficiency causes the accumulation of keratan sulfate (KS) and chondroitin-6-sulfate (C6S) in lysosomes and excessive excretion of these substrates in blood and urine. Major signs and symptoms are usually seen before one year of age, including kyphosis, protrusion of the chest, prominent forehead, and walking alone often delays. Although enzyme replacement therapy (ERT), gene therapy (GT), and hematopoietic stem cell transplantation (HSCT) have been reported as therapeutic methods, there is no curative therapy for skeletal dysplasia yet. To date, there have been only a few cases reports on HSCT in MPS IVA.

Here, we report our experience on HSCT in MPS IVA with 9 cases.

Methods: Between May 2021 and November 2022 nine children with MPS IVA underwent HSCT in Antalya and Istanbul Goztepe Medicalpark Hospitals Pediatric Stem Cell Transplantation Units. The characteristics of the patients are shown in Table 1. All patients received myeloablative conditioning. Bu+Flu+ATG±TT was given to 8 patients and the other one received Treo+Flu +TT + ATG. Graft rejection was seen in 2 patients. These patients

Case/ Gender	Age at Diagnosis>HSCT (months)	Genotype	Donor	aGvHD	Chimerism	Follow-up (FU, months)	Last Enzyme Level (nmol/mg)	Height (pre>post-HSCT)	ADL Score (pre>post-HSCT)
1/M	22 > 120	Undefined	MSD	No	full	7	143	98 > 103 cm	16 > 20
2/F	40 > 48	c.421T>A(p.Trp141Arg)	MUD	No	full	1	Early FU	Early FU	Early FU
3/M	29 > 66	c.1168delC(p.Leu390)	MUD	No	full	11	274	82 > 87 cm	16 > 20
4/F	59 > 108	c.860C>T(p.Ser287Leu)	MUD	Grade 2 Skin	full	12	389	98 > 100 cm	17 > 20
5/M	18 > 36	c.139G>A(p.Gly47Arg) c.898+1G>A	MUD	No	mixed	9	241	86 > 91 cm	20 > 20
6/M	19 > 84	c.1019G>A(p.Gly340Asp)	MUD	No	full	19	139	86 > 97 cm	16 > 20
7/M	22 > 48	c.230C>G(p.Pro77Arg)	MUD	No	full	9	290	96 > 97 cm	18 > 20
8/F	1 > 126	c.1168delC(p.Leu390)	MUD	No	mixed	7	Normal	92 > 103 cm	18 > 20
9/M	27 > 48	c1157G>A(p.Arg386His)	MUD	No	full	1	Early FU	Early FU	Early FU

underwent second HSCT from different donors and were successfully engrafted. All but one patient had received ERT before HSCT. To determine the change in daily activity after HSCT, the scoring system of Activities Daily Living (ADL) which was reported before (Tanjuakio, 2022), was used for the patients who completed at least 6 months of follow-up after HSCT. Instead of full ADL scoring, only the "movement" section was applied, and scored over 20 points.

Results: Characteristics and follow-up of the patients were presented in Table-1.

This study was planned for long-term follow-up of MPS IVA cases after HSCT. For this purpose, a 2-year follow-up was aimed. Long-term follow-up results of the study will allow comparison of HSCT with other treatment modalities. The preliminary results of our study are promising. In all cases, normal enzyme levels were reached after HSCT. Although mixed chimerism developed in 2 cases, normal enzyme levels were detected in these patients. During the short follow-up period, our cases showed an increase in stature and improvement in daily activity functions. All but one patient had impairment in ADL scoring before HSCT. At least 6 months after HSCT, all the patients had full scores (20 points) due to ADL scoring (movement).

Conclusions: HSCT is a promising modality for the treatment of MPS IVA patients. With more patients, multidisciplinary long-term follow-up of the cases after HSCT will give an idea about the effectiveness of this treatment method and will enable it to be compared with other treatment methods.

Disclosure: Nothing to declare

24 - Inborn Errors, Granulocyte and Osteoclast Disorders

O092

COMBINED ALLOGENEIC BONE MARROW TRANSPLANTATION AND INTRACEREBROVENTRICULAR ENZYME REPLACEMENT THERAPY FOR PATIENTS WITH NEURONOPATHIC MUCOPOLYSACCHARIDOSIS TYPE II

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Background: Mucopolysaccharidosis type II (MPS-II, Hunter syndrome) is a rare X-linked lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase (IDS). Recently, IDS-beta (Hunterase®) has been newly approved in Japan as the intracerebroventricular enzyme replacement therapy (ICV-ERT) for the patients with neuronopathic MPS-II. Herein, we aimed to assess the efficacy and feasibility of combined allogeneic bone marrow transplantation (allo-BMT) and ICV-ERT for neuronopathic MPS-II patients.

Methods: Between November 2020 and June 2022, five consecutive patients with neuronopathic MPS-II underwent combined allo-BMT and ICV-ERT in National Center for Child Health and Development, Tokyo, Japan. The median age at the time of diagnosis and allo-BMT was 1.8 years (range, 1.6–2.9 years) and 2.7 years (range, 2.0–5.8), respectively. The donors consisted of HLA (A,B,C,DRB1) 7/8 matched father (7/8MRD, $n = 1$), HLA 8/8 matched unrelated donor (8/8MUD, $n = 3$), and HLA 7/8 matched unrelated donor (7/8MUD, $n = 1$). All patients were prepared with the regimen consisting of targeted dose of busulfan (Bu, the median total area under curve was 73.5 mg h/l [range, 63.5–88.4 mg h/l]), 200 mg/kg of cyclophosphamide (Cy), and 5 mg/kg of rabbit anti-thymocyte globulin (rATG), and were administered tacrolimus and short-term methotrexate (15 mg/m^2 at day 1, 10 mg/m^2 at day 3, 6, and 11) for GvHD prophylaxis. In all patients, ICV-ERT was performed via Ommaya reservoir which is a ventricular access device for the purpose of repetitive access to the intrathecal space.

Results: All patients achieved neutrophil recovery; the median day of engraftment was 15 days (range, 15–19 days), and were confirmed the establishment of complete chimera by bone marrow examination. All three patients who were grafted by 8/8MUD did not develop grade 2–4 acute GvHD, however, the other 2 patients with 7/8MRD and 7/8MUD showed grade 3 and 4 acute GvHD, respectively. All patients received ICV-ERT via cerebroventricular reservoir. Two patients received allo-BMT before first ICV-ERT, and the interval between allo-BMT and the ICV reservoir

construction were 247 and 280 days, respectively. The other three patients received allo-BMT after starting ICV-ERT, the interval between allo-BMT and resumption of ICV-ERT were 40, 58, and 109 days, respectively. All five patients survived at the end of November 2022; the median duration of follow-up was 16 months (range, 5–25 months) and showed elevated blood IDS levels and decreased glycosaminoglycans in blood and cerebrospinal fluid. With the exception of one child who had a longer hospital stay due to grade 4 aGvHD and Steven-Johnson syndrome, we were able to observe the language and motor development of the other four children.

Conclusions: Combined allo-BMT with targeted Bu+Cy+ATG and ICV-ERT is suggested to be a promising novel strategy for patients with neuronopathic MPS-II.

Disclosure: Nothing to declare.

13 - Infectious Complications

O093

INFLUENCE OF PRE-EXISTING INVASIVE ASPERGILLOSIS ON ALLO-HSCT OUTCOME IN ACUTE LEUKEMIA PATIENTS: A PROSPECTIVE STUDY OF THE EBMT INFECTIOUS DISEASES WORKING PARTY

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Background: Invasive aspergillosis (IA) frequently occurs during treatment for acute leukemia (AL). Historically IA has been a major barrier for allogeneic hematopoietic stem cell transplantation (allo-HSCT). In the last decade there has been significant improvement of anti-fungal management including novel anti-fungal agents and diagnostic procedures. The influence of invasive IA on allo-SCT outcome in recently transplanted patients is unknown.

Methods: All EBMT centers were invited to participate by providing detailed prospective data on AL patients with and without IA undergoing first allo-HSCT. The aim of this study was to analyze the outcome of AL patients undergoing allo-HSCT with a prior history of probable or proven IA (pre-HSCT IA) as compared to patients without history of IA. The primary endpoint was 1-year non relapse mortality (NRM), estimated using the cumulative incidence method. The cause-specific Cox regression model was used to adjust the results for the main confounders: age, gender, underlying disease, status at SCT, time from diagnosis to SCT, donor type, source of SCT, donor age, d/r gender match, d/r CMV status, conditioning regimens, type of immunosuppression, DLI post SCT and center. The relapse free survival and the overall survival were analysed as secondary endpoints, using Kaplan-Meier method and Cox regression model for univariate and multivariate analysis, respectively. Sample size was initially calculated based on the assumption of a 5% incidence of proven/probable IA in this population.

Results: Thirty-seven EBMT centers from 20 countries participated. We started enrolment in 2016 and stopped in 2021 after recruiting the planned 95 patients with pre-HSCT probable/proven IA (6.2% of total cases). We included 1527 patients in the final analyses. Patient characteristics are given in Table 1. The cumulative incidence of 1-year NRM was 16.9% (95% CI 10.1–25.2) and 11.4% (9.8–13.1) for patients with and without pre-HSCT IA. In multivariate analyses the hazard ratio (HR) for 1-year NRM was 1.9 (1.1–3.3; $p = 0.0184$) for patients with pre-HSCT IA. One-year relapse-free survival was inferior in patients with pre-HSCT IA (58.7% [48.0–67.8] vs. 70.5 [68.1–72.8]; multivariate HR 1.5 [1.1–2.2]; $p = 0.0131$). Consequently, 1-year overall survival was lower in patients with pre-existing IA: (67.2 [56.7–75.6] vs. 78.7 [76.5–80.7]; multivariate HR 1.7 [1.2–2.6]; $p = 0.006$).

Conclusions: In patients with AL and pre-HSCT IA undergoing allo-HSCT the risk of NRM is nearly 2-fold increased, leading to inferior survival. On the other hand, this large prospective study shows that more than two thirds of patients with pre-existing IA were alive at one year after allo-HSCT.

Taken together these data suggest that:

1. pre-existing IA remains a significant risk factor for impaired allo-HSCT outcome
2. the majority of the patients with leukemia and pre-existing IA who underwent allo-HSCT in our study benefitted from this procedure

Disclosure: No conflict of interests

13 - Infectious Complications

	IA before HCT No (N = 1432)	IA before HCT Yes (N = 95)	Total (N = 1527)
Age at HCT Median (min – max)	40.9 (0.4–75.8)	36.6 (1.2–68.0)	40.9 (0.4–75.8)
Interval from IA to HCT (months)		6.6 (2.2–165.3)	
Underlying malignancy			
ALL	460 (32.1)	33 (34.7)	493 (32.3)
AML	972 (67.9)	62 (65.3)	1034 (67.7)
Acute leukemia status before HCT			
Other	1099 (76.7)	79 (83.2)	1178 (77.1)
CR	310 (21.6)	15 (15.8)	325 (21.3)
Donor type			
HLA-identical sibling	363 (25.3)	38 (40.0)	401 (26.3)
Haploidentical	233 (16.3)	17 (17.9)	250 (16.4)
Unrelated donor	836 (58.4)	40 (42.1)	876 (57.4)
Stem cell source			
Bone marrow	373 (26.0)	20 (21.1)	393 (25.7)
Peripheral Blood	1014 (70.8)	72 (75.8)	1086 (71.1)
Cord Blood	45 (3.1)	3 (3.2)	48 (3.1)
Conditioning regimen			
Myeloablative	1081 (75.5)	80 (84.2)	1161 (76.0)
Reduced	348 (24.3)	14 (14.7)	362 (23.7)
Total body irradiation			
No	999 (69.8)	62 (65.3)	1061 (69.5)
Yes	430 (30.0)	30 (31.6)	460 (30.1)
In-vivo T-cell depletion			
No	714 (49.9)	51 (53.7)	765 (50.1)
Yes	716 (50.0)	43 (45.3)	759 (49.7)

O094

A PHASE 3 RANDOMIZED, PLACEBO-CONTROLLED TRIAL EVALUATING SAFETY AND EFFICACY OF LETERMOVIR PROPHYLAXIS EXTENDED FROM 100 TO 200 DAYS POST-TRANSPLANT IN CYTOMEGALOVIRUS-SEROPOSITIVE ALLOGENEIC HSCT RECIPIENTS

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Background: The safety and efficacy of Letermovir (LET) for Cytomegalovirus (CMV) prophylaxis in seropositive (R+) allogeneic hematopoietic stem cell transplant (HSCT) recipients when administered through 100 days post-HSCT was previously demonstrated in a pivotal Phase 3 trial (P001). However, ~12% of participants (pts) in P001 developed clinically significant CMV infection (CMV disease or CMV viremia leading to pre-emptive treatment; CS-CMVi) after discontinuing LET between Weeks 14 and 24 post-HSCT. This Phase 3 trial (NCT03930615; P040) evaluated whether extending LET prophylaxis to 200 days post-HSCT resulted in additional benefit vs. placebo (PBO) in pts remaining at high risk for CS-CMVi beyond Day 100 post-HSCT.

Methods: Adult R + HSCT recipients who received LET for CMV prophylaxis through 100 days post-HSCT and were still at high risk for developing CS-CMVi beyond 100 days post-HSCT, were randomized 2:1 to receive an additional 100 days of LET or PBO. LET dose was 480 mg QD (240 mg QD with cyclosporin A). Risk of CS-CMVi was based on donor relatedness and degree of matching; stem cell source; use of T cell-depleted grafts, anti-thymocyte globulin, or alemtuzumab; and graft-versus-host disease (GVHD) or other conditions necessitating steroid use pre-randomization. The primary endpoint was the proportion of pts with CS-CMVi from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT.

Results: A total of 220 pts were randomized, and 218 pts treated (LET, $N = 144$; PBO, $N = 74$). The proportion of pts with CS-CMVi from Week 14 through Week 28 post-HSCT was lower in the LET arm than in the PBO arm (2.8% vs. 18.9%; one-sided p-value, 0.0005; Table 1). All-cause mortality from Week 14 through Week 48 post-HSCT was 8.3% in the LET arm and 8.1% in the PBO arm. Safety profiles were similar for LET and PBO; the most commonly reported adverse events (AEs) (LET vs. PBO) were GVHD (29.9% vs. 31.1%), nausea (11.1% vs. 17.6%), diarrhea (11.8% vs. 12.2%), and pyrexia (9.0% vs. 12.2%).

Table 1. Proportion of participants with CS-CMVi from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT (OF approach, full analysis set population).

Parameter	LET (200 days LET)[a] (N = 144)	PBO (100 days LET)[a] (N = 74)
Failures, *n* (%)[b]	4 (2.8)	14 (18.9)
CS-CMVi[c] through Week 28	2 (1.4)	13 (17.6)
PET initiation based on documented CMV viremia	1 (0.7)	11 (14.9)
CMV end-organ disease	1 (0.7)	2 (2.7)
Discontinuation from study with CMV viremia before Week 28	2 (1.4)	1 (1.4)
Stratum-adjusted treatment difference in response rate (%) (LET [200 days LET] – PBO [100 days LET])[d]		

Parameter	LET (200 days LET)[a] (*N* = 144)	PBO (100 days LET)[a] (*N* = 74)
Difference (95% CI)	−16.1 (−25.8, −6.5)	
P value	0.0005	

CI confidence interval, *CMV* cytomegalovirus, *CS-CMVi* clinically significant CMV infection, *HSCT* hematopoietic stem cell transplant, *LET* letermovir, *OF* Observed Failure, *PBO* placebo, *PET* pre-emptive therapy.
[a]All participants received 100 days of LET post-HSCT prior to entering the study, followed by an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).
[b]Missing values were handled using the OF approach, in which failures were defined as all participants who developed CS-CMVi or discontinued prematurely from the study with CMV viremia from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT. The categories of failure are mutually exclusive and are listed in hierarchical order.
[c]CS-CMVi was defined as CMV end-organ disease (proven or probable), or PET initiation based on documented CMV viremia and the participant's clinical condition.
[d]The 95% CI and one-sided P value for the treatment difference in response rate were calculated using the stratum-adjusted Mantel-Haenszel method, with the difference weighted by the harmonic mean of the sample size per arm for each stratum (haploidentical or non-haploidentical donor). Statistical significance was defined as $P \leq 0.0249$ (one-sided).

Conclusions: LET prophylaxis extended to 200 days was superior to PBO in reducing the rate of CS-CMVi from Week 14 through Week 28 post-HSCT in allogeneic R + HSCT recipients. LET had an AE profile similar to PBO and was well tolerated.

Clinical Trial Registry: NCT03930615; P040

Disclosure: Domenico Russo No potential conflicts of interest to declare

Sanjeet Dadwal No potential conflicts of interest to declare

Michael Schmitt Has received research grants from Apogenix, Hexal, and Novartis; travel support from Hexal and Kite; financial support for educational activities and conferences from bluebird bio, BMS, Kite/Gilead, and Novartis; and compensation as a member of the scientific advisory board of MSD and GSK; and is co-founder and shareholder of ToleroGenixX Ltd.

Sylvain Pilorge No potential conflicts of interest to declare

Valerie L Teal, Barbara Haber, Charlene Bopp, and Cyrus Badshah are current employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and may own stock/stock options in the Company

13 - Infectious Complications

O095

FINAL CLINICAL AND BIOMARKER DATA FROM A PHASE 2 TRIAL OF POSOLEUCEL, AN OFF-THE-SHELF, MULTIVIRUS-SPECIFIC T-CELL THERAPY, FOR PREVENTION OF CLINICALLY SIGNIFICANT VIRAL INFECTIONS POST-HCT

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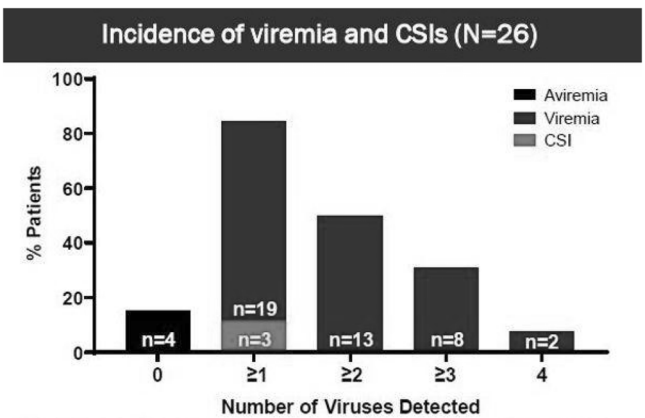
Background: Nearly 70% of high-risk recipients of allogeneic hemopoietic cell transplant (allo-HCT) may develop clinically significant infections (CSIs), defined as viremia + treatment or end-organ disease, from reactivated adenovirus (AdV), BK virus, cytomegalovirus (CMV), Epstein Barr virus (EBV), human herpesvirus-6 (HHV-6), and/or JC virus. We conducted a phase 2 trial to evaluate posoleucel, a partially HLA-matched, off-the-shelf, multivirus-specific T cell investigational product, for preventing viremia of these six viruses from progressing to CSI.

Methods: This open-label trial enrolled high-risk allo-HCT patients, defined as those with grafts from haploidentical donors, umbilical cord blood, mismatched unrelated donors, and matched unrelated donors with lymphocytes <180/mm^3, as well as patients who underwent T cell depletion. Eligible patients were engrafted and within 15–49 days of allo-HCT. Those with grade ≥3 GVHD and those on high-dose steroids were excluded. Patients received up to 7 infusions of posoleucel every 14 days and were tested weekly for viremia. The primary endpoint was the number of CSIs due to AdV, BKV, CMV, EBV, HHV-6, and/or JCV by week 14. To evaluate the relationship between VSTs and control of viremia as well as the in vivo persistence of our cells we performed functional immune reconstitution and posoleucel tracking studies in serial blood samples by interferon (IFN)-γ ELISpot and T cell receptor (TCR)-vβ immunosequencing, respectively.

Results: Twenty-six patients were dosed with posoleucel a median of 43 days (range 24-53) after allo-HCT. Twenty-two (85%) patients had viral DNA in blood (reactivation) from ≥1 virus, 13 (50%) had ≥2 reactivations, 8 (31%) had ≥3 reactivations, and 2 (8%) had 4 reactivations in the 14 weeks after the start of dosing (Figure). However, by week 14, only 3 patients (12%) had developed CSIs (2 asymptomatic CMV viremia requiring preemptive treatment and 1 EBV-post-transplant lymphoproliferative disorder in setting of high-dose steroids). No patient had a CSI with >1 virus. Two patients (8%) had SAEs possibly related to treatment (skin and pulmonary GVHD) and 1 (4%) had an SAE probably related (allergic reaction). Five patients (19%) had acute GVHD Grade II-IV. Four patients (15%) discontinued posoleucel due to AEs. One patient (4%) had secondary graft failure not related to treatment. No patient experienced cytokine release syndrome. The majority of patients who developed viremia ($n = 22$) had a detectable increase in the frequency of VSTs reactive against the infecting virus(es) during the posoleucel dosing period, with subsequent reduction in viral load. TCR-vβ sequencing demonstrated that posoleucel cells were present for up to 14 weeks after the last infusion, with peak detection during the dosing phase.



Although viral reactivation was observed at expected rates, the proportion of patients experiencing CSIs appeared to be lower than in historical control data. All patients with CSIs developed infection from only one virus, despite reactivation of multiple viruses.

Conclusions: High-risk allo-HCT patients who received posoleucel had lower than expected rates of CSIs from the 6 targeted viruses despite the high incidence of viral reactivations. Repeat dosing of posoleucel was generally safe and well tolerated. Viral control was associated with expansion of functional T cells against multiple infecting viruses during the dosing period with persistence of posoleucel-derived clones confirmed after the infusion period. A placebo-controlled phase 3 trial evaluating posoleucel to prevent clinically significant AdV, BKV, CMV, EBV, HHV-6, and JCV infections is ongoing (NCT05305040).

Clinical Trial Registry: Clinicaltrials.gov NCT04693637

Disclosure: Sanjeet Dadwal SD has served on an advisory board for Merck; has served as a speaker for Takeda, Merck, and Astellas; has received research funding from AlloVir, Karius, Ansun Biopharma, Merck, and Amplyx/Pfizer; and has stock options with Aseptiscope, Inc. G. Doug Myers has served on an advisory board and speakers bureau for Novartis, he has consulted for Eliana, and has received research funding from AlloVir. Jo-Anne Young, Rajat Bansal, Jean Yared have nothing to declare. Michelle Matzko, Sama Adnan, Sarah Gilmore are employees of and hold stock in AlloVir. Spyridoula Vasileiou and Ann Leen are consultants for AlloVir. Joshua Hill has served as a consultant for Amplyx.

13 - Infectious Complications

O096

DONOR NKG2C + ADAPTIVE NATURAL KILLER CELL (ANK) GENOTYPE AND ANK RECONSTITUTION KINETICS DETERMINE THE OUTCOME OF CMV REACTIVATION FOLLOWING HAPLOIDENTICAL HCT WITH ABATACEPT AND PTCY

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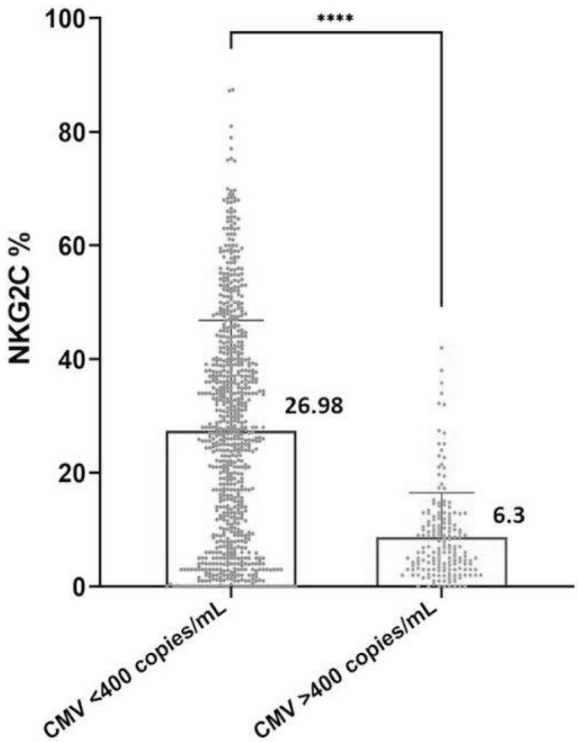
Background: Adaptive NK cells (ANK), characterised by high expression of an activating receptor, NKG2C expand following exposure to CMV in normal healthy adults, depending on the genotype of KLRC2 gene encoding NKG2C, which exists as wt/wt, wt/del or del/del; deletion genotypes being associated with low to absent expression of the receptor. Few studies have shown expansion of NKG2C + ANK following CMV reactivation post-HCT, but the impact of these cells on protection against CMV in the post-HCT period is largely unexplored.

Methods: We studied KLRC2 genotype of the donors and longitudinal reconstitution of NKG2C + ANK cells following HCT from haploidentical family donors (HFD). The study cohort included 136 patients with hematological malignancies receiving mostly myeloablative conditioning and PTCy-CNI as GVHD prophylaxis along with abatacept-primed donor lymphocyte infusions on days+7, +21 and +35. CMV copies were monitored weekly until day 100. Those with CMV reactivation before d + 100 and on corticosteroids were monitored weekly for another 3 months. CMV reactivation was defined as >400 copies/ml and treatment was initiated on two consecutive positive results or a single value of >1000 copies/ml. ANK from peripheral blood was measured with both immunophenotyping and functional assays every 15 days until d + 100, and monthly for 12 months.

Results: 136 patients (age 2–65 years) were studied for a median of 3 years. All patients and donors were CMV seropositive. 37 patients were transplanted from a donor with KLRC2 del (*d*-KLRC2*del)* genotype. The incidence of CMV reactivation was significantly higher in *d*-KLRC2*del* (100% vs 77.1, $p = 0.001$), as was the earlier onset (26 vs 33 days, $p = 0.008$) and longer duration (42 vs 34 days, $p = 0.04$) of reactivation along with peak CMV load (20 vs $4x10^3$/ml, $p = 0.002$). ANK reconstitution was delayed in those with *d*-KLRC2*del* at day 60, but not beyond. Only one patient developed CMV disease. The non-relapse mortality and relapse rate were 9.6% and 20.5%, with an overall survival of 82%, not influenced by CMV reactivation.

956 samples were simultaneously monitored for viral load and ANK cells in 136 patients. There was a strong correlation between ANK cell% and viral load with a cut-off of 400 copies/ml ($p<0.0001$, Fig. 1). On recursive partitioning, ANK cells at 15% were found to be discriminant. The time to reach an ANK of 15% was longer in those with d-KLRC2del genotype (34 vs 17.5 days in *d*-KLRC2*wt*). 38 patients had recurrent CMV reactivations. This was not related to *d*-KLRC2*del*, but was strongly influenced by corticosteroid exposure ($p = 0.001$). Those with ANK% > 15 at recurrence had a much shorter duration of viral load without treatment ($p = 0.02$). ANK also showed sustained cytotoxicity and lack of exhaustion markers throughout the study period.

Fig 1.



Conclusions: NKG2C + ANK cells expand rapidly following CMV reactivation following HFD-HCT if transplanted from a donor with *d*-KLRC2*wt* genotype. The kinetics of ANK recovery strongly influenced the peak and duration of viremia with prompt control of CMV recurrence in presence of optimum ANK numbers without corticosteroid exposure. Our study suggests that monitoring of NKG2C + ANK repertoire might be a useful tool in the algorithm for managing CMV reactivation post-HCT.

Clinical Trial Registry: CTRI: REF/2021/08/046552 www.ctri.nic.in

Disclosure: The authors declare no conflict of interest.

13 - Infectious Complications

O097

CYTOMEGALOVIRUS (CMV)-SPECIFIC T-CELL IMMUNE RECONSTITUTION IN HEMATOPOIETIC CELL TRANSPLANT (HCT) RECIPIENTS FOLLOWING LETERMOVIR PROPHYLAXIS USING T-SPOT.*CMV*

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Background: Letermovir prophylaxis after HCT has been associated with delayed polyfunctional CMV-specific T-cell immune reconstitution (Zamora *Blood* 2021). We assessed CMV-specific cell-mediated immunity (CMV-CMI) using a standardized, commercially available enzyme-linked immunosorbent spot (ELISpot) assay in HCT recipients who received letermovir prophylaxis to determine its potential applicability to the era of modern antiviral prophylaxis.

Methods: CMV-seropositive, allogeneic HCT recipients who received letermovir prophylaxis had immune testing by T-SPOT.*CMV* (Oxford-Immunotec, Marlborough, MA) performed on cryopreserved peripheral blood mononuclear cells (PBMCs) prospectively collected ~100 days post-HCT when letermovir was routinely discontinued. Interferon gamma (IFN-γ) expressing T-cells specific to CMV phosphoprotein 65 (pp65) and immediate early (IE)-1 antigens were calculated as spots per 250,000 cells. T-SPOT.*CMV* results were categorized as high (>100 spots per 250,000 cells) versus low (≤ 100 spots per 250,000 cells) for pp65 and IE-1. Logistic regression was used to identify factors associated with high versus low CMV-specific immune reconstitution. A subset of patients also had PBMCs tested by a multiparameter, intracellular cytokine staining (ICS) assay following stimulation with pp65 and IE-1 peptide libraries and CMV-CMI by both assays was correlated. For ICS, T-cell subsets were categorized as monofunctional or polyfunctional based on the expression of IFN-γ only or IFN-γ plus ≥1 functional marker, respectively.

Results: One hundred twenty-four HCT recipients (41% female, 44% donor CMV seropositive) a median age of 55 years (interquartile range [IQR] 43-62 years) were tested by T-SPOT.CMV. A total of 67 (54%) patients had any CMV reactivation by CMV DNA PCR in the first 100 days post-HCT while on letermovir, with a median peak CMV DNAemia of 57.9 IU/mL (IQR 0.0–267.5 IU/mL). Any CMV reactivation before day 100 post-HCT, decreased recipient age, and donor CMV serostatus were associated with significantly higher pp65 and IE-1 T-SPOT.*CMV* results at 100 days post-HCT in multivariable regression models. T-SPOT.CMV results were highly correlated with monofunctional and polyfunctional CMV-specfic CD8+ and CD4 + T-cell subsets by ICS. The relationship was strongest for pp65 T-SPOT.*CMV*results with monofunctional and polyfunctional CD8+ pp65-specific T-cells combined (Spearman $R = 0.81$, $p < 0.0001$).

Conclusions: In summary, CMV-CMI by T-SPOT.*CMV* was enhanced by CMV reactivation in the first 100 days post-HCT, decreased recipient age, and CMV donor seropositivity in HCT recipients upon discontinuation of letermovir prophylaxis. T-SPOT.*CMV* results were highly correlated with results from a laboratory-developed multifunctional ICS assay. Further studies are needed to determine the ability of T-SPOT.*CMV* to predict late CMV infection in HCT recipients following discontinuation of letermovir prophylaxis.

Disclosure: Michael Boeckh declares the following conflicts of interest: Research support from Oxford-Immunotec and Merck; Consulting for Allovir.

Joshua Hill declares the following conflicts of interest: Research support from Oxford-Immunotec, Merck, and Allovir, Merck; Consulting for Allovir.

All other authors have no other conflicts to declare.

13 - Infectious Complications

O098

OPPORTUNISTIC INFECTIONS IN PATIENTS RECEIVING POST-TRANSPLANT CYCLOPHOSPHAMIDE (PTCY): OUTCOMES IN HAPLOIDENTICAL VERSUS MATCHED OR MISMATCHED UNRELATED DONOR (MUD/MMURD) ALLOGRAFTS

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Background: Recent data suggest that post-transplant cyclophosphamide (PTCy) may become the new standard of care for GVHD prophylaxis in matched and mismatched unrelated donor HCT. PTCy has been associated with an increased risk of infectious complications in haploidentical recipients, but risk for infections in matched and mismatched donor HCT with PTCy has not been well described.

Methods: We evaluated 355 adults at our center undergoing HCT with PTCy-based GVHD prophylaxis between January 1, 2015 and February 1, 2022. Opportunistic infections including adenovirus (AdV) infection, clinically significant cytomegalovirus (CS-CMV) infection (CMV infection requiring treatment), Epstein-barr virus (EBV) infection, and invasive fungal disease (IFD) were identified for one-year post-HCT in two groups: haploidentical ($n = 193$) and matched unrelated donor (MUD) or mismatched unrelated donor (MMURD) allograft recipients ($n = 162$). The one-year cumulative incidence function (CIF) of opportunistic infections was calculated based on time to first infection using dates of infection-free death, disease relapse, and repeat HCT as competing risks. Secondary analysis evaluated risk factors for opportunistic infections using a multivariable Cox regression model.

Results: Baseline and transplant characteristics were similar between the groups, however the MUD/MMURD group received more peripheral blood grafts (Haplo 83% vs. MUD/MMURD 63%; $p < 0.001$). Transplant outcomes including acute GVHD, disease relapse, and survival at one year were similar between the two cohorts. The use of high-dose (>1mg/kg/day) corticosteroids for treatment of acute GVHD was similar between haploidentical and MUD/MMURD recipients (Haplo 29% vs. MUD/MMURD 22%; $p = 0.12$). Haploidentical recipients experienced more cytokine release syndrome (CRS; Haplo 64% vs. MUD/MMURD 22%; $p < 0.001$) and increased use of tocilizumab for treatment of CRS (Haplo 20% vs. MUD/MMURD 2%; $p < 0.001$). The one-year CIF for infections was increased in haploidentical recipients as compared to MUD/MMURD (haplo 38.9, 95% CI 32.6–46.4 vs. MUD/MMURD 25.5%, 95% CI 19.4–33.0; $p = 0.007$). CS-CMVi and AdV infections were significantly increased in the haploidentical group, while EBV viremia, treatment with rituximab for EBV reactivation, and PTLD, as well as IFD occurred more frequently in the haploidentical group but were nonsignificant (Table 1). On

Table 1. Logistic Regression of Clinical/Transplantation Factors on High T-SPOT.CMV Counts.

	Univariable Analysis				Multivariable Analysis			
	Variable	**Category**	**OR (95% CI)**	***P*-value**	**Variable**	**Category**	**OR (95% CI)**	***P*-value**
pp65								
	Any CMV day 0-100 post-HCT	**No**	1		**Any CMV day 0-100 post-HCT**	**No**	1	
		Yes	3.01 (1.44–6.29)	**0.003**		**Yes**	7.11 (2.52–20.1)	**<0.001**
	Donor CMV serostatus	**-**	1		**Donor CMV serostatus**	**-**	1	
		+	5.57 (2.50–12.4)	**<0.001**		+	7.73 (2.95–20.2)	**<0.001**
IE-1								
	Any CMV day 0-100 post-HCT	**No**	1		**Any CMV day 0-100 post-HCT**	**No**	1	
		Yes	2.62 (1.01–6.84)	**0.048**		**Yes**	3.82 (1.30–11.2)	**0.02**
	Donor CMV serostatus	**-**	1		**Donor CMV serostatus**	**-**	1	
		+	4.31 (1.64–11.3)	**0.003**		+	5.68 (1.97–16.3)	**0.001**
	Age	**<=60 yr**	1		**Age**	**<=60 yr**	1	
		>60 yr	0.26 (0.07–0.93)	**0.04**		**>60 yr**	0.23 (0.06–0.92)	**0.04**

Any CMV defined as any positive CMV DNA PCR test including those below the assay limit of quantitation (50 IU/mL).
Multivariable pp65 models included GVHD prophylaxis as an additional adjustment variable which was significant in the univariable models but not in the final multivariable models.
CI confidence interval, *CNI* calcineurin inhibitor, *GVHD* graft-versus-host disease, *MMF* mycophenolate, *MTX* methotrexate, *OR* odds ratio, *PTCy* post-transplantation cyclophosphamide, *siro* sirolimus.

multivariable analysis, haploidentical donor allograft (HR 1.90; $p = 0.004$), prior HCT (HR 1.94; $p = 0.007$), and grade 3-4 GVHD (HR 2.32; $p = 0.016$) were associated with increased risk of infection within the first year post-HCT. Age, disease type, graft source, conditioning intensity, and diagnosis of CRS were not associated with increased risk of infection on multivariable analysis.

Table 1. Opportunistic Infections Following PTCy

Opportunistic Infections	**Haploidentical HCT *n* = 193**	**MUD/ MMURD HCT *n* = 162**	***P*-value**
Total Infections, no.	101	52	**0.01**
Any Infection, no. (%)	75 (39)	41 (25)	**0.01**
Adenovirus Infection, no. (%)	14 (7)	3 (2)	**0.02**
Median time to Adenovirus, days	89	87	-
CS-CMVi, no. (%)	48 (25)	25 (15)	**0.03**
Median time to CS-CMVi, days	52	49	-
Quantifiable EBV viremia, no. (%)	17 (9)	11 (7)	0.56
Median time to EBV viremia, days	139	99	-
EBV viremia requiring rituximab, no. (%)	5 (3)	2 (1)	0.46
Median time to rituximab, days	142	200	-
EBV PTLD, no. (%)	4 (2)	1 (0.6)	0.38
Median time to EBV PTLD, days	145	314	-
Invasive Fungal Disease (IFD), no. (%)	23 (12)	13 (8)	0.29
Median time to IFD, days	22	32	-

Conclusions: MUD / MMURD HCT recipients receiving PTCy have a significantly lower risk of opportunistic infections as compared to haploidentical HCT recipients. Mechanisms for this finding have yet to be elucidated, but it may be related to delayed immune reconstitution or impaired antigen presentation in the setting of HLA mismatch. Further investigation to evaluate immune reconstitution and its association with infections in haploidentical versus MUD/MMURD HCT is ongoing.

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13 - Infectious Complications

O099

FREQUENCY, MANAGEMENT AND NEW TREATMENT MODALITIES OF EBV-DNA-EMIA AND EBV-PTLD AFTER ALLO-HCT: SURVEY OF IDWP-EBMT

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Background: The aim of this study was to determine the current approach of transplant centers to EBV infection in context of monitoring, diagnosis, frequency and treatment.

Methods: All allogeneic EBMT transplant centers were invited to participate in the survey on EBV management and frequency of EBV-related complications.

Results: Overall 111 centers performing allo-HCTs, including 55 adult, 26 pediatric and 30 combined, participated in the study. During period 2020-2021, these centers have done 15,317 allo-HCT, including 12,292 in adults and 3,025 in children.

Routine serology testing in patient and donor before HCT is performed in 95.5% centers. Pretransplant testing for EBV-DNA is routinely done in 33.3% centers, and in selected patients in 9.0% centers (indications: positive IgM, previous EBV infection, EBV-driven lymphoma, patients treated with MoAbs before HCT, inborn errors of immunity [IEI]).

Monitoring for EBV infection is feasible in 98.2% centers: in all cases with PCR, using mainly blood (65.8%) or plasma (20.7%). Overall, 65.8% centers use standardized PCR, providing results in IU/mL (43.8%), copies/mL (47.9%) or both (5.5%). Additional screening for EBV-DNA include mainly CNS fluid (71.1%).

Post-HCT regular monitoring is performed in all patients in 80.2% centers and in selected groups in 10.8%. Selected patients include: matched MUD-HCT, mismatched MUD-HCT, related CBT, unrelated CBT, ex vivo T-depleted haploidentical-HCT, T-replete haploidentical-HCT with PTCy, use of ATG. Monitoring is done routinely mainly weekly (57.7%), twice weekly (9.9%), every 2 weeks (7.2%); up to day +120 (55.8%), until cGVHD treatment (45.0%), until resolution of lymphopenia (23.4%), or until CD4+ counts increase over 50/µl (15.3%).

Anti-EBV prophylaxis is used in 27.9% centers, with rituximab (12.6%) or antivirals in other cases. Frequency of EBV-DNA-emia after HCT, requiring pre-emptive therapy, was 7.4% (6.2% adults, 12.6% children), including 5.6% MSD, 10.4% MUD, 8.2% MMUD, 3.8% PTCy-haplo, 6.2% other haplo, and 3.6% CBT (data from 72 centers; 8228 patients at risk).

The PCR threshold used to start preemptive treatment was differentiated among centers: most often >1000 (31.5%) or >10,000 (40.5%) copies/mL. First-/second-line preemptive therapy included reduction of immunosuppressive therapy (RIS) (60.4%/23.4%) and rituximab (47.7%/43.2%). The rate of failure of first-line preemptive treatment was 9.4%. Preemptive treatment is continued until one (32.4%) or two negative (48.6%) results. Reported rate of failure of first-line treatment of EBV infection was 72/766 (9.4%) (data from 72 centers).

Frequency of EBV-PTLD was 1.55% (1.21% adults; 3.53% children), including 0.80% MSD, 2.12% MUD, 1.72% MMUD, 2.38% PTCy-haplo, 0.69% other haplo, 3.82% CBT (data from 56 centers, 7152 patients at risk). First-line therapy of EBV-PTLD was rituximab (69.4%), and RIS (62.2%); second-line therapy: chemotherapy (23.4%), rituximab (22.5%), RIS (17.1%), EBV-CTL (15.3%). Adoptive immunotherapy (VST, viral-specific T-lymphocytes) for EBV disease was available in 44.1% centers, mainly for second-line therapy. A number of new experimental therapies were given in 28 patients with resistant/refractory PTLD.

Conclusions: The frequency of EBV-DNA-emia and EBV-PTLD over a period 2020-2021 possibly decreased in comparison to historical data. New trends (wider access to VST, new experimental therapies) are being observed in management of EBV infection after allo-HCT.

Disclosure: Nothing to declare.

13 - Infectious Complications

O100

AN OPEN-LABEL, SINGLE-ARM STUDY OF LETERMOVIR (LTV) FOR PREVENTION OF RECURRENT CMV INFECTION IN HIGH-RISK ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT (HCT) RECIPIENTS

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Background: Letermovir (LTV) primary prophylaxis (pr-ppx) is effective in preventing clinically significant CMV infection (cs-CMVi) in the first 100 days after allogeneic hematopoietic cell transplant (HCT). We report on the efficacy and safety of LTV as CMV secondary ppx (sec-ppx) in high risk HCT patients (pts).

Methods: Open-label study conducted at Memorial Sloan Kettering and University of Minnesota, USA (ClinicalTrials.gov identifier: NCT04017962. Eligibility criteria: i) HCT with ≥1 CMV high risk criteria including mismatched donor, ex-vivo T-cell depletion, anti-thymocyte globulin (ATG), posttransplant Cyclophosphamide (PTCy), graft versus host disease (GVHD) requiring systemic immunosuppressants or corticosteroids for any reason; AND ii) receipt of (val)ganciclovir and/or foscarnet for cs-CMVi AND CMV viral load ≤ 136 IU/mLx1 or < 300 IU/mL x2 consecutive values within 7 days prior to enrollment. Prior LTV pr-ppx was allowed unless LTV resistance was suspected. LTV sec-ppx was given for 14 weeks or cs-CMVi whichever occurred first. Pts were followed for 12 weeks after discontinuation of sec-ppx (F/U). The total study duration was 26 weeks. Pts were censored at death or last follow up. During the study, CMV was monitored by qPCR and treated per institutional standards of care. The primary endpoint was cs-CMVi by week 14. Secondary endpoints were cs-CMVi during FU, CMV end-organ disease (EOD), LTV resistance associated mutations (RAM) and adverse events (AE) related to LTV during the study.

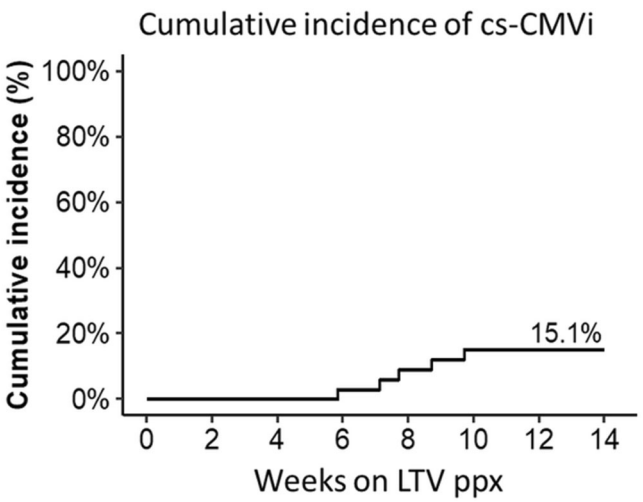
Results: From August 2019 through October 2022, 36 pts were enrolled (currently 33 off-study; 3 on sec-ppx). Indication for HCT was leukemia/myelodysplastic syndrome in 27 (82%), lymphoma in 5 (15%) and aplastic anemia in 1(3%) pts. Fourteen (42%), 14(46%) and 4(12%) pts received myeloablative, reduced intensity and non-ablative conditioning respectively. High risk criteria are shown on the table below. Overall, 28(78%) pts had received LTV pr-ppx; including 12 (33%) pts who received pr-ppx for <14 days and 16 (45%) for 15->100 days. LTV sec-ppx started at a median 71 days (IQR 29-208) post HCT. Six (18%) pts discontinued sec-ppx prematurely; due to progression of disease (POD) (2), transition to comfort care (2) or death 2 (due to GVHD and multiorgan failure, 1 pt each). By week 14, 5 pts developed cs-CMVi (4 pts on sec-ppx and 1 pt off sec-ppx) for a cumulative incidence of 15.1 % (Figure). Two of 4 pts with cs-CMVi on sec-ppx had LTV RAM (1 pt was not tested). There were no AEs related to LTV, and no CMV-EOD during

sec-ppx. During F/U 4 pts died before week 26; due to GVHD (1), POD (2) and hemorrhage (1). Two pts developed cs-CMVi treated successfully; there was no CMV-EOD or death related to CMV during F/U.

Table

Characteristic (Total, *N* = 36)	*N* (%)
Age, years, median (range)	59 (17,84)
Sex: Female/Male	18 (50)/18 (50)
CMV recipient seropositive	33 (92)
Donor HLA match	
Matched related/unrelated	4 (11)/20 (55)
Mismatched unrelated	9 (25)
Haploidentical	3 (8)
Stem cell source	
Peripheral blood	31 (86)
Cord blood	5 (14)
GVHD prophylaxis	
Ex-vivo T-cell depletion ($CD34^+$ selection)	11 (31)
Cyclophosphamide/Mycophenolate Mofetil/Tacrolimus	10 (28)
Cyclosporine/Mycophenolate Mofetil ±Other	4 (11)
Methotrexate/Tacrolimus and/or Others	11 (30)
Anti-thymocyte globulin (ATG)	17 (47)
Corticosteroids at enrollment	10 (28)
GVHD grade 2-4 on systemic immunosuppressants	17 (47)
Prior LTV primary prophylaxis	28 (78)?

Figure



Conclusions: LTV secondary prophylaxis was safe and effective in preventing recurrent cs-CMVi in 85% of high risk HCT pts including pts with prior LTV exposure. Our data supports the utility of LTV when secondary prophylaxis is clinically indicated.

Clinical Trial Registry: https://www.clinicaltrials.gov/ct2/show/NCT04017962

ClinicalTrials.gov identifier: NCT04017962

Disclosure: This is an investigator initiated study funded by MSD

Gyuri Han, Anat stern, Yiqi Su, Brian Shaffer, JoAnn Young: Nothing to declare

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13 - Infectious Complications

O101

REAL-WORLD OUTCOMES OF LETERMOVIR USE IN PRIMARY PROPHYLAXIS IN ADULT CYTOMEGALOVIRUS SEROPOSITIVE ALLOGENEIC HCT RECIPIENTS: A MULTICENTER RETROSPECTIVE COHORT IDWP STUDY FROM THE EBMT REGISTRY

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Background: Letermovir (LET) prophylaxis in CMV seropositive allogeneic hematopoietic stem cell transplant (HCT) recipients (R+) was approved in 2017 based on a Phase 3 randomized clinical trial (RCT) demonstrating lower rates of clinically significant CMV infection (csCMVi) (37.5% vs. 60.6% at week 24 after HCT) and all-cause mortality among LET treated participants. While RCTs demonstrate causal effects between treatments and outcomes, RW data answer practical aspects of outcomes of LET use.

The objective of this single-arm study was to assess LET real world (RW) outcome in adult CMV seropositive recipients (R+) of allo-HCT in a large cohort of multiple centers in Europe participating in the EBMT registry.

Methods: A retrospective observational cohort design was used to examine the RW utilization patterns and effectiveness of LET among CMV R+ of an allo-HCT in France, Germany and Italy. Inclusion criteria were CMV R+ recipients ≥18 yrs who received LET for primary prophylaxis between Jan 1, 2018 - Dec 31, 2020 and had data available for at least 100 days post-HCT.

Results: In this interim analysis, 132 allo-HCT recipients (62.1% male) with median age 48 yrs (min-max 20-69) received LET as primary prophylaxis. Patients were treated for: acute leukemia (65.1%), MDS/MPN (15.9%), lymphoma (9.1%), chronic leukemia (3.8%), plasma cell disorders (0.8%), bone marrow failure (4.5%), or hemoglobinopathies (0.8%).

Donor/recipient CMV serostatus was D+/R+ 62.1%, D-/R+ 37.9%. Donor type was 58.3% unrelated, 28.0% sibling,

13.6% mismatched relative. Standard conditioning was used in 65.9% and reduced-intensity in 34.1%. Peripheral blood stem cells were the source in 87.1%. ATG/alemtuzumab was used in 62.1%. All centers followed WHO standardization guidelines for CMV viral load assay by PCR. The median duration of LET prophylaxis use was 99 days (min-max 59-434).

Cumulative incidence of clinically significant CMV infection (csCMVi) was 0.76% (0.07–3.81) at 3 months, 5.30% (2.33–10.07) at 6-months, and 9.09% (4.95–14.76) at 12-months. The median time from HCT to CMV infection is 184 days (min-max 83-441). In univariate analysis two factors contributed to csCMVi: older age, as continuous variable (HR = 1.64; 95%CI = 1.02–2.64; $p = 0.040$; for 10-year effect) and higher BMI (HR = 1.11; 95% CI = 1.00-1.23; $p = 0.046$). There was no difference on incidence of csCMVi between patients who stopped LMV at D100 and those who continued it beyond D100 (p = 0.7). Due to the limited number of events, multivariate analysis was not performed.

The median follow-up was 26.9 months (95%CI = 25.3–28.0). Overall survival was 99.24% (95%CI = 94.74–99.89%) at 3 months, 94.70% (95%CI = 89.20–97.44%) at 6-months, and 84.09% (95% CI = 76.65–89.32%) at 12-months. No significant variables were detected in the univariate analysis for overall survival. Acute GVHD occurred in 48.5%, chronic GVHD in 36.2% evaluable patients.

CMV disease treatment during the initial hospitalization was necessary in 1 (0.8%) patient. Rehospitalisation for csCMVi occurred in 8/132 (6%) patients and required preemptive therapy ($n = 4$) or disease treatment ($n = 4$).

Conclusions: In this interim RW LET analysis the cumulative incidence of clinically significant CMV infection was lower compared to the phase 3 RCT (9.09% vs 37.5%). Further studies are needed to determine drivers of LET outcome in RW settings.

Disclosure: Jan Styczynski received lecture fee and conference fee from Merck. Irina Kolobova and Sanjay Merchant are employee of Merck and Co, Inc. Other Authors have nothing to disclose.

13 - Infectious Complications

O102

CMV REACTIVATION AFTER STOPPING LETERMOVIR PRIMARY PROPHYLAXIS IN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS

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Background: Limited real-life data exist on CMV viremia monitoring after letermovir prophylaxis discontinuation in allogeneic hematopoietic cell transplant recipients (allo-HCTr). The clinical significance of CMV DNAemia during letermovir administration and its potential impact on the development of CMV-specific T-cell immunity and hence protection of post-letermovir csCMV infections remain to be defined.

Methods: We conducted a single-center, retrospective, cohort study from May 1, 2019, to May 1, 2022 including 61 consecutive adult allo-HCTr, who received primary CMV-prophylaxis with letermovir for the first 3 months post-transplant. The primary objective was to describe the 3-month cumulative incidence of clinically-significant CMV infections (csCMVi) after letermovir discontinuation. Associations between CMV-DNAemia while on letermovir and csCMVi incidence during the first 3 months after letermovir discontinuation were tested.

Results: Letermovir was initiated in 30 (49%) and 31 (52%) CMV donor-/recipient+ (D-/R +) and CMV D + /R+ HCTr, respectively. Twenty-seven (44%) patients had an haploidentical donor and 28 (46%) patients experienced grade 2 acute graft-versus-host disease (aGvHD). Letermovir median duration of administration was 103 days (IQR 96, 127). Median time between letermovir discontinuation and csCMV infection was 54 days (IQR 36, 69). The cumulative incidence of csCMVi within 3 months after letermovir prophylaxis interruption was 23% (14/61), with a significantly higher incidence in HCTr with haploidentical donors (71%; 10/14) compared to others (29%; 4/14, logrank=0.02). Haploidentical donor was identified as the only significant predictor of csCMVi after letermovir discontinuation (OR: 4.41, 95%CI 1.2, 16; $p = 0.03$). Breakthrough csCMVi was diagnosed in 10 (16%) patients, while 66% (40/61) patients experienced at least 1 episode of detectable (21-150 IU/mL) CMV-DNAemia while on letermovir (including 14/61 (23%) patients with CMV-DNAemia between 100–149 UI/mL). There were no associations between CMV-DNAemia or breakthrough csCMVi while on letermovir and csCMVi post-letermovir discontinuation in univariable analyses.

Conclusions: Almost 1 in 4 patients developed csCMVi within the first 3 months post-letermovir discontinuation, particularly in allo-HCTr with a haploidentical donor. No correlation was found between CMV-DNAemia while on letermovir and csCMV infection post-letermovir discontinuation. More data are required to define the optimal duration of prophylaxis in higher risk patient subgroups, such as allo-HCTr with haploidentical donors, and the threshold for pre-emptive treatment initiation while on letermovir to allow for CMV T-cell immunity development.

Disclosure: L.C., L.R., S.M-L., A-C.M., F.G., S.M., C.v.D.: no conflicts of interest.

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D.N. has received research support from MSD and Pfizer, and consulting fees from MSD, Pfizer, Basilea, and Gilead.

13 - Infectious Complications

O103

CYTOMEGALOVIRUS REACTIVATION AFTER MATCHED UNRELATED DONOR AND HAPLOIDENTICAL HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Cytomegalovirus (CMV) reactivation remains a challenging and life-threatening complication after allogeneic hematopoietic cell transplantation (HCT). We aimed to investigate CMV viremia and disease after matched unrelated donor (MUD) and haploidentical (haplo) HCT, associated factors, and its impact on overall survival (OS).

Methods: We conducted a single-center retrospective study, including all adult haplo and MUD HCT recipients in the past 5 years at the University of Kansas Medical Center who had at least one year of follow-up (08/2016-07/2021). Data were analyzed using SPSS v28. Bivariate analyses, using the chi-

Characteristics		Total ($n = 452$)	CMV viremia ($n = 181$)	P value	CMV disease ($n = 32$)	P value
Age, median years (range)		57 (18–77)	56 (18–77)	0.286	55 (25–74)	0.724
Male, *n* (%)		277 (61.3%)	105 (37.9%)	0.243	19 (6.9%)	0.818
Caucasians, *n* (%)		381 (84.3%)	134 (35.2%)	<0.001	24 (6.3%)	0.025
HCT-CI ≥3, *n* (%)		251 (55.5%)	95 (37.8%)	0.287	17 (6.8%)	0.776
Recipient CMV status, *n* (%)	Negative	185 (40.9%)	7 (3.8%)	<0.001	2 (1.1%)	<0.001
	Positive	267 (59.1%)	174 (65.2%)		30 (11.2%)	
Donor CMV status, *n* (%)	Negative	218 (48.2%)	67 (30.7%)	<0.001	13 (6%)	0.372
	Positive	234 (51.8%)	114 (48.7%)		19 (8.1%)	
Letermovir[a]	Yes	176 (65.9%)	113 (64.2%)	0.646	20 (11.4%)	0.927
	No	91 (34.1%)	61 (67%)		10 (11%)	
Conditioning, *n* (%)	Myeloablative	169 (37.4%)	65 (38.5%)	0.596	13 (7.7%)	0.695
	Reduced intensity	283 (62.6%)	116 (41%)		19 (6.7%)	
Graft source, *n* (%)	PBSC	224 (49.6%)	87 (38.8%)	0.604	16 (7.1%)	0.959
	Bone marrow	228 (50.4%)	94 (41.2%)		16 (7%)	
GVHD prophylaxis, *n* (%)	Tac/MTX	241 (53.3%)	92 (38.2%)	0.386	16 (6.6%)	0.696
	PT-Cy-based	211 (46.7%)	89 (42.2%)		16 (7.6%)	
Donor type, *n* (%)	MUD	276 (61.1%)	105 (38%)	0.277	19 (6.9%)	0.839
	Haplo	176 (38.9%)	76 (43.2%)		13 (7.4%)	

Total represents column percentages; CMV viremia and disease represent row percentages. *KPS* Karnofsky performance status, HCT-CI, Hematopoietic cell transplantation-specific comorbidity index, *CMV* cytomegalovirus, *PBSC* Peripheral blood stem cells, *Tac/MTX* Tacrolimus/methotrexate, *PT-Cy* post-transplant cyclophosphamide, *MUD* matched unrelated donor, *Haplo* haploidentical related donor, [a]Letermovir data is only in CMV seropositive recipients ($n = 267$).

square and t-test, were performed. Kaplan-Meier and regression analyses were conducted. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Statistical significance was considered at p≤0.05.

Results: The study included 452 allogeneic HCT recipients, including 276 (61%) MUD and 176 (39%) Haplo transplants. The median age was 57 (18-77) years; 84% were Caucasians and 61% were males. Hematologic diagnoses included myeloid (71%), lymphoid (22%), and others (7%). Myeloablative (37%) and reduced-intensity conditioning (63%) were performed. Graft sources were peripheral blood stem cells (50%) and bone marrow (50%). The median follow-up was 24.4 (0.2-72.9) months. CMV viremia and disease were observed in 181 (40%) and 32 (7%) patients, respectively, with a significantly higher incidence in ethnic minorities and CMV seropositive recipients. Patients with grade 2-4 acute GVHD ($p = 0.005$) and chronic GVHD ($p = 0.012$) were more likely to have CMV disease. Patients with CMV disease had higher non-relapse mortality (NRM) (47% vs 20%, $p < 0.001$). Patients with CMV disease had a lower OS than recipients without CMV disease (median 14.1 months vs. not reached, $p = 0.024$); however, CMV viremia did not impact OS (median not reached in both groups, $p = 0.640$). Among patients who received post-transplant cyclophosphamide (PT-Cy)-based GVHD prophylaxis ($n = 211$; haplo=176, MUD = 35), donor type did not impact CMV viremia (haplo 43% vs MUD 37%, $p = 0.509$) or disease (haplo 7% vs MUD 9%, $p = 0.809$). Among 267 CMV seropositive recipients, Letermovir prophylaxis did not significantly impact the incidence of CMV viremia (64.2% vs. 67%, $p = 0.646$) or CMV disease (11.4% vs 11%, $p = 0.927$). Ethnicity, CMV seropositive recipient, and CMV seropositive donor (all $p < 0.001$) were associated with the risk of CMV viremia. In the multivariate regression model, African Americans as compared to Caucasians (OR 3.3, 95% CI 1.1–9.7, $p = 0.029$) and CMV seropositive as compared to seronegative recipients (OR 51.5, 95% CI 22.4-118.1, $p < 0.001$) independently predicted the risk of CMV viremia. Ethnicity ($p = 0.025$) and CMV seropositive recipient ($p < 0.001$) were associated with the risk of CMV disease. In the multivariate regression model, CMV seropositive recipients as compared to seronegative recipients (OR 11.4, 95% CI 2.7–48.7, $p < 0.001$) independently predicted the risk of CMV disease.

Conclusions: CMV disease significantly lowers survival after allogeneic HCT. Recipient CMV seropositive status is the strongest predictor of CMV viremia and disease post-transplantation. In our analysis, conditioning intensity, graft source, donor type, or GVHD prophylaxis regimen was not associated with CMV reactivation and disease. Letermovir prophylaxis did not decrease the incidence of CMV viremia and disease in CMV seropositive patients.

Disclosure: None

13 - Infectious Complications

O104

REINFORCEMENT OF CELL-MEDIATED IMMUNITY DRIVEN BY TUMOR-ASSOCIATED EPSTEIN-BARR VIRUS (EBV)-SPECIFIC T CELLS DURING TARGETED B-CELL THERAPY WITH RITUXIMAB

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Background: In immunocompromised patients, Epstein-Barr virus (EBV) infection or reactivation is associated with increased morbidity and mortality, including the development of a wide range of B-cell lymphomas. The first-line treatment consists of reduction of immunosuppression and administration of the chimeric monoclonal CD20 antibody rituximab. Furthermore, the presence of EBV-specific T cells against latent EBV proteins is crucial for the control of EBV-associated diseases. Therefore, in addition to effective treatment strategies, appropriate monitoring

of T cells of high-risk patients is of great importance for improving clinical outcome. We hypothesized that rituximab-mediated lysis of malignant EBV-infected B cells leads to the release and presentation of EBV-associated antigens and results in an augmentation of EBV-specific effector T-cell responses.

Methods: EBV-infected B lymphoblastoid cell lines (EBV^+ B-LCLs) were used as a model for EBV-associated lymphomas, which are capable of expressing latency stage II and III EBV proteins present in all known EBV-positive malignant cells. Rituximab was administered to obtain cell lysates containing EBV antigens. Efficiency of EBV-antigen cross-presentation by EBV^+ B-LCLs compared to EBV antigen cross-presentation by professional antigen presenting cells (APCs) using dendritic cells and B cells was investigated by in vitro T-cell immunoassays. Deep T-cell profiling of the tumor-reactive EBV-specific T cells was performed, assessing the expression of T-cell differentiation and activation markers as well as regulatory and cytotoxic molecules by EliSpot assay, multicolor flow cytometry, and multiplex analyses.

Results: By inhibiting parts of the cross-presentation pathway, EBV^+ B-LCLs were shown to cross-present obtained exogenous antigens mainly through major histocompatibility complex (MHC) class I, comparable to dendritic cells and B cells, thereby inducing strong EBV-specific $CD8^+$ cytotoxic T-cell responses. Stimulation also led to the activation of $CD4^+$ T helper cells, suggesting that longer peptide fragments are processed via the classical MHC class II pathway. Moreover, EBV^+ B-LCLs were found to be able also to take up apoptotic cells and rituximab-untreated cells by endocytosis resulting in antigen cross-presentation and induction of EBV-specific T-cell responses but in a significant lower extent then by cross-presentation of antigens derived from rituximab-treated cells. Increased expression of activation markers CD25, CD69 and CD137 were detected on EBV-specific T cells, which showed high proliferative and cytotoxic capacity as indicated by enhanced EBV-specific frequencies and increased secretion levels of cytotoxic effector molecules (e.g., IFN-γ, granzyme B, and perforin). Expression of the regulatory molecule Tim-3, but not PD-1 and CTLA-4 was induced but had no negative impact on effector functions.

Conclusions: In this study we showed for the first time that rituximab-mediated lysis of EBV-infected tumor cells can efficiently boost EBV-specific endogenous effector memory T-cell responses through cross-presentation of EBV-derived antigens. This promotes the restoration of antiviral cellular immunity and presents an efficient mechanism to improve the treatment of $CD20^+$ EBV-associated malignancies. This effect is also conceivable for other therapeutic antibodies or even for therapeutically applied unmodified or genetically-modified T cells, which lead to the release of tumor antigens after specific cell lysis.

Disclosure: Nothing to declare

13 - Infectious Complications

O105

CLINICAL OUTCOMES OF COCCIDIOIDOMYCOSIS IN HEMATOPOIETIC CELL TRANSPLANT (HCT) AND CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY (CART) RECIPIENTS

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Background: *Coccidioides*, an endemic fungus of the Southwest US, can cause disseminated infection in immunocompromised patients. Its incidence in HCT and CART patients is rarely documented, including in large prospective trials in the US using the Transnet (Transplant-Associated Infection Surveillance Network) database.

Methods: We identified patients with coccidioidomycosis from our comprehensive microbiology/pathology database (2005-2022) and performed a retrospective chart review of patients with coccidioidomycosis in the setting of HCT and CART. Data was collected on demographics, HCT type, median time to diagnosis, diagnostic modality that identified the infection, site of infection, treatment, and clinical outcome.

Results: A total of 5336 allogeneic HCTs, 5692 autologous HCTs and 739 CARTs were performed at our institution from 1/2005 to 7/2022. Eleven patients (7 allogeneic HCT – 2 haploidentical, 1 mismatched unrelated, 1 cord blood, 3 matched related donor type – 3 autologous HCT, and 1 CART) were diagnosed with coccidioidomycosis (incidence of 0.001%). All were residents of California, 8 from southern California and 3 from central California. Eight (73%) were male and median age was 58 years (range 17 – 63 years). Seven patients had a baseline (pre-cellular therapy) chest imaging that had non-specific pulmonary findings described as nodules or calcifications. Only 1 patient had baseline *Coccidioides* serology testing. Reactivation was suspected in 7 patients and primary infection in 4. The median time to diagnosis of infection from cellular therapy was 174 days (range 16 – 1846 days). Eight patients developed infection within 12 months of cellular therapy with 6 developing within first 6 months. Five patients were receiving antifungal prophylaxis at diagnosis: 2 on azole and 3 on echinocandin. 7/11 patients tested negative with serum Coccidioides antibody panel (IgG, IgM, complement fixation-CF, and immunodiffusion-ID) and the diagnosis was made by direct visualization on cytology in 3, histopathology in 1, culture in 10, and serum/urine Coccidioides antigen in 6. One patient also tested positive by serum cell free DNA test (KARIUS). As for site of infection, 10 had pulmonary disease and 1 had an ARDS like presentation. Four patients had disseminated disease – 1 with lung and peritoneal involvement, 2nd with lymph nodes, bone, central nervous system (CNS), skin, and bone marrow involvement, 3rd with lung and CNS involvement, and 4th with lung, bone and CNS involvement. Primary treatment was with azoles in 6 patients, while amphotericin B (lipid/liposomal) was predominantly used in patients with disseminated infection. Five patients died: 3 deaths were related to other medical conditions/relapse of hematologic malignancy and 2 deaths were attributable to coccidioidomycosis (both died within 6 months of cellular therapy – 1 allogeneic HCT and 1 CART). The mortality rate attributable to coccidioidomycosis in this patient cohort was 18%.

Conclusions: Although the incidence of coccidioidomycosis is rare in the HCT and CART patient population, there is significant morbidity and mortality associated with either primary infection or reactivation. Antibody panel was non-diagnostic in the majority of patients and the use of other approaches to establish the diagnosis such as tissue sampling, antigen-based testing and possibly cell free DNA testing is indicated.

Disclosure: Sanjeet Singh Dadwal, MD: Investigator - Amplyx/Pfizer. Speakers bureau: Merck and Astellas

All other authors - no relevant disclosures to report

13 - Infectious Complications

O106

INCIDENCE AND RISK FACTORS OF POST-ENGRAFTMENT OPPORTUNISTIC INFECTIONS IN AUTOLOGOUS STEM CELL

TRANSPLANTATION: A NATIONWIDE, POPULATION-BASED COHORT STUDY IN KOREA

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Background: Despite the advances in medicine, infection is still an important complication related to the prognosis of autologous stem cell transplantation (ASCT) and can affect the quality of life. However, compared with allogeneic hematopoietic stem cell transplantation, ASCT has a lower risk of infection; therefore, few studies related to infection have been conducted. In this study, we investigated the incidence and risk factors of fungal and viral infections after ASCT, especially in the post-engraftment period.

Methods: In a nationwide population-based study, using the Korean Health Insurance Review and Assessment Service database, patients with lymphoma and multiple myeloma (MM) who underwent ASCT from 2002 to 2016 were retrospectively analyzed. Infections were limited to cases that occurred at least 30 days after ASCT. Each infection was defined by a registered diagnostic code or therapeutic drug codes. Oral candidiasis, Herpes simplex virus and Epstein−Barr virus infections were excluded. Cumulative incidence rates (CIRs) and risk factors of opportunistic infections were investigated.

Results: A total of 6516 patients who underwent ASCT for lymphoma ($n = 3236$) and MM ($n = 3280$) were analyzed. The CIRs at 12 months for fungal, VZV, CMV, and *P. jirovecii* infection in lymphoma were 4.9%, 11.3%, 4.7%, and 2.9%, respectively, and the CIRs in MM were 2.0%, 10.6%, 2.2%, and 1.7%, respectively. The CIRs at 5 years for fungal, VZV, CMV, and *P. jirovecii* infection in lymphoma were 7.9%, 16.0%, 7.4%, and 5.1%, respectively, and the CIRs in MM were 6.3%, 19.1%, 4.2%, and 5.6%, respectively. Fungal infection was significantly higher in patients with previous fungal infection (Hazard ratio (HR) 2.003, $p = 0.005$) in lymphoma. Incidence of CMV infection was significantly higher in patients with prior CMV infection: HR 4.920, $p < 0.001$ (lymphoma); HR 3.022, $p = 0.030$ (MM). VZV infection was significantly lower in patients receiving prophylaxis: HR 0.082, $p < 0.001$ (lymphoma); HR 0.096, $p < 0.001$ (MM). For *P. jirovecii* infection, busulfex and melphalan conditioning (HR 1.875, $p = 0.032$) and previous *P. jirovecii* infection (HR 4.810, $p < 0.001$) had a higher incidence in MM.

Conclusions: In conclusion, based on the incidence and effectiveness of prophylaxis, patients undergoing ASCT should receive prophylaxis for VZV. In our study, since the CIR of VZV reactivation increased steeply up to 1 year, we think it would be better to provide prophylaxis for 1 year. In addition, prophylaxis for fungal infections and PJP needs to be considered in patients who have previously had an infection with the same organism. Further studies are required to determine the appropriate duration and dose of prophylaxis.

Disclosure: Nothing to declare

13 - Infectious Complications

O107

MULTINATIONAL STUDY ASSESSING TREATMENT PATTERNS, OUTCOMES, AND HEALTHCARE RESOURCE UTILIZATION IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS WITH REFRACTORY/RESISTANT CYTOMEGALOVIRUS INFECTION, OR INTOLERANCE TO ANTI-CYTOMEGALOVIRUS THERAPIES

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Background: Given contemporary, real-world data on the management of cytomegalovirus (CMV) infection following hematopoietic stem cell transplant (HSCT) are limited, this retrospective study aimed to generate real-world evidence on the burden of CMV infection/disease in HSCT recipients who had refractory/resistant CMV, or were intolerant to current treatments (RRI).

Methods: This retrospective study pooled de-identified data from HSCT recipients with RRI CMV and aged ≥18 years across 14 transplant centers in the USA or Europe (France, Germany, Italy, Spain, UK). Data on CMV treatment patterns, clinical outcomes, and healthcare resource utilization were collected and analyzed descriptively.

Results: Data from 250 patients (55.2% USA, 44.8% Europe) were analyzed (median age: 57 years; male: 50.8%). Median time from transplant to first CMV episode: 32 days (Q1–Q3: 19–44 days). Post-HSCT, there were 427 CMV episodes. Most patients (92.8%) were identified as RRI during the first CMV episode; 88.8% were asymptomatic at RRI identification. At the time of CMV index date (RRI identification), 164 patients were identified as refractory/resistant, and 86 as intolerant. Overall, 76.8% of patients used valganciclovir for the management of CMV episodes, 66.4% used foscarnet, 53.2% used ganciclovir, 10.4% used cidofovir, and 6.4% used letermovir as single/combination anti-CMV therapy. For treatment of CMV episodes, 81.9% (204/249) of patients received ≥2 therapies. Most patients (95.2%) had ≥1 anti-CMV therapy dose change or discontinuation for RRI CMV. CMV infection or disease resolution was reported in <40% of patients as the reason for discontinuation/dose changes among each of the treatments, during an RRI CMV episode. Following RRI identification, 41.2% of patients experienced a myelosuppression event with neutropenia events being most common (87/145 [60%] events). A total of 105 (42.0%) patients failed to achieve clearance of the CMV index episode (determined by the site investigator). CMV recurred in 35.2% (88/250) of patients (**Table**; median time from end of CMV index episode to first recurrence: 29.0 days). Among patients with CMV recurrence, 35.2% (31/88) did not report achieving viremia clearance. Graft failure

Table 1

Patient	Age	Sex	Area of Residency	Hematologic Malignancy	Type of Cellular Therapy	Days to Diagnosis from Cellular Therapy (Days)	Site of Infection	Diagnostic Methodology	Outcome
1	62	Male	SCAL*	AML	Allo HCT	305	Lungs	Subcarinal lymph node aspiration fungal culture IgG antibody	Deceased due to relapsed AML
2	58	Male	SCAL	Mantle cell lymphoma	Auto HCT	503	Lungs Peritoneum	Ascites fluid fungal culture Antibody CF and IgG	Deceased from advanced cholangiocarcinoma with ESLD
3	63	Male	SCAL	Hodgkin lymphoma	Auto HCT followed by allo HCT	28	Lungs	BAL fungal culture	Deceased within 60 days of transplant due to multiorgan failure
4	54	Male	CCAL	Peripheral T-cell lymphoma	Allo HCT	16	Lungs	BAL cytology	Alive
5	60	Male	SCAL	Multiple myeloma	Auto HCT	505	Lungs	BAL fungal stain and culture Antibody CF, IgG, IgM	Alive
6	25	Male	SCAL	B-cell ALL	Allo HCT	84	Lymph nodes Skin Bone CNS Bone marrow	Axillary lymph node core needle biopsy Chest lesion shave skin biopsy Vertebral body lytic lesion biopsy Bone marrow biopsy Serum antigen Urine antigen	Ongoing antifungal treatment
7	62	Male	CCAL^	DLBCL	Yescarta CAR T cell therapy	174	Lungs CNS	BAL fungal stain and culture BAL cytology Serum antigen Urine antigen	Deceased due to respiratory failure and persistent infection
8	59	Fem	CCAL	Myelofibrosis	Allo HCT (haplo)	150	Lungs	BAL fungal culture Serum antigen Urine antigen	Alive
9	58	Fem	SCAL	NHL	Auto HCT	260	Lungs	BAL fungal culture Ab IgG and IgM	Deceased due to relapsed NHL
10	17	Fem	SCAL	ALL	Allo HCT (haplo)	28	Lungs	BAL fungal culture BAL cytology Serum antigen Urine antigen KARIUS test	Alive
11	34	Male	SCAL	T-cell lymphoblastic leukemia	Allo HCT (double cord blood)	1846	Lungs Bone CNS	L5 posterior spinous process biopsy CSF Ab IgG Ab CF Serum antigen Urine antigen	Ongoing antifungal treatment

was reported in 10 (4.0%) patients; 5 (2.0%) failures occurred after RRI identification. Overall, 60.0% of patients experienced at least one graft-versus-host disease (GvHD) event post-HSCT, with 55.6% having at least one acute GvHD event. Most GvHD events (104/191 [54.5%]) occurred after RRI identification. All-cause mortality was 56.0%. Mortality 1-year post-RRI identification occurred in 113 (45.2%) patients. Overall, 37.6% of patients reported ≥1 CMV-related hospitalization (median length of stay: 18 days [Q1–Q3: 9–31 days]). Most hospitalizations (80.1%) occurred during an RRI episode.

Table. Summary of RRI CMV index episode and recurrent CMV episodes for HSCT recipients

	Overall
Patients with RRI CMV index episode, *n*	**250**
Patients who achieved CMV viremia clearance for RRI CMV index episode[a,b], *n* (%)	145 (58.0)
Median time (Q1–Q3) from start of RRI CMV index episode to CMV viremia clearance[a,b] days	46.5 (31.0–81.0)
Patients with recurrent CMV episodes, *n* (%)	**88 (35.2)**
Median time (Q1–Q3) from end of CMV index episode to first recurrence[c] days	29.0 (14.5–56.5)
Patients with recurrent CMV episodes who achieved CMV viremia clearance[a,c], *n* (%)	57 (64.8)

[a]CMV episodes still active at the end of follow-up were not considered.
[b]CMV viremia clearance: when the patient was considered to have achieved clearance of active CMV viremia, as determined by the site investigator
[c]Recurrent episodes: CMV episodes following RRI CMV index episode.

Conclusions: Results from this study highlight the real-world complexities and high burden of CMV infection for HSCT recipients. With available anti-CMV agents, a notable proportion of patients failed to achieve viremia clearance once developing RRI CMV and/or experienced recurrence, and were at risk of adverse outcomes, including myelosuppression and mortality. There is a need for therapies that achieve and maintain CMV clearance with improved safety profiles.

Clinical Trial Registry: N/A

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Inês Mendonça, Luís Veloso: employee: CTI Clinical Trial & Consulting Services (which is paid to provide consulting services including medical writing and statistical analysis).

Aimee Sundberg, Tien Bo, Ishan Hirji: employee, ownership interest: Takeda.

Kimberly Davis: employee: Takeda.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

O108

IMPROVEMENTS IN OUTCOMES OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION FOR RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA BETWEEN 1990-2019. A RETROSPECTIVE ANALYSIS OF THE LWP OF THE EBMT

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Background: Autologous (auto-HSCT) and allogeneic (allo-HSCT) transplantation of haematopoietic stem cells are established treatment options for patients (pts) with relapsed/ refractory (r/r) diffuse large B-cell lymphomas (DLBCL). Some patients received auto-HSCT for consolidation after achieving CR/PR with first-line (immuno-)chemotherapy. New drugs and cellular therapies influenced transplantation activity over time.

Methods: We conducted a registry-based analysis of transplantation activity reported to the EBMT for patients with r/r DLBCL between 1990 and 2019. Patients meeting the following criteria were included: age > 18 years, diagnosis of r/r DLBCL, auto-HSCT as first HSCT or allo-HSCT either as first HSCT or after auto-HSCT (tandem auto-/allo-HSCT were excluded). Minimal essential data-A were retrieved from the EBMT database.

Results: In total, 4970 pts were identified with sufficient data availability [3944 auto-HSCT and 1026 allo-HSCT (508 1st allo-HSCT and 518 allo-HSCT after auto-HSCT)]. Auto-HSCT steadily increased from 284 in 1990–2000 to a maximum of 1751 in 2015-2019; allo-HSCT also increased from 65 up to 585 for the respective time periods. Recipients of auto-HSCT were significantly older at HSCT [median: 48.8 yrs (1990–2000) vs. 57.0 yrs (2015–2019), $p < 0.0001$], had a shorter interval between diagnosis and HSCT [17.7 mo (1990–2000) vs. 14.2 mo (2015–2019), $p < 0.0001$] and were more fit with a performance status >=80% [86% (1990-2000) vs 92% (2015–2019), $p < 0.02$]. The proportion of patients receiving auto-HSCT in complete remission (CR)/partial remission (PR) increased overtime [33.1% (1990–2000] vs. 75.3% (2015-2019), p<0.0001]. Peripheral blood (PB) became the universal stem cell source [87% (1990–2000) vs. 99% (2015–2019), $p < 0.0001$] and total body irradiation for auto-HSCT has practically been abandoned [12.9% (1990-2000) vs 0.4% (2015–2019), $p < 0.0001$]. Similarly, for allo-HSCT pts, the time between diagnosis and HSCT became shorter over time [25.5 mo (1990–2000) vs 19.2 mo (2015–2019), $p < 0.01$], PB became the universal stem cell source [43% (1990–2000) vs 92% (2015–2019), $p < 0.0001$] and reduced intensity conditioning regimens were more frequently used [43% (1990–2000) vs 63% (2015–2019), $p < 0.0001$]. The proportion of allo-transplanted pts in CR/PR increased during the study period [27.7% (1990–2000) vs 73.3% (2015–2019), $p < 0.0001$]. Donor type profiles showed steep increases in unrelated and haploidentical donors [22.2% (1990-2000) vs 49.6% (2015-2019) and 0% (1990–2000) vs 19.7% (2015-2019), $p < 0.0001$], respectively. For auto-HSCT, 36-month OS has significantly improved over time [48.3% (1990–2000) vs 57.8% (2015–2019), $p = 0.003$] as well as non-relapse mortality (NRM) [7.3% (1990–12000) vs 4% (2015–2019), $p = 0.04$]. For allo-HSCT, 36-mo OS also improved [33.0% (1990–2000) vs 43.9% (2015–2019), $p = 0.08$)] as well as PFS [28.1% (1990–2000) vs 38.6% (2015–2019), $p = 0.01$], with numerical improvements in NRM [31.3% (1990–2000) vs 22% (2015–2019), $p = 0.44$].

Conclusions: Analysing transplantation activities in DLBCL over 30 years, major changes in transplant indications and methodology were observed. Numbers of auto-HSCT and allo-HSCT steeply increased over time. Clinical characteristics of transplanted patients moved towards an older but medically fit population undergoing transplantation earlier in the course of disease in CR/PR. Importantly, OS and PFS after transplantation significantly improved over time for auto- and allo-HSCT, which was associated with decreases in NRM. Major improvements in supportive care and a better selection of pts may have contributed to these changes.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

O109

TRANSIENT CD19 MASKING WITH TAFASITAMAB DIMINISHES CART19 APOPTOSIS AND TUMOR PYROPTOSIS, RESULTING IN INCREASED THERAPEUTIC INDEX OF CART19 THERAPY IN PRECLINICAL MODELS

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Background: Treatment options for large B-cell lymphoma have changed dramatically over the last 20 years as multiple agents, including anti-CD19 monoclonal antibodies or CD19-directed chimeric antigen receptor T-cell (CART19) therapy, have been developed. However, the sequence of treatment at the time of relapse have not been established, and it is unclear if CD19 monoclonal antibodies may affect subsequent CART19 therapy.

The success of CART19 therapy can be limited for some patients by poor durable responses and life-threatening toxicities, including cytokine release syndrome (CRS). Emerging data suggest these limitations are related to CART over-activation.

Methods: CART19 (FMC63-4-1BB), CD19^{+}luciferase^{+}Jeko-1, and patient-derived B-cell acute lymphoblastic leukemia (B-ALL) cells were used in this study. Immunocompromised NSG mice were utilized to test the efficacy and toxicity of CART19.

Results: First, we co-cultured CART19 with Jeko-1 and tafasitamab and observed reduction of CART19 activity due to CD19 binding competition. However, when unbound tafasitamab was washed away before the assays, CART19 exhibited comparable functions to the control. We then sought to validate these findings in vivo. NSG mice were inoculated with Jeko-1 at day -14. On day -7, mice were randomized to 1) PBS or 2) tafasitamab. On day -1, mice were re-imaged and the tafasitamab-treated group was randomized to tafasitamab discontinuation (sequenced) or continuation (concurrent). All groups received CART19 on day 0. Concurrent treatment reduced CART19 anti-tumor effects while sequential treatment enhanced them. Mice receiving sequential treatment showed superior tumor control, longer survival, and serial peripheral blood (PB) analysis demonstrated delayed but superior CART19 expansion in these mice compared to all other groups. We hypothesized that prior treatment with tafasitamab results in modulation of CART19 activation. Spleens of satellite mice were harvested on day 1 and revealed that mice with sequential treatment showed significantly reduced CART19 CD69/HLA-DR expression and apoptosis compared with mice treated with CART19 alone.

Next, we hypothesized this sequential therapy may reduce CRS after CART19. Here, we utilized our CART toxicity model (PMID:30463995). NSG mice were inoculated with patient-derived B-ALL cells on day 28. On day 7, mice were randomized to receive 1) IgG control (GI), 2) tafasitamab (GII), or 3) no treatment (GIII). GII showed significant reduction of free/detectable CD19. On D0, GI and GII received CART19. GI demonstrated significant weight reduction, motor weakness, and rapid CART19 expansion compared to GII. GI reached an endpoint at day 5 due to CRS, while GII displayed no signs of CRS. Significant elevation of CRS-related cytokines was seen in G1. Overall survival was significantly longer in GII. Spleens from GI and GIII were significantly enlarged and filled with tumor cells compared to GII, which were smaller with no tumor cells. Spleens from satellite mice were assessed with western blot and revealed significantly lower GSDME and higher cleaved-GSDME on tumor cells in GI compared with GII, indicating reduced tumor pyroptosis.

Conclusions: Sequential therapy of tafasitamab followed by CART19 enhanced therapeutic index of CART19 in preclinical models.

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26 - Lymphoma and Chronic Lymphocytic Leukaemia

O110

CONSOLIDATION OF RESPONSE WITH AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION FOR T-CELL PROLYMPHOCYTIC LEUKEMIA. RETROSPECTIVE STUDY ON BEHALF OF THE CHRONIC MALIGNANCIES WORKING PARTY OF THE EBMT

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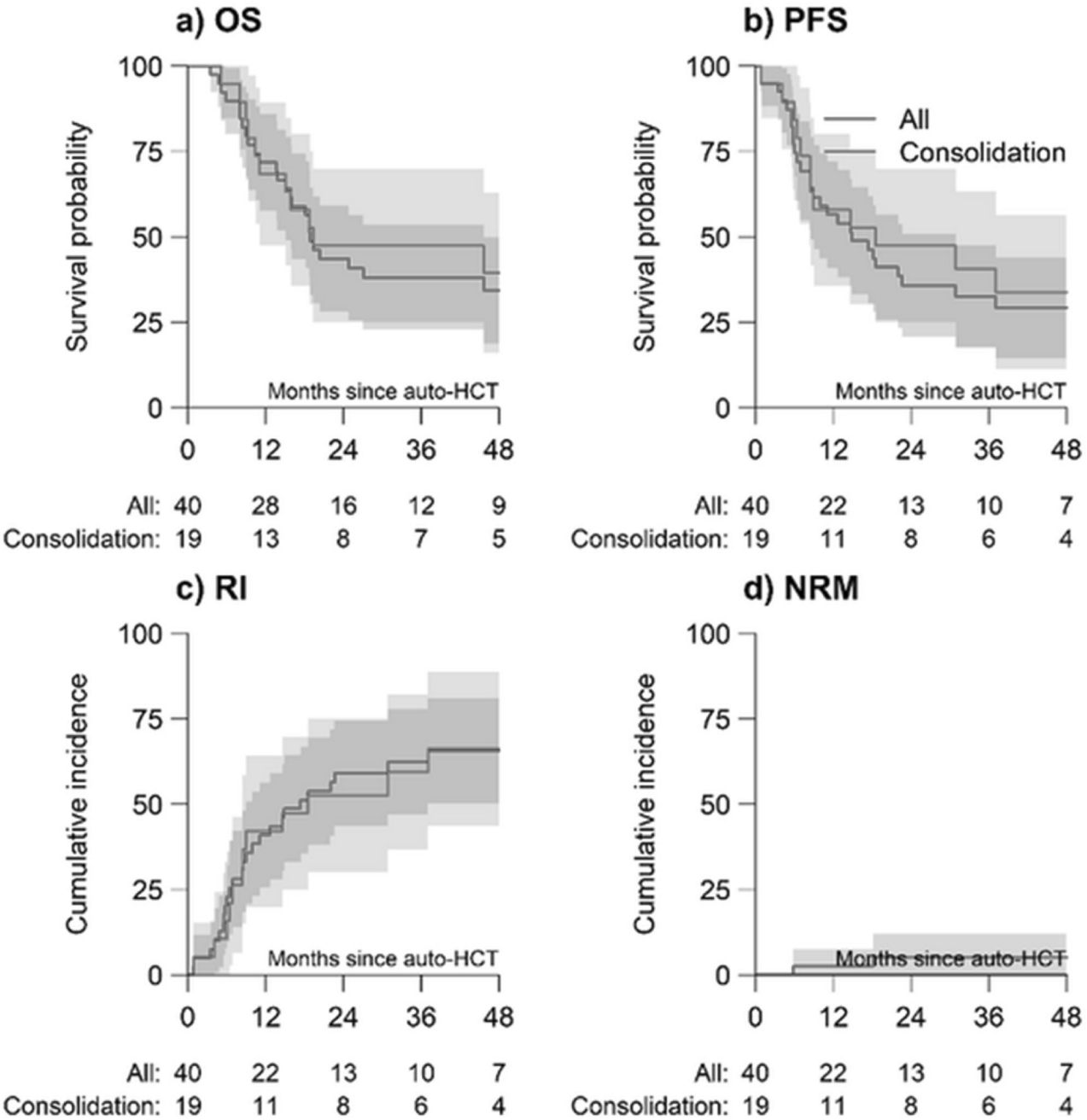
Background: T-cell prolymphocytic leukemia (T-PLL) is a rare mature T-cell lymphoma with a dismal prognosis. Treatment options for T-PLL are extremely limited. Alemtuzumab is the mainstay of the first-line treatment with a progression-free survival (PFS) of approximately one year. Eligible patients are offered allogeneic hematopoietic cell transplantation (allo-HCT) in consolidation as the only curative approach. Autologous hematopoietic transplantation (auto-HCT) is cited as an option in T-PLL management; however, extremely scarce data is available on this therapeutic option. We hereby present characteristics and outcomes in a cohort of patients with T-PLL undergoing auto-HCT.

Methods: Patients aged ≥18 years old with a T-PLL diagnosis who underwent a first auto-HCT between 2000 and 2019 were selected from the EBMT database. Additional data to verify the diagnosis, as well as clarification on treatment prior to and post auto-HCT, HCT-CI score, and cause of death, was requested from participating centres.

Results: Forty patients from 31 centers were included out of 42 initially identified. Median age at auto-HCT was 62 years (IQR 53-67) with males accounting for 58% of the cohort. Median interval between diagnosis and auto-HCT was 8.8 months (IQR 6.4-17.7), and the median calendar year of auto-HCT was 2011 (IQR 2007-2014). A total of 22% of patients had a Karnofsky performance score (KPS) of ≤80% and 27% HCT-CI score of 3 or more. All patients, for whom the data was available, received treatment before auto-HCT. Eighty percent received only 1 previous therapy and 96% had been exposed to alemtuzumab. At time of auto-HCT, 68% were in complete remission (CR) and 25% in partial remission (PR). Conditioning was chemotherapy-based in the majority with TBI administered to 10%. Engraftment was achieved in all patients. CR rate at 100 days post-auto-HCT was 88% (95% CI 73-97%).



With a median follow-up of 88 months (IQR, 42–90) 2-year OS was estimated at 44% (95% CI, 28–59%) (Figure 1a), with a 2-year PFS of 36% (95% CI, 21–51%) (Figure 1b). 2-year RI was 59% (95% CI, 44–75%) (Figure 1c), while 2-year NRM was 5% (95% CI, 0–12%) (Figure 1d).

For 19 patients (76%), for whom auto-HCT was used as consolidation of response after 1st line alemtuzumab, the CR rate at 100 days after auto-HCT was 85% (95% CI 65–96%). The 2-year estimates for OS and PFS were 47% (95% CI 25–70%) and 47% (95% CI 25–70%), respectively, while the 2-year RI was 53% (95% CI 30–75%), and the 2-year NRM 0%.

None of the prognostic factors evaluated (sex, interval from diagnosis to auto-HCT, KPS, number of lines of prior therapy, use of TBI and calendar year, disease status, and age at auto-HCT) were significantly associated with OS, PFS, RI, or NRM.

Conclusions: Auto-HCT is associated with acceptable efficacy with low NRM and might significantly extend response duration after alemtuzumab. Auto-HCT may represent an important alternative to allo-HCT. Auto-HCT could possibly be used as a tandem option to maintain or increase disease control prior to reduced-intensity allo-HCT.

Disclosure: nothing to declare

26 - Lymphoma and Chronic Lymphocytic Leukaemia

O111

EFFICACY OF SUBCUTANEOUS EPCORITAMAB VERSUS CHEMOIMMUNOTHERAPY AND AXI-CEL IN R/R LBCL: AN INDIRECT COMPARISON

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Background: Epcoritamab is a novel, subcutaneous CD3xCD20 bispecific antibody showing potent single-agent efficacy in patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) and a manageable safety profile. The phase 1/2 EPCORE NHL-1 trial (NCT03625037) evaluated epcoritamab in R/R LBCL patients who received ≥2 prior lines of systemic therapy. No head-to-head data have compared epcoritamab with chemoimmunotherapy (CIT) or chimeric antigen receptor T-cell (CAR T) therapy. We conducted an unanchored, matching-adjusted, indirect comparison of the efficacy of epcoritamab with that of CIT and axicabtagene ciloleucel (axi-cel).

Methods: Published data on overall response rate (ORR), complete response rate (CRR), and overall survival (OS) for CIT (SCHOLAR-1 trial) and axi-cel (ZUMA-1 trial) were used to conduct the comparisons versus individual patient-level data (IPD) for epcoritamab (EPCORE NHL-1 trial). Patients with prior CAR T therapy enrolled in EPCORE NHL-1 were excluded because SCHOLAR-1 and ZUMA-1 included only patients without prior CAR T therapy. Analyses adjusted for imbalances in baseline characteristics between IPD from EPCORE NHL-1 and aggregate data from SCHOLAR-1 and ZUMA-1. Propensity score weights resulting from the adjustment were applied to estimate risk differences for ORR and CRR, and weighted Cox proportional-hazards models were used to estimate OS hazard ratio (HR).

Results: Patients without prior CAR T therapy enrolled in the EPCORE NHL-1 trial ($N = 96$) were mostly men ≥65 y who had stage III or IV disease, primary refractory disease, and were refractory to ≥2 consecutive lines of therapy. After adjustments, patients receiving epcoritamab had significantly higher response rates than CIT (ORR: 74.5% vs 34.1%; difference in ORR, 40.4%; $P < 0.001$; CRR: 52.4% vs 12.1%; difference in CRR, 40.4%; $P < 0.001$). No statistically significant differences in response rates were observed between patients treated with epcoritamab and axi-cel. Patients treated with epcoritamab also demonstrated statistically significant improvements in OS versus CIT (HR: 0.283; 95% CI: 0.161, 0.497; $P < 0.001$). Median OS for CIT was 5.4 months, whereas median OS for epcoritamab had not been reached (median follow-up: 10.7 months). There was no statistically significant difference in OS between epcoritamab and axi-cel.

Conclusions: Findings from this cross-study comparison suggest that epcoritamab has significantly higher response rates, including CRR, and OS versus CIT and no statistically significant difference in efficacy versus axi-cel. As an unmet need exists for additional therapies in R/R LBCL, these findings are encouraging and underscore the potential of epcoritamab as a core therapy for these patients.

Funding and Sponsorship: Epcoritamab is jointly developed by Genmab A/S and AbbVie Inc.; AbbVie and Genmab are sponsoring this study.

Clinical Trial Registry: NCT03625037 (clinicaltrials.gov)

Disclosure: **Gilles, Salles:** Received in the last 12 months financial compensation for participating in advisory boards or consulting from AbbVie, Bayer, BeiGene, BMS/Celgene, Epizyme, Genentech/Roche, Genmab, Incyte, Janssen, Kite/Gilead, Loxo, Miltenyi, MorphoSys, Novartis, Rapt, Regeneron, and Takeda

Anthony, Wang: Employees of AbbVie and own AbbVie stock

Abualbishr, Alshreef: Employees of AbbVie and own AbbVie stock

Alex, Mutebi: Employee of Genmab and owns Genmab stock

Kalatu, Davies: Employee of AbbVie

Viktor, Chirikov: Employees of OPEN Health, which received funding support from AbbVie to conduct the research

Gijs, van de Wetering: Employees of OPEN Health, which received funding support from AbbVie to conduct the research

26 - Lymphoma and Chronic Lymphocytic Leukaemia

O112

STRUCTURED MANAGEMENT OF RELAPSE/PROGRESSION AFTER CAR T-CELLS IN LARGE B-CELL LYMPHOMA FOLLOWING THE GLA ALGORITHM – A SINGLE-CENTER EXPERIENCE

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Background: Patients with multiply relapsed/refractory large B-cell lymphoma (LBCL) failing CD19-directed chimeric antigen receptor T-cell therapy (CART) have a poor outlook. The German Lymphoma Alliance (GLA) has proposed a management algorithm for this setting, suggesting a hierarchical strategy of addressing biopsy-identified molecular targets, histology-associated targets, and repetition of successful pretreatment, with the superordinate aim of enabling a potentially curative allogeneic hematopoietic cell transplantation (alloHCT). Here we present the results of this strategy applied to a single-center sample.

Methods: Eligible were all patients with relapse/progression (R/P) after standard of care (SOC) CART treatment for LBCL at our institution between July 2018 and December 2021.

Results: Of 63 patients who had undergone SOC CART treatment during the index period, R/P occurred in 40 patients (63%). 28 (70%) of these had received axicabtagene ciloleucel (axi-cel) and 12 (30%) patients tisagenlecleucel (tisa-cel).

The median follow-up of survivors measured from R/P was 19.4 months (range, 4.2–39.5 months), the median time until R/P was 2.9 months (0.3–19.6). 33 patients (83%) received at least one systemic salvage treatment after CART failure. Of note, work-up of tumor biopsies for identification of druggable molecular targets became routinely available only in 2021 and could be applied to 9 patients, resulting in target identification in 5 of them (55%), which were however not readily available at the time when first salvage was needed. With this limitation, selection of first salvage regimen according to the GLA algorithm was possible in 10 patients (30%; 3 biological target, 1 identified target, 6 repeat successful pretreatment) and resulted in an overall response rate (ORR) of 60% (CR 30%). In contrast, ORR to 1st salvage was only 26% (CR 4%) in the 23 patients where adherence to the GLA algorithm was not possible due to lack of target structure and pretreatment response, or other reasons. AlloHCT was intended in 20 patients and was accomplished in 14 cases (70%). Whereas 10 patients (71%) died after alloHCT (NRM 4; R/P 6), 4 patients live disease-free 5, 12, 27, and 28 months post-transplant. In addition, 4 non-transplanted patients are alive after salvage immunotherapy with bispecific antibodies ($n = 2$, 29+ and 35+ months) and checkpoint inhibition ($n = 2$, 16+ and 39+ months), resulting in a post R/P 12-month OS rate of 21%. OS of patients with R/P within

3 months after CART was particularly poor. 24-month estimates for OS for patients with R/P within 3 months vs R/P after 3 months was 6.0% vs 41.3%, $p = 0.0144$.

Conclusions: The hierarchical GLA post CART R/P management algorithm appears to be feasible and effective. Validation of this approach in larger samples with comprehensive molecular target identification is warranted. The fact that long-term survival after post-CART R/P was exclusively associated with direct or indirect cellular immunotherapy underlines the importance of this therapeutic principle for successful rescue of CD19-CART failures.

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26 - Lymphoma and Chronic Lymphocytic Leukaemia

O113

BRENTUXIMAB VEDOTIN PLUS BENDAMUSTINE VERSUS PLATINUM-BASED REGIMENS AS 1ST SALVAGE THERAPY AND "BRIDGE" TO AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA

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Background: The incorporation of the anti-CD30 monoclonal antibody (Brentuximab vedotin, Bv) into salvage regimens, resulted in almost 2-fold higher complete metabolic remission (CMR) rates as compared to those that have been reported from a variety of platinum- or gemcitabine -based regimens (65–100% vs. 30–50%). Nevertheless, since these results are coming from phase-II trials, the potential superiority of the "novel" salvage regimens cannot be proven.

Methods: We retrospectively compared the outcomes of 46 relapsed/refractory Hodgkin lymphoma (RRHL) patients aged of 25.5 (17–76) years, who received as 1st salvage therapy either Bv plus Bendamustine (BvB, $n = 16$) or platinum-based regimen [ESHAP ($n = 23$) or DHAP ($n = 7$)]. Before salvage, 80% had primary induction failure (PIF) or early relapse (<12 months), 76% advanced disease [stage IIb-IV, extra-nodal or bulky disease] and 46% B-symptoms. More patients from the BvB-group had B-symptoms (68% vs. 30%, $p = 0.04$) and advanced disease (81% vs. 73%, $p = 0.08$). Only one patient (from the platinum-based group) had bulky disease.

Results: After a median of 2(2-4) cycles of BvB and 2(2-3) cycles of platinum-based regimens, the overall response rate was 87% vs. 76% respectively ($p = 0.09$). The CMR rate was 1.8-fold higher for the BvB-group (62% vs. 36%, $p = 0.09$). Among those patients who failed to achieve CMR, significantly lower number from the BvB-group considered as inadequately responders and received 2nd salvage treatment before autologous hematopoietic stem cell transplantation (ASCT) [2(12%) vs 12(40%), $p = 0.01$]. Even for patients with PIF or early relapsed HL, the CMR rate was 1.5-fold higher in the BvB-group (53% vs. 37%, $p = 0.3$) and also significantly less patients required 2nd salvage regimen [2(15%) vs. 11(40%), $p = 0.04$]. No toxicity WHO ≥ grade 3 occurred in either treatment group. The BvB regimen was administered exclusively in outpatient basis and none patient required admission/hospitalization. On the contrary, all patients from the platinum-based group required admission of 13(10-36) days, for chemotherapy administration, or for post-chemotherapy complications management.

The CD34+ cell mobilization/collection was successful for all the patients and 35/36 proceeded to ASCT. After a median follow up of 3(0.4–7) years, the 4-year overall survival (OS) and progression free survival (PFS) rates for the transplanted patients, were 100% vs. 85% and 63% vs. 40% for the BvB-group and the platinum-based group respectively ($p > 0.1$). In the sub-group of autografted patients for PIF or early relapsed disease, the 4-year OS and PFS rates are 100% vs. 94% and 60% vs. 51% for the BvB-group and the platinum based group respectively ($p > 0.1$).

Conclusions: Despite the limitations of retrospective origin and small series of patients, to our knowledge, this is the first study which compares BvB vs. "traditional" platinum-based regimens. Even though more patients in the BvB-group had unfavorable disease characteristics, its efficacy was at least equal if not superior as compared to platinum-based regimens, with acceptable toxicities. The low demands for hospitalization days offers an additional advantage of a potential lower treatment cost, saving also hospital beds. These data, in alignment with others, strongly support that BvB is a fully reliable regimen and merits of further investigation as 1st salvage approach for patients with RRHL.

Clinical Trial Registry: not applicable

Disclosure: nothing to declare

26 - Lymphoma and Chronic Lymphocytic Leukaemia

O114

T-CELL SUB GROUP ANALYSIS AND T-CELL EXHAUSTION AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION IN LYMPHOMA PATIENTS

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Background: The composition and function of cells, regenerated in the bone marrow after autologous stem cell transplantation (ASCT), are among the factors affecting the success of the treatment. One of the defined concepts associated with dysfunction is T cell exhaustion. This concept is characterized by the loss of ability of the T cells to secrete cytokines and proliferate as a result of chronic antigen exposure and the expression of multiple inhibitory receptors. In this study, it is aimed to evaluate the change of T cell sub groups and T cell exhaustion in lymphoma patients after autologous stem cell transplantation.

Methods: Peripheral blood samples of 32 Hodgkin and Non-Hodgkin lymphoma patients were obtained before

	Non-Relapsed	Relapsed	p
n	26	6	
Age (median, range)	58.3 (23–70)	53 (47–60)	0.35
Gender (female/male)	4/12	1/5	0.08
Histology			0.12
DLBCL	8	5	
PCNSL	5	0	
HL	4	1	
FL	1	0	
MCL	6	0	
PTCL	2	0	
HL/NHL	4/22	1/5	0.93
Lines of Systemic Treatments Before ASCT	2 (1–4)	2.5 (2–5)	0.10
Disease Status Before ASCT			0.52
CR	24	5	
PR	2	1	
Neutrophil Engrafment Time (median, range)	9 (7–10)	9 (8–10)	0.65
Thrombocyte Engrafment Time (median, range)	10 (6–29)	9 (7–15)	0.38
1-Year OS	%100	%44	0.001

conditioning and on the 1st, 3rd, 6th months after autologous stem cell transplantation. Frequencies of T cell subsets analyzed as well as T cells which were expressing exhaustion markers
(CTLA-4, LAG-3 and PD-1) were assessed by using flow cytometry. $CD57^+$ $CD28^-$ T cells were examined to demonstrate senescence.

Results: The median follow-up time was 6.23 months. 6 patients out of 32 patients relapsed within this time. The characteristics of the patients are shown in Table 1. The number of $CD4^+$ T cells was found to be significantly low after transplantation and a statistically significant decrease was observed on the $CD4^+/CD8^+$ratio. Before transplantation, T cells of the patients expressed senescence markers in the range of 40-60%, and it was noted that this situation persisted after transplantation. CTLA-4 was analyzed only in Tregs, and the expression significantly increased on the 6th month post-transplant ($p < 0.01$). LAG-3 and PD-1 expressions were present before transplantation. Since the expression of multiple inhibitory receptors is more indicative for describing the state of exhaustion, the combined expressions of LAG-3 and PD-1 were assessed. It was observed that both combined and both single expressions of these receptors decreased early after transplantation. However, it was detected that LAG-3 expression increased on the 3rd month and PD-1 expression increased on the 6th month after transplantation in all patients. Double expression of PD-1 and LAG-3 did not change in $CD4^+$ cells, but significantly ($p < 0.001$) in $CD8^+$ cells overall. The changes in inhibitory markers were more evident for the relapsed patients. It is noticed that inhibitory receptors were significantly higher at the post-transplant first month, comparing to non-relapsed patients. Double expression of LAG-3 and PD-1, for analyzing exhaustion, was also remarkably high comparing to non-relapsed patients ($p < 0.05$).

Conclusions: The results show that, both the composition and functional properties of T cells change after ASCT. High levels of inhibitory receptors and senescence markers of relapsed patients suggest that these molecules may be predictive for relapsing patients in the post-transplant setting. Our study had some limitations since it was set as a pilot study, including a small group of patients with heterogeneous characteristics. Studying these molecules in a larger patient population and elucidating bone marrow immunomodulation will pave the way for appropriate interventions in the treatment by identifying the high-risk group.

Disclosure: Nothing to declare

17 - Minimal Residual Disease, Tolerance, Chimerism and Immune Reconstitution

O115

LETERMOVIR CYTOMEGALOVIRUS PROPHYLAXIS IMPACTS ON POLYCLONAL IMMUNO-RECONSTITUTION DYNAMICS IN HSCT RECIPIENTS

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Background: Cytomegalovirus (CMV) reactivations are known strong stimulator of immune reconstitution in hematopoietic stem cell transplantation (HSCT) recipients. Letermovir CMV prophylaxis [Marty-2017] is associated with significant decrease CMV-reactivation[Lorentino-2022]. The dynamics of immune-reconstitution (IR) after HSCT in patients receiving letermovir are still to be defined [Sperotto-2021]. We compare here polyclonal IR with or without exposure to letermovir.

Methods: We analyzed 317 CMV-seropositive consecutive patients undergoing HSCT from August 2017 to March 2021 in our center (Table1): 208 (66%) were letermovir-free. After March 2019, 109 consecutive patients (34%) were transplanted and received letermovir prophylaxis until day100 post HSCT.

We performed IR panels with lymphocytes subsets and immunoglobins quantification at day90 and day180 after HSCT. Statistical analyses were performed by Jmp13-softwares.

	Letermovir cohort $N = 109$	No-letermovir cohort $N = 208$
Median age at HSCT (range)	60 years (21–73)	52 years (15–76)
Disease type	Acute myeloid leukemia $n = 63$ Acute lymphoblastic leukemia $n = 8$ Lymphoma and myeloma $n = 11$ Myelodysplasia and myeloproliferative neoplasms $n = 27$	Acute myeloid leukemia $n = 121$ Acute lymphoblastic leukemia $n = 28$ Lymphoma and myeloma $n = 25$ Myelodysplasia and myeloproliferative neoplasms $n = 32$ Non-malignant $n = 2$
Disease status at HSCT		

	Letermovir cohort N = 109	No-letermovir cohort N = 208
	Complete and partial remission $n = 64$ Active disease $n = 45$	Complete and partial remission $n = 123$ Active disease n = 85
Type of transplant	MRD $n = 11$, MUD/ MMUD $n = 67$ MMRD $n = 20$ CBU $n = 11$	MRD $n = 34$, MUD/ MMUD $n = 69$ MMRD $n = 91$ CBU $n = 14$
Conditioning regimen#	MAC $n = 52$ RTC $n = 57$	MAC $n = 155$, RTC $n = 52$
CMV patient /donor serology	pos/pos $n = 53$ pos/neg $n = 56$	pos/pos $n = 148$ pos/neg $n = 60$
GVH prophylaxis	PTCy + sirolimus $n = 11$ PTCy + sirolimus + MMF $n = 74$ sirolimus + MMF $n = 7$ Others* $n = 17$	PTCy + sirolimus $n = 37$ PTCy + sirolimus + MMF $n = 159$ sirolimus + MMF $n = 10$ Others* $n = 2$

Results: At day90, median CD3/mm^3 was significantly lower in the letermovir-cohort by univariate analysis: 445 [range 42;6850] *versus* 544 [1;4738] in the no-letermovir-cohort, $p = 0.048$.

Median CD19/mm^3 was higher in the letermovir-cohort: 5.5 [0;594] *versus* 2 [0;294], $p = 0.008$. No difference was found in CD4, CD8 and NK cells.

At day180 median CD3, CD4 and CD8/mm^3 values were comparable between groups. Higher CD19/mm^3 counts could still be observed in the letermovir-cohort: 62 [0; 2983] *versus* 42 [0; 863] in the no-letermovir-cohort, $p = 0.036$. Significantly higher median NK/mm^3 values were seen in the letermovir-cohort: 225.5 [0;763] *versus* 162 [0;744], $p = 0.0003$.

Regarding the immunoglobulin levels, we observed at day90 higher IgA g/L and IgG g/L median values in the letermovir-cohort: IgA 0.535 [0;2.3] *versus* 0.3 [0;3.55] in no-letermovir-cohort, $p = 0.006$; IgG 6.25 [2.03;16.84] *versus* 4.25 [0.85;6.74], $p < 0.001$. No difference was seen in IgM levels. At day180, IgA g/L median was 0.43 [0.01; 2.58] in letermovir recipients *versus* 0.305 [0; 2.42] in the no-letermovir-cohort, $p = 0.028$. No difference could be found in IgG and IgM levels.

We confirmed a lower 1-year cumulative incidence of moderate-severe cGVHD in letermovir recipients (18% versus 37%, $p < 0.001$)[Lorentino-2022]. The incidence of aGVHD is 39% in letermovir-group and 44% in no-Letermovir group. Clinically relevant CMV reactivation is associated with higher rates of aGvHD in no-Letermovir group ($p < 0.0001$) by univariate analysis.

Sixty-two percent of letermovir recipients experienced CMV viremia, mainly classified as DNAemia blips (80%) with subsequent spontaneous negativization. Clinically relevant CMV reactivation occurred in 13% in the letermovir-cohort after drug discontinuation and 32% in the no-letermovir-cohort, $p < 0.0001$. Among HSCT-recipients from CMV-seronegative donors, 25% developed clinically relevant CMV reactivation in the letermovir-cohort *versus* 43% in the no-letermovir-cohort, $p < 0.001$.

The impact of letermovir on B-cell at 3 months and NK-cell levels at 6 months was retained also in multivariate analysis, $p < 0.01$. Moreover, we confirmed the impact on cGVHD in the analysis, p<0.0001.

Conclusions: In our sequential comparative cohorts of HSCT recipients, letermovir CMV prophylaxis was not associated with a delayed T-cell immune reconstitution. Conversely, letermovir administration was associated with a slight improvement of B-cell reconstitution.

Interestingly, NK-cells are higher among letermovir recipients. In this regard, role of CMV DNAemia blips and tardive CMV reactivations require further investigations.

In our cohort, we confirmed a significant reduction of clinically relevant CMV in letermovir-recipients, and a reduction of moderate-to-severe cGVHD.

Clinical Trial Registry: NA

Disclosure: All authors declare they have no CoI

27 - Multiple Myeloma

O116

CILTA-CEL EFFICACY AND SAFETY IN PATIENTS WITH PROGRESSIVE MULTIPLE MYELOMA (MM) AFTER NON-CELLULAR ANTI-BCMA IMMUNOTHERAPY

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Background: With the availability of multiple therapy classes targeting BCMA for multiple myeloma (MM), there is a need to understand treatment sequencing. The phase 2, multicohort study CARTITUDE-2 (NCT04133636) is evaluating cilta-cel, an anti-BCMA CAR-T therapy, in several MM patient populations. We present updated results on cohort C patients with previous exposure to non-cellular anti-BCMA immunotherapy.

Methods: Cohort C patients with progressive MM after a proteasome inhibitor, immunomodulatory drug, anti-CD38 antibody, and non-cellular BCMA-targeting agent received a single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg) 5–7 days post lymphodepletion. Primary endpoint: minimal residual disease (MRD) negativity at 10^{-5}. Secondary endpoints: overall response rate (ORR), duration of response (DOR), and adverse events (AEs).

Results: As of June 1, 2022, 20 patients received cilta-cel. Four patients did not receive cilta-cel due to either low cellular yield or death due to progressive disease (PD) prior to dosing. Six patients (30%) received anti-BCMA treatment as last line of therapy (LOT). At baseline, median age was 62.5 years, 60% were male, 3 (15%) had high risk cytogenetics, and 5 (25%) had baseline extramedullary disease. Patients had received a median of 8 prior LOT. Median time from last anti-BCMA agent to cilta-cel infusion was 195 days. Median cilta-cel dose was $0.65\text{x}10^6$ CAR+ viable T cells/kg. At a median follow-up of 18.0 months, 7/10 evaluable patients (70%) were MRD-negative at 10^{-5} (5/7 evaluable patients [71.4%] in the ADC group and 2/3 evaluable patients [66.7%] in the BsAb group). ORR: 60% in the full cohort, 61.5% in the ADC group, and 57.1% in the BsAb

group. Median DOR: 12.8 months in the full cohort, 12.8 months in the ADC group, and 8.2 months in the BsAb group. Median PFS: 9.1 months in the full cohort, 9.5 months in the ADC group, and 5.3 months in the BsAb group. Cilta-cel responders had a shorter median duration of last anti-BCMA agent exposure (29.5 days) compared with non-responders (63.5 days) and a longer median time from last anti-BCMA treatment exposure to apheresis (161.0 days) compared with non-responders (56.5 days). Most common AEs were hematologic. CRS occurred in 12 (60%) patients (all grade 1/2); median time to onset: 7.5 days and median duration: 6.0 days. ICANS occurred in 4 (20%) patients (2 grade 3/4); median time to onset: 9.0 days and median duration: 7.0 days. ICANS recovered or resolved in 3 patients. No patient had movement or neurocognitive treatment emergent AE/parkinsonism. 12 deaths occurred (8 due to PD, 2 due to COVID-19 pneumonia [not treatment related], and 1 each due to subarachnoid hemorrhage [not treatment related] and *C. difficile* colitis [treatment related]).

Conclusions: Favorable responses to cilta-cel were observed in heavily pretreated MM patients with previous exposure to non-cellular anti-BCMA therapy. However, depth and DOR appear lower than that observed in anti-BCMA-naïve patients who received cilta-cel (median DOR was not reached in heavily pretreated but anti-BCMA naïve patients in CARTITUDE-1 at 27.7 months). These data may inform treatment plans, including sequencing and washout period between BCMA-targeting agents.

Clinical Trial Registry: NCT04133636

Disclosure: **MVM:** *Janssen, Celgene, Takeda, Amgen, GSK, AbbVie, Pfizer, Regeneron, Roche, Sanofi, Oncopeptides, Seagen:*Honoraria; *Janssen, Celgene, Takeda, Amgen, GSK, AbbVie, Pfizer, Regeneron, Roche, Sanofi, Oncopeptides:*Membership/advisory committee

ADC: *BMS, Celgene, GlaxoSmithKline, Ichnos, Janssen Oncology, Oncopeptides, Pfizer, Seattle Genetics, Genentech/Roche, AstraZeneca, and Takeda:*Consultancy/Membership/advisory committees; *GlaxoSmithKline and Novartis:*Research Funding; *Novartis:*Patents & Royalties:CART-cells and biomarkers of cytokine-release syndrome

YCC: *Amgen, GSK, Janssen, Medison, Neopharm, Takeda:*Honoraria; *Takeda:*Research Funding; *Janssen:*Consultancy; *Amgen:*Research Funding.

PRO: *BMS, GSK, Janssen, Pfizer, Sanofi:Consultancy; Amgen, BMS-Celgene, GSK, Janssen, Regeneron, Sanofi:Speaker; Hematology Clínica Universidad de Navarra:Employment*

BP: *Adaptive, Amgen, BMS, Glied, GSK, Janssen, Roche Glycart AG, Oncopeptide, Sanofi, Takeda:*Honoraria; *BMS, EngMab, GSK, Roche Glycart AG, Sanofi, Takeda:*Research Funding; *BMS, Janssen, Sanofi:*Consultancy

NVDD: *Amgen, BMS, Janssen, Novartis, Celgene:*Membership/advisory committees, Research Funding; *Adaptive Biotechnologies, Bayer, Cellectis, Roche, Servier, Takeda:*Membership/advisory committees; *Cellectis:*Research Funding

TM: *Amgen, Johnson & Johnson/Janssen, Sanofi, and Seattle Genetics:*Research Funding; *GSK, Legend Biotech:*Consultancy

AS: *Regeneron, Sutro Biopharma:*Research Funding; *BMS/Celgene, Janssen Oncology:*Consultancy, Honoraria, Research Funding; *GSK:*Consultancy/Membership/advisory committees, Research Funding

DM: *BMS, Celgene, GSK, Kinevant, Legend Biotech, Sanofi, and Takeda:*Consultancy; *Allogene, Amgen, BMS, and Celgene:*Research funding; *Employement:*Janssen

CC: *Janssen R&D:*Employment

CC, JMS, KCDB, CCJ, HV, WD, TR, PM, XX, KL, EZ: *Janssen:*Employment

MA,LP: *Legend Biotech USA:*Employment

IA: *Novartis, Kite, a Gilead Company:*Speaker

JSM: *Abbvie, Amgen,BMS,Celgene,GSK, Haemalogix, Janssen-Cilag, Karyopharm, MSD, Novartis, Takeda, Regeneron, Roche, Sanofi, and SecuraBio:*Consultancy/Advisory Board

27 - Multiple Myeloma

O117

UNDERSTANDING IMMUNE CELLULAR PROCESSES SHAPING SARS-COV-2 VACCINE RESPONSES IN PATIENTS WITH MULTIPLE MYELOMA

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Background: Vaccination against SARS-CoV-2 is the most effective way to protect immunocompromised patients with multiple myeloma (MM) from critical course of COVID-19. Even though vaccinations are routinely practiced for these patients during the ongoing pandemic, the immunization responses were found to be heterogenous and conclusive data on the underlying immune cellular processes are lacking.

Methods: To gain better understanding of the cellular patterns driving the differences in the individual vaccine response quality, we performed a multidimensional longitudinal study where we tracked the immune response to mRNA-based SARS-CoV-2 vaccinations in a cohort of 100 patients with MM and 23 healthy controls (HC). We broadly characterized the immune responses against the wildtype (WT) strain and different variants of concerns (VOC) of SARS-CoV-2 at various timepoints after vaccination. Therefore, we conducted flow cytometric analysis of surface markers, measurement of strain specific antibody and neutralization titers and functional antiviral T- and NK-cell assays to determine humoral and cellular (non)responders. We further performed single-cell RNA sequencing combined with surface proteome analysis of peripheral T-, B- and NK-cells from humoral and cellular (non)responders. Finally, we expanded the immune profiling after basic immunization and boost vaccination with breakthrough infection after third dose vaccination against SARS-CoV-2 to study differences in the molecular processes determining the different vaccination responses.

Results: We found diminished humoral response levels in MM patients compared to controls which was in part associated with low CD19 + B-cell counts. Even though SARS-CoV-2 specific IgG levels and neutralization capacity increased by multiple vaccine injections, humoral responses of MM patients were still impaired compared to HC. In contrast, WT-strain specific T-cell response levels did not display significant differences to healthy individuals after three doses of vaccination. Most patients achieved an adequate T-cell response (86.7% CD4+ responder, 76.7% CD8+ responder) despite the disease- and therapy-associated

immunological impairment. However, antibody and T-cell responses were diminished against Delta and Omicron VOC compared to WT strain.

Addressing the underlying molecular processes leading to the segregation between humoral and T-cell responders and non-responders, single-cell sequencing data of patient samples revealed prominent alterations in gene/surface protein expression and cell abundance between the response status. Vaccine responders showed an overrepresentation of mature CD38 + NK-cells, cytotoxic CD4 + T-cells and differences in the CD8 + T-cell effector memory compartment.

Conclusions: Overall, we found that patients with MM exhibit ambiguous serological responses but sufficient T-cell responses against the WT strain after three doses of mRNA-based SARS-CoV-2 vaccine. Both response levels were reduced for different SARS-CoV-2 variants, emphasizing the immune escape of emerging VOCs and the need for variant-adapted vaccines. We characterized peripheral immune cell response patterns by single-cell sequencing analysis revealing relevant differences in immune cell composition and molecular motifs. Additional ongoing investigations of the response to the BA.4/BA.5 adapted mRNA vaccines in patients with MM may help to draw meaningful conclusions on the design of more efficient and variant-adapted vaccines for these immunocompromised patients in the future.

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Sandra Ciesek: BioNTech/Pfizer: Honoraria.

Ivana von Metzler: BMS: Honoraria; GSK: Honoraria; Amgen: Honoraria; Sanofi: Honoraria; Pfizer: Honoraria; Janssen: Honoraria; Takeda: Honoraria; AstraZeneca: Honoraria.

Evelyn Ullrich: BMS: Honoraria; Phialogics: Honoraria.

27 - Multiple Myeloma

O118

ABATACEPT AND IL-15 INDUCED NK CELL INFUSION (ABANI-15) FROM HAPLOIDENTICAL FAMILY DONOR FOLLOWING AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION: A NOVEL APPROACH FOR HIGH RISK MYELOMA

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Background: The outcome of myeloma with high-risk cytogenetics or poor chemosensitivity (HRMM) is not encouraging with autologous hematopoietic cells transplantation (AHCT) alone. Natural killer (NK) cell based therapy has been explored with NKG2C+ adaptive NK (ANK) cells having potential to target via HLA-E on myeloma cells. Abatacept (CTLA4Ig) blocks T cell costimulation but promotes NK cell cytotoxicity. Our prior experience with abatacept-primed donor lymphocyte infusion (DLI) following haploidentical transplantation in advanced malignancies showed early and sustained ANK proliferation. We further explored the effect of abatacept along with IL-2 or IL-15 or IL-12/15/18 on in-vitro NK cell cytotoxicity(CTRI: REF/2021/08/046552). Based on encouraging results from in-vitro studies, we carried out a pilot study on abatacept and IL-15 induced haploidentical NK cell based immunotherapy (ABANI-15) following AHCT in HRMM.

Methods: We enrolled 11 patients (median age 57 years, range 19–67) with adverse cytogenetic risk ($n = 9$) and/or relapsed/refractory status($n = 2$). Following lymphopheresis from haploidentical family donor, 3 aliquots of DLI were prepared with a minimum of CD56+cells of 1 x10^6/kg of patient body weight. Each aliquot was treated with abatacept and IL15 for 18 h before infusion (ABANI-15). Following an AHCT, patients received ABANI-15 infusions on d + 30, +45 and +60. PBMC was collected from the patients on D + 35, +45, +60, +100 and 3 monthly until 1 year for immunophenotyping and NK cytotoxicity assays against both K562 and RPMI866 cell lines. The patients were monitored for disease status at 3, 6, 9 and 12 months and 3 monthly thereafter until progression or last follow up.

Adaptive NK cells were defined as NKG2C + NKG2A-NK cells. The patients were categorised based on KLRC2 sequence (gene coding for NKG2C) as KLRC2 wildtype (wt/wt) [KLRC2wt group] and KLRC2 deletion homozygous (del/del) or heterozygous (del/wt) [KLRC2del group].

Results: There was no infusion related adverse events. All patients achieved a complete remission at D + 100. At a median follow up of 18 months [range 12–36], 2 patients have relapsed at 9 and 24 months. There was rapid surge in adaptive NK (ANK) cells from 15 days post ABANI-15 infusion and it was sustained throughout 1st year of AHCT (8.1% vs 40.8% at 1 year, $p < 0.01$, Fig1). Likewise proportionate reduction in NKG2A + NK was observed as well (74.5% vs 25.2% at 1 year, $p < 0.01$, Fig1) and a similar increase in the NK cytotoxicity against both myeloid and myeloma cells was demonstrated at longitudinal timepoints post-ABANI-15 infusion ($p < 0.05$, Fig 2A & 2B). Chimerism analysis carried out on 3 patients showed donor chimerism of 5-30%, 72 hours post infusion, which did not last beyond 7 days. ANK cells were found to be greater in KLRC2wt group as compared to KLRC2del group at one year post-ABANI-15 infusion (median 47% vs 19%, $p = 0.03$).

Fig 1.

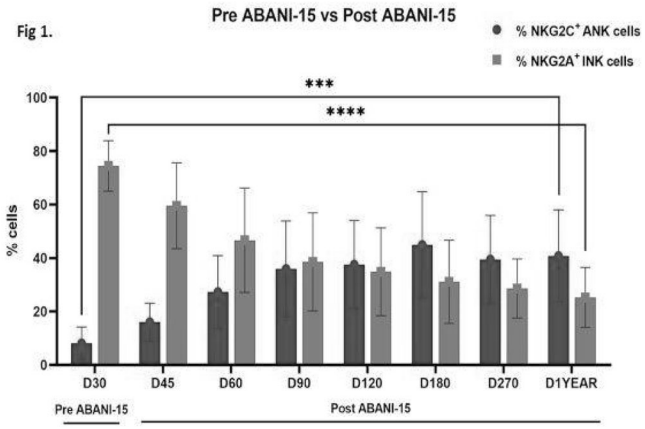
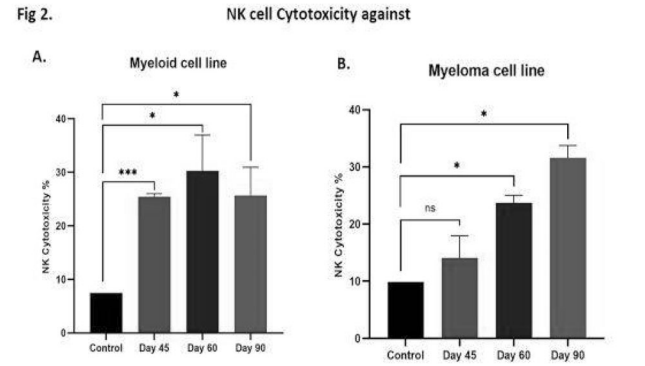


Fig 2.



Conclusions: ABANI-15 is a novel strategy of haploidentical NK cell based immunotherapy, which is feasible after an AHCT in high-risk myeloma resulting in sustained increase in NKG2C + ANK in KLRC2wt patients, along with augmentation in NK cell cytotoxicity in-vitro. Early clinical results are encouraging and support further exploration of this approach.

Clinical Trial Registry: CTRI: REF/2021/08/046552 www.ctri.nic.in

Disclosure: The authors declare no conflict of interest.

27 - Multiple Myeloma

O119

EXTERNAL VALIDATION OF THREE EXISTING EARLY MYELOMA RELAPSE SCORES (BY EBMT, CIBMTR, AND GIMEMA) IN A SINGLE CENTER SHOWS MAJOR DIFFERENCES

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Background: Despite progress in induction regimens, early relapse of multiple myeloma (MM) following autologous hematopoietic cell transplantation (AHCT) is still a frequent complication that confers poor prognosis. Recently, three groups (CIBMTR, GIMEMA (S-ERMM), and EBMT) have published scoring systems to predict early relapse. In this retrospective analysis, we aimed to validate and compare these novel scores in a homogenous population treated in a single center.

Methods: This retrospective study included 410 consecutive newly diagnosed myeloma patients treated in our center, all of whom received 3-8 cycles (median 4) of mostly (69.5%) bortezomib based doublet or triplet (VCD) regimens prior to AHCT with Mel200 from October 2005 to January 2021, with a minimum follow-up of ≥12 months after ASCT. Consolidation was administered until CR; maintenance was not standard unless high-risk disease was detected at diagnosis. No tandem transplants were included.

Results: The median age of all patients in the analysis was 62 years (36-83 years), and female/male:43.4%/56.6%. In our cohort, 60 (19.5%) patients received consolidation while maintenance treatment was given to 108 (26.3%) patients. The median follow-up after AHCT for all patients is 38.4 m (12-156 m) and 82 patients (20%) have relapsed within 12 months. Neither pre- nor post-AHCT response alone or FISH findings were associated with early relapse. With EBMT scoring (which encompasses ISS, response, and performance status at the time of AHCT), early relapse was observed among Score 0 (1.4%) and 1(12.6%), CIBMTR low (13.4%) and S-ERMM low-risk (14.4%) scores showing the EBMT score 0 to recognize very low risk better than CIBMTR and GIMEMA models. Likewise, EBMT score 3(36.3%) and 4(56.3%) compared to CIBMTR high (17.6%), S-ERMM high (43.7%) point to EBMT score 5 to recognize early relapse risk the best. Similarly, "no relapse risk" distribution across risk groups points to EBMT score 0, to recognize very good patients best compared to "low risk" with CIBMTR or S-ERMM scores. The Hazard Risk for early relapse was also the highest and most significant within EBMT scores: **3.4** (95% CI, 1.9–6.6; S-ERMM high vs low; $p < 0.001$), **5.6** (95% CI, 3.1-10.4; EBMT score 3–4 vs. 0–1; $p < 0.001$), and **1.3** (95% CI, 0.4–4.5; CIBMTR high vs low $p =$ NS).

Conclusions: Efforts are ongoing on prediction models of early relapse. S-ERMM and CIBMTR scores are either limited to specific populations based on induction/conditioning or parameters not applicable to daily practice worldwide. EBMT score presented at ASH 2021 (Beksac et al.) differs from earlier scores by being based on a large real-world frequently used triplet induction and conditioning regimen dataset. In this analysis, we attempted to validate the EBMT, CIBMTR, and S-ERMM scoring models in an external cohort, demonstrating that the EBMT is a reliable tool that recognizes very low and very high-risk patients at the time of AHCT prior to the onset of clinical relapse. In the future, with the introduction of molecular features, this prototype model may be improved.

Disclosure: Nothing to declare.

27 - Multiple Myeloma

O120

COST-EFFECTIVENESS OF EARLY VERSUS DELAYED AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR MULTIPLE MYELOMA (MM)

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Background: The recently reported DETERMINATION trial demonstrates superior progression-free survival (PFS) among patients with MM treated with first-line (1L) lenalidomide, bortezomib, and dexamethasone (RVd) followed by ASCT (RVd+ASCT) and lenalidomide maintenance compared to those who received RVd followed by lenalidomide maintenance with delayed or no ASCT (RVd-alone). However, given the lack of an overall survival (OS) benefit, the lack of progression-free survival (PFS) difference among patients who achieve negative measurable residual disease, and in the context of highly effective therapies, such as anti-CD38 antibodies, added to earlier lines of therapy, the cost-effectiveness of upfront ASCT is not known. Thus, we developed a state-transition microsimulation model to simulate clinical outcomes and costs associated with therapy for patients with MM in subsequent relapses.

Methods: The model begins at initiation of first-line therapy comparing RVd+ASCT or RVd-alone. We examined a lifetime horizon, as well as subsequent lines of therapy, using open-source Amua 0.3.0 software. Base case analysis was performed using 10,000 first-order Monte Carlo simulations. Model OS and 1L PFS for both arms were from DETERMINATION. OS data was extrapolated to the end-of-life using a 3% annual mortality rate. 2L PFS was based on anti-CD38-regimens: APOLLO, POLLUX, CANDOR, CASTOR, IKEMA, ICARIA-MM. 2L ASCT PFS was from *Lemieux et al*, with 13% of RVd-alone receiving 2L ASCT, per DETERMINATION. 3L PFS was from ELOQUENT, ELOQUENT-3, VenDVd, BELLINI, VenKd, ASPIRE, KPd, OPTIMISMM, and BOSTON. 4L PFS was from IxaCyDex, CarCyDex, and PomCyDex (arm C). 5L PFS was from CARTITUDE-1 and KarMMa. Conditional probabilities were extracted from Kaplan-Meier curves from pivotal clinical trials using WebPlotDigitizer. Costs were estimated from RED BOOK and DFCI charge reporting in US Dollars ($) after inflation adjustment to 2022 and 3% discounting, and effects were measured in quality-adjusted life years (QALY) using EQ-5D data from *Hatswell et al*.

Results: The model demonstrated lifetime costs and effectiveness per patient of $2,475,519 (SD $1,756,877) and 5.67 QALYs (SD 3.52) with 1L RVd and delayed ASCT, and $2,732,894 (SD $1,734,335) and 6.10 QALYs (SD 3.59) with RVd and upfront ASCT,

with an incremental cost-effectiveness ratio (ICER) of $593,826/QALY.

Conclusions: The model demonstrated marginal improved QALYs with RVd+ASCT, due to improved quality-of-life from longer PFS. ASCT+RVd compared to RVd-alone was not cost-effective, as the ICER exceeded $150,000/QALY, a commonly used willingness-to-pay threshold in the US. In a sensitivity analysis, frontline ASCT was not cost-effective at any price, due to similar outcomes with RVd-alone and few patients receiving 2L ASCT. In the US context, despite the high prices of many subsequent MM therapies, the value of ASCT following frontline therapy for a standard-risk population is low, though higher-risk subgroups may still benefit from this approach.

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27 - Multiple Myeloma

O121

RESPONSE RATES AND OUTCOMES IN NEWLY-DIAGNOSED MULTIPLE MYELOMA (NDMM) PATIENT SUBGROUPS RECEIVING RVD±ASCT PLUS LENALIDOMIDE MAINTENANCE UNTIL PROGRESSION IN THE PHASE 3 DETERMINATION TRIAL

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Background: The DETERMINATION trial of lenalidomide-bortezomib-dexamethasone (RVd)-alone versus RVd+autologous stem cell transplantation (ASCT) showed a highly significant progression-free survival (PFS) benefit (primary endpoint; median 46.2 vs 67.5 months; hazard ratio [HR] 1.53). However, there was a narrowing of benefit in terms of event-free survival (post hoc sensitivity analysis incorporating non-protocol therapy as an event; HR 1.23), and no benefit in terms of response (complete response [CR] or better: 42.0% vs 46.8%) or, importantly, overall survival (5-year rate: 79.2% vs 80.7%) with RVd+ASCT, despite only 28% of RVd-alone patients having received subsequent ASCT (Richardson PG, et al. *NEJM* 2022). Moreover, higher rates of grade ≥3 treatment-related toxicity and second primary AML/MDS as well as a transient but clinically meaningful decrease in quality of life with RVd+ASCT were observed.

Methods: Patients aged 18–65 years received three cycles of RVd induction and then another five cycles of RVd (RVd-alone: n = 357) or high-dose melphalan, ASCT, and another two cycles of RVd (RVd+ASCT: n = 365), followed by lenalidomide maintenance until progression/intolerance. Response and progression were assessed per IMWG criteria (day 1, each RVd cycle; post-ASCT; pre-maintenance; every 4 weeks during maintenance).

DETERMINATION was not specifically powered for subgroup comparisons, and in this context no statistically significant interactions ($p<0.05$) were seen; however, PFS HRs varied between subgroups (0.96–3.40). We report post hoc exploratory analyses of factors potentially associated with these clinically noteworthy differential outcomes with RVd-alone and RVd+ASCT in subgroups defined by race, body mass index (BMI), disease stage, and cytogenetics. Select patient and disease characteristics with imbalances among subgroups and/or with univariate PFS association ($p<0.20$, Cox proportional hazards regression) in the overall population were included in multivariable complete-case analyses of PFS and ≥CR rate, overall and independently by treatment arm.

Results: Relative rates of ≥CR in subgroups were consistent with overall findings (Table), except for a lower rate in black patients receiving RVd+ASCT and a notable difference between arms in patients with high-risk cytogenetics. As previously reported, relative PFS benefit differed across subgroups (Table).

On multivariable analysis of the overall population, higher ISS stage and high-risk cytogenetics were independent prognostic factors for poorer PFS and higher ISS stage was associated with lower ≥CR rate. However, independent multivariable models in the RVd-alone and RVd+ASCT arms demonstrated differential prognostic impact between arms for multiple factors, with early ASCT appearing

	Number of patients		Median PFS, months			≥CR rate, %		
	RVd-alone	RVd+ASCT	RVd-alone	RVd+ASCT	HR (95% CI)	RVd-alone	RVd+ASCT	OR (95% CI)
ITT	365	357	46.2	67.5	1.53 (1.23–1.91)	42	47	0.82 (0.61–1.12)
Race								
White	268	272	44.3	67.2	1.67 (1.29–2.15)	42	51	0.68 (0.47–0.96)
Black	66	66	NR	61.4	1.07 (0.61–1.89)	45	30	1.91 (0.89–4.18)
BMI								
<25	80	81	33.6	NR	2.60 (1.56–4.31)	42	49	0.76 (0.39–1.48)
25–30	141	127	52.3	64.3	1.24 (0.86–1.80)	44	49	0.82 (0.49–1.37)
≥30	136	157	45.8	64.4	1.41 (0.98–2.02)	40	44	0.84 (0.51–1.37)
ISS disease stage								
I	178	184	52.0	NR	1.83 (1.32–2.54)	47	53	0.80 (0.52–1.24)
II	130	134	46.2	62.5	1.38 (0.96–1.96)	36	41	0.81 (0.48–1.38)
III	49	47	40.3	35.9	1.14 (0.64–2.01)	39	40	0.93 (0.38–2.29)
Cytogenetic risk								
High risk	66	66	17.1	55.5	1.99 (1.21–3.26)	36	53	0.51 (0.24–1.07)
Standard risk	268	274	53.2	82.3	1.38 (1.07–1.79)	43	47	0.87 (0.61–1.24)

*Data not shown for patients with other/missing race (RVd-alone, $n = 23$; RVd+ASCT, $n = 27$)

to abrogate the poor prognosis for PFS seen with white race (vs Black), ECOG performance status >0, high-risk cytogenetics, and elevated LDH in patients receiving RVd-alone. Importantly, RVd +ASCT but not RVd-alone appeared to offer greater PFS benefit in ISS stage I patients.

Evaluation of response rates and outcomes, including relapse from CR, by EBMT criteria and concordance with findings per IMWG criteria is being conducted and will be presented.

Conclusions: These hypothesis-generating results from DETERMINATION suggest select differential outcomes with RVd-alone and RVd+ASCT across patient subgroups and show a differential impact of prognostic factors between treatment approaches, supporting the concept that 'one size does not fit all' in the management of transplant-eligible NDMM.

Clinical Trial Registry: ClinicalTrials.gov, NCT01208662

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LDA: Honoraria, advisory committees, AbbVie, Amgen, Beigene, BMS, Celgene, GSK, Janssen, Karyopharm, Pharmacyclics, Prothena, Sanofi.

CPM: Speakers bureau, AstraZeneca, BeiGene USA, Blueprint Medicines, BMS, Incyte.

CG: Consultancy, AbbVie, GSK, Karyopharm, Pfizer, SANOFI US; Speakers bureau, Celgene, GSK, Karyopharm, SANOFI US.

MEA: Equity holder, member of Board of Directors or advisory committees, GenCART.

AMK: Consultancy, research funding, Secura Bio; Speakers bureau, Amgen, Sanofi; Honoraria, Janssen.

DDH: Equity holder, Johnson & Johnson, BMS/Celgene, Merck, Pfizer.

DEA: Advisory committees, Aviv MedTech, BMS, Celgene, Chugai, Juno, Karyopharm, Kite, Legend, Partners, Takeda; Research funding, Celgene, Pharmacyclics, Kite; Consultancy, Janssen, Kite, Kowa, Parexel, Sanofi, Takeda

CC: Honoraria, research funding, BMS, Takeda, Janssen, Pfizer.

AJ: Consultancy, honoraria, advisory committees, Janssen.

JLK: Consultancy, AbbVie, Genentech, BMS; Committee membership for AbbVie, Incyte.

AJY: Consultancy, AbbVie, Adaptive Biotechnologies, Amgen, BMS, Celgene, GSK, Janssen, Karyopharm, Oncopeptides, Regeneron, Sanofi, Takeda; Research funding, Amgen, BMS, Janssen.

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ON: Advisory committees, Adaptive Biotechnologies, BMS, GPCR Therapeutics, GSK, Janssen, Karyopharm; Research funding, Janssen, Takeda.

JPL: Honoraria, Lignancies.

MCP: Research funding, BMS, Janssen, Kite, Novartis; Consultancy, BMS.

SG: Advisory committees, Actinuum, Amgen, Celgene, Janssen, Jazz, Johnson & Johnson, Kite, Novartis, SPECTRUM, Takeda; Research funding, Actinuum, Amgen, Celgene, Johnson & Johnson, Miltenyi, OMEROS, Takeda

AP: Honoraria, Abbvie, Amgen, BMS, GSK, Janssen, Sanofi, Takeda; Advisory committees, Amgen, BMS, GSK, Janssen, Pfizer, Takeda; Research funding, Takeda.

PM: Honoraria, AbbVie, Janssen, Celgene, Amgen, Sanofi.

EW: Research funding, Takeda.

NCM: Consultancy, Abbvie, Adaptive Biotechnology, Amgen, BMS, Celgene, GSK, Janssen, Karyopharm, Legend, Novartis, Oncopep, Pfizer, Takeda; Equity holder, Oncopep; Scientific founder, Patents & Royalties, Oncopep

KCA: Scientific founder, C4 Therapeutics, NextRNA, OncoPep, Raqia; Equity ownership, Dynamic Cell Therapy; Advisory committees/board membership, Amgen, AstraZeneca, Dynamic Cell Therapy, Janssen, Mana Therapeutics, Pfizer, Precision Biosciences; Starton, Window.

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27 - Multiple Myeloma

O122

CARTITUDE-2 COHORT B 18-MONTH FOLLOW-UP: CILTACABTAGENE AUTOLEUCEL (CILTA-CEL), A BCMA-DIRECTED CAR-T CELL THERAPY, IN PATIENTS WITH MULTIPLE MYELOMA (MM) AND EARLY RELAPSE AFTER INITIAL THERAPY

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Background: CARTITUDE-2 (NCT04133636) cohort B is evaluating cilta-cel in patients with multiple myeloma (MM) and early relapse (≤12 months after autologous stem cell transplant [ASCT] or ≤12 months after start of initial treatment with anti-myeloma therapy). Because progression within 1 year of starting initial therapy is associated with poor prognosis (overall survival <2 years), these patients have functionally high-risk disease and represent an unmet medical need. Here we report updated clinical results and cytokine analyses.

Methods: Patients with MM, 1 prior line of therapy (proteasome inhibitor and immunomodulatory drug required), early disease progression (≤12 mo after ASCT or ≤12 mo after start of anti-myeloma therapy for patients who did not undergo ASCT), and no previous treatment with CAR-T/anti-B-cell maturation antigen (BCMA) therapies were eligible. Bridging therapy was permitted between apheresis and CAR-T cell infusion. A single cilta-cel infusion was administered (target dose: 0.75×10^6 CAR+ viable T cells/kg) post lymphodepletion. Safety and efficacy were evaluated. Primary endpoint was minimal residual disease (MRD) negativity at 10^{-5} by next generation sequencing. Management strategies were used to reduce the risk of movement/neurocognitive treatment-emergent adverse events (MNTs)/parkinsonism. Pharmacokinetics, CAR-T cell phenotype, and cytokine profiles are also being analyzed.

Results: Overall, 19 patients (median age 58 years [range 44–67]; 74% male; 16% high-risk cytogenetics, 63.2% standard risk, 21.1% unknown) received cilta-cel and 16 remained on study as of June 1, 2022. 79% of patients received prior ASCT. Median follow-up was 17.8 months (range 5.2–26.3). Overall response rate was 100% (100% with very good partial response or better; 90% with complete response or better). Median time to first response was 0.95 months (range 0.9–9.7) and median time to best response was 5.1 months (range 0.9–11.8). Of 15 MRD-evaluable patients, 14 (93%) achieved MRD 10^{-5} negativity during the study. Median duration of response was not reached. At 12 months, event-free rate was 84% and progression-free survival rate was 90%. Most common treatment-emergent AEs were hematologic (Grade 3/4: neutropenia [90%]; lymphopenia [42%]; thrombocytopenia [26%]; leukopenia [26%]). Cytokine release syndrome (CRS) occurred in 16 (84.2%) patients (Grade 4, $n = 1$). Median time from cilta-cel infusion to onset CRS was 8 days (range 5–11); CRS resolved in all patients. 1 patient each had immune effector cell-associated neurotoxicity syndrome (Grade 1), and movement and neurocognitive TEAEs/parkinsonism (Grade 3) (previously reported). 3 patients died following cilta-cel at days 158, 417, and 451 due to progressive disease. Levels of interleukin (IL)-6, interferon gamma, IL-2Rα, and IL-10 increased after infusion and peaked at days 7–14, coinciding with the timing of CRS and returning to baseline levels within 2–3 months post infusion.

Conclusions: At 1-year post cilta-cel infusion, 90% of patients in this functionally high-risk population, all of whom relapsed within a year of treatment with standard of care upfront therapy (including 79% with ASCT) remained progression-free. Data at this longer 18-month follow-up show durability and deepening of response to cilta-cel and maintenance of PFS rate, representing a potentially significant advancement in a population with high unmet need.

Clinical Trial Registry: NCT04133636

Disclosure: **ND:** BMS, Celgene, Novartis; Amgen, and Janssen Pharmaceuticals: advisory/Research Funding; Adaptive Biotechnologies, Servier, Takeda, Roche, Bayer: Advisory; Cellectis: Research funding.

MA: GenCART Inc.: Current equity holder in private company, Advisory.

AC: BMS, Celgene, GSK, Ichnos, Janssen Oncology, Oncopeptides, Pfizer, Seattle Genetics, Genentech/Roche, AstraZeneca, and Takeda: Consultancy/Advisory; GSK and Novartis: Research Funding; Novartis: Patents & Royalties: CAR T-cells and biomarkers of cytokine-release syndrome.

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SA and TS: None

WR and JS: Janssen-Current Employment, Current holder of stock options in a privately-held company.

DM: Employed by Janssen; consulting role for BMS, Celgene, GSK, Kinevant, Legend Biotech USA Inc., Sanofi, and Takeda; and has received research funding from Allogene, Amgen, BMS, and Celgene.

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HV, PM, and XX: Janssen-Current Employment.

TR: Janssen-Current Employment, Current equity holder in publicly-traded company.

KL: Janssen R&D, a Johnson and Johnson company-Current Employment, Current equity holder in publicly-traded company.

EZ: Janssen R&D, Johnson and Johnson-Current Employment.

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PS: Karyopharm, Amgen, Janssen, Celgene, BMS: Advisory/Research Funding; Pfizer: Advisory.

SZ: Oncopeptides, BMS, Takeda, Sanofi and Janssen: Advisory.

28 - Myelodysplastic Syndromes

O123

OUTCOME PREDICTION IN PATIENTS WITH MYELODYSPLASTIC SYNDROME UNDERGOING HEMATOPOIETIC CELL TRANSPLANT IN THE MOLECULAR ERA OF IPSS-M

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Background: The quest for incorporating molecular information into MDS prognostication, historically relying on hematological and cytogenetics parameters, culminated in the recent development of the IPSS-M.1 A caveat to this score is that only 30% of the cohort used in the original study received disease-modifying treatment (DMT), and only 9% underwent HSCT, potentially limiting its applicability in a specific transplant setting.

Methods: Cognizant of the instrumental clinical utility of precisely allocating MDS patients to HSCT, a procedure possibly burdened by a high rate of complications, we explored IPSS-M and transplant interactions in a large, international, real-life cohort of 416 MDS patients.

Results: Median age at MDS diagnosis was 62 years (53-67), with 39% of patients being female. According to IPSS-R, patients clustered in very low (6%), low (17%), intermediate (19%), high (26%) and very high (32%) risk groups. Only 36% of our cohort underwent transplant upfront, whereas majority (85%) of treated cases received HMA as a bridge. HSCT was performed after a median time of 6.7 months (6.1-7.3) from MDS onset. Donor's choice consisted of matched related in 20%, matched unrelated in 60%, mismatched related in 6%, and mismatched unrelated in 14% of our cohort. Majority of cases underwent reduced-intensity conditioning regimens (74%). As a result, peripheral blood stem cells served as graft source in 84% of cases. With a median follow-up time of 51 months (44-58) after HSCT, the 5-year OS and RFS achieved 46% and 40%, respectively.We then computed IPSS-M scores which resulted in a redistribution of risk categories as follows: very low (27%), low (18%), moderate low (14%), moderate high (15%), high (10%), and very high (16%). OS at 5 years according to IPSS-M was 51%, 63%, 53%, 41%, 32%, and 26%, respectively ($P < 0.001$). Compared to IPSS-R, the incorporation of molecular information led to a significant re-stratification of patients ($P < 0.001$).

Indeed, at least 57% of our cases carried IPSS-M molecular markers, thereby corroborating such observed differences in risk group allocation. Specifically, about 30% of patients previously assigned to IPSS-R intermediate risk group were upstaged to higher risk categories.

Computation of Harrell's c-statistics showed a c-index for OS of 0.583 vs 0.547 in IPSS-M vs IPSS-R, whereas in terms of RFS c-index was 0.584 vs 0.552, respectively. We then compared IPSS-M with previous risk scores explicitly developed for MDS patients undergoing HSCT.2,3,4 We found that c-indexes for survival outcomes were lower than those of the original IPSS-M study, better if compared to IPSS-R, and similar to previous HSCT-specific MDS risk scores, even if accounting solely for disease-specific variables. Finally, we generated a combined clinical-molecular MDS transplant risk score, which demonstrated a strong prognostic separation.

Conclusions: The addition of molecular information represents a crucial (although still modest) advantage in prognostication of MDS undergoing HSCT. The lower c-indexes found in ours as compared to the original study highlight that in MDS undergoing HSCT additional risk factors inherent to the transplant procedure may still hold a prognostic significance, beyond the consideration of disease-specific variables, even molecular characteristics.

Disclosure: None

22 - Myeloproliferative Neoplasm

O124

IMPACT OF COMORBIDITIES AND BMI ON THE OUTCOMES OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN MYELOFIBROSIS: AN INTERNATIONAL ANALYSIS ON BEHALF OF THE CMWP OF EBMT

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Background: To date, no study has specifically focused on the role of comorbidities and body mass index (BMI) in myelofibrosis (MF) patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT).

Methods: On behalf of the Chronic-Malignancies-Working-Party of the EBMT, we collected a cohort of 3347 MF patients with available information on pre-transplant comorbidities and BMI who underwent allo-HCT from 2009 to 2019. Median follow-up was 4.05 years (95%CI, 3.96-4.21). The primary aim was to evaluate the impact of comorbidity and BMI on non-relapse mortality (NRM) and overall survival (OS).

Results: **Table 1** illustrates the cohort's characteristics.

Overall, 1798 patients had at least one comorbidity (54%), resulting in a hematopoietic comorbidity index (HCT-CI) of low, intermediate and high risk in 54%, 24% and 22% of cases with available information, respectively. Pulmonary was the most frequently encountered comorbidity (22.37%), followed by cardiac (8.63%), diabetes (5.62%) and solid tumor (5.44%). As expected, a higher proportion of patients with higher HCT-CI risk received reduced intensity conditioning regimens and had lower Karnofsky performance status (KPS). Of interest, pre-transplant splenectomy was more frequently employed among patients with high HCT-CI risk, leading to a lower percentage of individuals with massive palpatory (>15cm) splenomegaly.

A total of 2451 patients had information on BMI, 1198 (48.9%) patients had a normal BMI (18.5-24.9), 44 (1.8%) were underweight (<18.5), 883 (36.0%) overweight (25-29.9) and 326 (13.3%) obese (≥30). Most overweight/obese patients were male (69%) and had diabetes (92%). Pre-transplant ruxolitinib was more frequent in overweight/obese than in underweight/normal weight patients (43% vs 37%). Conversely, underweight/normal weight patients had a higher prevalence of moderate-severe pulmonary disease (22.3% vs 17.5%) and pre-transplant infections (4.8% vs 3.1%). However, the distribution of HCT-CI risk groups was similar for underweight/normal weight and overweight/obese patients. DIPSS risk category was also homogeneously distributed across different HCT-CI and BMI groups.

Overall, 5y-NRM and 5y-OS were 32% (95% CI, 30–33%) and 54% (95%CI, 52–55%), respectively. In univariable analysis, HCT-CI proved to be predictive of NRM (5y-NRM 29% [low] vs 33% [intermediate] vs 37% [high], $p < 0.001$) and OS (5y-OS 58% vs 51% vs 46%, $p < 0.001$). Higher HCT-CI retained prognostic information on both NRM and OS also in multivariable Cox models (HR 1.24, 0.99–1.55, $p = 0.06$ and HR 1.27, 1.06-1.52, $p = 0.010$).

BMI was modelled as a continuous covariate using restricted cubic splines, and further adjusting patient age, sex, KPS, donor relation, conditioning regimen, patient/donor CMV status and ruxolitinib exposure. While the non-linear trend was not significant ($p = 0.42$), visual inspection suggests that relative to a reference BMI of 25 (rounded median BMI in the cohort), a lower BMI at transplant may be associated with increased risk of NRM and decreased OS.

Characteristic	N = 3347
Patient age in years (IQR)	58.7 (52.6–63.9)
Male sex	2120 (63%)
DIPSS risk categories (missing 1366)	
Low-intermediate-1	743 (38%)
Intermediate-2 (3-4)	796 (40%)
High (5-6)	442 (22%)
Karnofsky Performance status ≤80 (missing 162)	1084 (34%)
Donor/patient match (missing 3)	
HLA-Identical sibling	920 (28%)
MUD	1393 (42%)
Patient/donor CMV serology (missing 82)	
-/-	949 (29%)
Reduced Intensity Conditioning (missing 34)	2175 (66%)
Spleen palpable >15 cm below LCM (missing 2584)	186 (24%)
Splenectomy (missing 1475)	201 (11%)
Ruxolitinib pre allo-HCT (missing 932)	888 (37%)?

Conclusions: Comorbidities seem to be associated with poor transplant outcome in MF patients. The role of BMI is less clear, though lower BMI may be associated with worse results, whereas high BMI appears to have no impact. Evaluation of both comorbidities and BMI prior to transplant might be useful in guiding pre-transplant interventions (e.g., nutritional counseling) to improve transplant outcomes.

Disclosure: Nothing to declare

22 - Myeloproliferative Neoplasm

O125

PROSPECTIVE VALIDATION OF THE PROGNOSTIC IMPACT OF HIGH MOLECULAR RISK MUTATIONS AFTER ALLOGENEIC STEM CELL TRANSPLATION IN MYELOFIBROSIS

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Background: In myelofibrosis (MF), the presence of high molecular risk (HMR) mutations harbors a detrimental effect on survival, and it has been incorporated in different prognostic scoring systems. In this multicenter study we aimed to determine the impact of HMR mutations on allogeneic stem cell transplantation (HSTC) outcome in MF patients.

Methods: We studied two cohorts of patients: 44 patients (training, retrospective cohort) were part of a multicenter, randomized GITMO (Gruppo Italiano Trapianti di Midollo Osseo) clinical trial and 29 patients (validation, prospective cohort) were subsequently recruited at the Bergamo Bone Marrow Transplant Unit. Patients from the training cohort (median age 56) were conditioned with busulfan-fludarabine or thiotepa-fludarabin while patients in the validation cohort (median age 61) were conditioned with a reduced intensity thiotepa-busulfan-fludarabin regimen. The mutational profile was performed by sequencing 30 myeloid related genes by applying SOPHia GENETICS Myeloid Solution on Illumina MiniSeq platform.

Results: In the training retrospective cohort, driver mutations were detected in 40 (*29 JAK2/8 CALR/3 MPL*) patients. At least one HMR mutation was detected in 43% of patients. According to the Mutation-Enhanced International Prognostic Scoring System 70 plus (MIPPS70 +) scoring system, 77% of patients were allocated in the high/very high groups. With a median follow up of 4.2 years, the 5-years Overall Survival (OS) and Progression Free Survival (PFS) were 61% and 45% respectively. The 5-years Non-Relapse Mortality (NRM) and Cumulative Incidence of Relapse (CIR) were 25% and 30%. A higher risk of death and progression was observed in patients with high/very high risk MIPPS70+ (HR for OS 4.3, HR for PFS 4.1). Conversely, the presence of HMR mutations did not significantly affect OS, PFS, NRM or CIR.

In the prospective validation cohort, a driver mutation was detected in all patients (*15 JAK2/7 CALR/7MPL*). At least one HMR mutation was detected in 48% of patients. Patients allocated to the MIPPS70+ high/very group were 52%. After a median follow up of 10.7 months, the 2-years OS and PFS were 61% and 49% and the 2-years NRM and CIR were 33% and 18% respectively. The prognostic significance of MIPSS70+ risk classification was confirmed (HR for OS 3.2, HR for PFS 3.8 for the high/very high MIPSS70+ group). Similarly, it was confirmed that the presence of HMR mutations did not affect transplant outcome, with no impact on OS, PFS, NRM or CIR.

In the whole group of 73 patients, the presence of JAK2V617F mutation showed an adverse prognostic impact on CIR, while MIPPS70+ confirmed its role on PFS.

Preliminary data of minimal residual disease monitoring (MRD) obtained by digital droplet PCR (ddPCR) suggests that MRD negativity at 180 days after transplant is predictive of long-term remission maintenance.

Conclusions: In this study we prospectively confirmed that the presence of HMR mutations did not impact on transplant outcome. HSTC can lead to a significant cure rate of MF patients, regardless the presence of HMR mutations. ddPCR is a promising method for MRD monitoring after transplant.

Disclosure: Nothing to declare

22 - Myeloproliferative Neoplasm

O126

IMPACT OF GVHD ON RELAPSE IN MYELOFIBROSIS UNDERGOING HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Allogeneic hematopoietic stem cell transplantation (alloHSCT) remains the only curative treatment option for myelofibrosis. As it comes with a high risk of treatment-related morbidity and mortality, it is essential to balance the graft-versus-myelofibrosis effect (associated with curative potential) with graft-versus-host disease (associated with morbidity and mortality). Previous work suggested that GVHD might also be associated with risk of relapse. Nevertheless, extensive cohort studies proving the beneficial effects of GVHD associated with lower relapse rates and better overall survival remain scarce. Therefore, this study was performed to further investigate the role and significance of GVHD concerning relapse after alloHSCT in myelofibrosis.

Methods: This extensive single-center retrospective study included a total of 341 patients, of whom 218 were diagnosed with primary myelofibrosis (PMF), 66 with post-essential thrombocythemia myelofibrosis (post-ET MF), and 59 with post-polycythemia vera myelofibrosis (post-PV MF). Patients were undergoing their first ($n = 308$) or second ($n = 33$) alloHSCT, which was performed between 1994 and 2021. Multistate and time-dependent models were created to evaluate the role of GVHD on outcomes. Main endpoints were overall survival (OS), nonrelapse mortality (NRM) and relapse incidence (RI).

Results: Median age at time of first alloHSCT was 57 years, 57% were male. In terms of driver mutation genotype, 10% of patients were triple negative 65% of patients tested positive for *JAK2*, 20% for *CALR*, and 5% for *MPL*. Mean variant allele frequency was 31%, 37% and 52%, respectively. DIPSS at time of alloHSCT was low (1%), intermediate-1 (20%), intermediate-2 (56%), and high (21%). Ruxolitinib was received by 50% of patients prior to alloHSCT. Conditioning regimen was mostly reduced intensity (92%) with the combination of busulfan and fludarabine. Almost all patients (97%) received ATG and a combination of ciclosporin A and mycophenolate mofetil. Most patients received unrelated donor alloHSCT. Median time to engraftment was 13 days and 30 days for leukocytes and thrombocytes, respectively.

62% developed acute GVHD (aGvHD), occurred after a mean of 66 days. Grade III + IV were observed in 18% of all aGvHD events. Most commonly affected organs were skin and gastrointestinal tract. Within the aGVHD group, leukocyte engraftment ($p = 0.01$) and mutation in *CALR* ($p = 0.03$) showed significant impact on aGvHD. 62% of patients experienced chronic GVHD (cGVHD), with severe events observed only in 6%. Most commonly affected organs were skin and liver. Variables that had significant impact on the development of cGVHD were patient-donor relationship (related vs. unrelated; $p = 0.03$), leukocyte engraftment ($p = 0.003$), and platelet engraftment ($p<0.001$).

Median follow-up was 5 years, and 5-year OS was 65% (60-70%). 1-year NRM and RI were 17% and 11%, respectively. In terms of outcomes, aGVHD was not associated with different OS ($P = 0.13$), while cGVHD was significantly associated with better OS ($P<0.001$), with a 50% reduced risk for death. Similarly, cGVHD ($P = 0.001$) but not aGVHD was associated with reduced risk for relapse. aGVHD was not associated with worse NRM.

Conclusions: Chronic GVHD showed significantly reduced risk for relapse in myelofibrosis, whereas aGVHD showed no impact on overall outcomes. More analysis on subgroups and potential risk factors will be presented at the meeting.

Disclosure: None

22 - Myeloproliferative Neoplasm

O127

PRE-TRANSPLANT SPLENIC RADIOTHERAPY IN PATIENTS AFFECTED BY HIGH-RISK IDIOPATHIC/SECONDARY MYELOFIBROSIS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL THERAPY (HSCT)

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Background: In the era of JAK inhibitors, allogeneic HSCT remains the only curative treatment for Myelofibrosis (MF). Due to the unfavourable marrow microenvironment, MF patients often remain transfusion-dependent long after transplant and experience PGF. This is further complicated by the common occurrence of splenomegaly and hypersplenism, which are not always satisfactorily tackled by pharmacological pre-treatment with small-molecule inhibitors. Splenic irradiation (SI) may be used to reduce the spleen size and related symptoms.

Methods: We conducted a retrospective analysis on 14 patients (**table 1**) with intermediate/high-risk idiopathic or post-polycythemia/thrombocytosis MF who underwent allogeneic transplant with SI from any donor source at our centre between June 2016 and March 2021.

Risk scores were available for 11 patients: all of them had either DIPSS-plus intermediate-2/high or MYSEC/MIPSS 70+ high-risk disorders. Baseline, all patients were transfusion-dependent and had splenomegaly (median bipolar diameter by ultrasound: **20.75 cm**). Overall, 12 patients had received ruxolitinib prior to transplant.

Results: All patients received a conditioning regimen based on treosulfan (42 g/m2) and fludarabine (150 mg/m2) as per our institutional guidelines; 36% received an intensified conditioning with the addition of melphalan. Patients received SI with 10 Gy involved-field radiotherapy in five 2-Gy fractions over the course of a week prior to the beginning of conditioning treatment. A single patient received an additional fraction for a total of 12 Gy. The majority of patients received unmanipulated PBSCs (93%). Patients received PT/Cy and sirolimus as GvHD prophylaxis; MMF was added in MUD and haploidentical donors; one patient received additional ATG due to the high graft CD3+ count.

Median graft CD34+ and CD3+ cell doses were respectively 6.92x10^6/Kg (1.62–10.00) and 21.21x10^8/Kg (2.29–35.73). The majority of patients reached neutrophil (86%) engraftment within 30 days after HSCT.

At 90 days after HSCT, 4 patients met the criteria for PGF (excluding those who relapsed and ultimately lost the graft): three of them received medical therapy (i.e., eltrombopag), one a CD34+ selected stem cell boost. Ultrasound re-evaluation of spleen dimensions was available for 13 patients: median splenic bipolar diameter after at least 3 months from transplant was **15.5 cm**.

Grades II-IV and III-IV aGVHD at 100 days were reported in 8 and 2 patients respectively, while cGVHD in 7 patients. With a median post-transplant follow-up of 25 months, 6 patients (43%) remain in CR with full-donor chimerism, 3 patients died due to TRM. Overall, 5 patients relapsed (36%); four of them underwent a second HSCT (one died for TRM), one received palliative care.

Overall, nine patients, including the 3 cases who received a second transplant after a disease relapse, are currently alive and achieved transfusion-independence.

Population Characteristics ($n = 14$)		
Patient age, y median (range)		56.5 (39–70)
Gender, male (%)		10 (71)
Diagnosis, *n* (%)		
	Idiopathic MF/MPN-U	8 (57)
	Post-PV/ET MF	6 (43)
Pre-HSCT splenic bipolar diameter, median cm (range)		20.75 (14–35)
Pretreatment, *n* (%)	Ruxolitinib	12 (86)
	5-HU	8 (57)
	IFN-alfa	2 (14)
	FLAI	3 (21)
HCT-CI score, median (range)		2.5 (0–6)
Type of donor, *n* (%)	MRD	4 (28)
	UD	6 (43)
	MMRD	4 (28)
Stem cell source, *n* (%)	PB	13 (93)
	BM	1 (7)
Conditioning regimen, *n* (%)	MAC	5 (36)
	RTC	9 (64)
Post-HSCT splenic bipolar diameter, median cm (range)		15.5 (9.4–20)

Conclusions: In a small cohort of mostly ruxolitinib treated patients, SI and treosulfan-based conditioning appeared a safe and effective tool to reduce spleen dimensions by at least 25%, and ameliorate symptoms. Future prospective studies with adequate sample size are warranted to further investigate the usefulness and safety of this approach to maximize transplant outcomes in MF, trying to discriminate the relative contribution of conditioning and SI.

Disclosure: No conflicts of interest to disclose.

7 - New Drugs and Cell-based Immune Therapies

O128

LONG-TERM SURVIVAL AND TREATMENT RELATED TOXICITIES OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE LYMPHOBLASTIC LEUKEMIA WITH PREVIOUS CHIMERIC ANTIGEN RECEPTOR-MODIFIED T-CELL THERAPY

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Background: Chimeric antigen receptor-modified T-cell (CAR-T) and allogeneic hematopoietic stem cell transplantation (allo-HSCT) greatly improved the remission rates and survival of relapsed/refractory acute lymphoblastic leukemia. However, the treatment-

related toxicity of patients who received allo-HSCT after CAR-T therapy remains less clear.

Methods: Consecutive patients who received CAR-T therapy and then underwent allo-HSCT during June 1st, 2016 and April 1st, 2022 were included.

Results: Forty-three patients with acute B cell lymphoblastic leukemia and four patients with acute T cell lymphoblastic leukemia were included in this study. Most patients (78.7%) received anti-CD19 CAR-T, three patients received anti-CD19/CD22 CAR-T and four patients received anti-CD7 CAR-T. The median age was 34 (17-63) years old. All the patients achieved complete remission before transplantation. The median time from CAR-T infusion to allo-HSCT was 81 (35-507) days. Most patients (91.5%) received allo-HSCT from haploidentical donor, three patients had unrelated matched donor and one patient had matched sibling donor. Forty-four patients successfully engrafted while three patients underwent engraftment failure. The median time of neutrophil and platelet engraftment were 13 (10–18) and 15 (9–25) days. There was fourteen patients experienced hemorrhagic cystitis and the cumulative incidence was 29.7%. The cumulative incidence of EB and CMV reactivation were 78.7% and 74.6%, respectively. One patients developed posttransplant lymphoproliferative disorders and no CMV disease occurred. Eleven patients experienced virus infection, seventeen patients experienced bacterial infection and five patients experienced fungus infection. Transplant-associated thrombotic microangiopathy occurred in three patients. The 3-year overall survival (OS) and progression-free survival (PFS) were 68.2% and 65.4%, respectively. The cumulative incidence of relapse (CIR) and treatment-related mortality were 28.6% and 10.4%. The 100-days cumulative incidence of III-IV grades acute graft-versus-host disease (GVHD) and moderate to severe chronic GVHD were 13.0% and 18.2%. There were eighteen patients received prophylactic DLI while twenty patients didn't received DLI. Patients who received prophylactic DLI achieved a trend of lower 3-year CIR (11.9% versus 25.0%, $P = 0.26$) and improved OS (82.4% versus 67.9%, $P = 0.17$) when compared with patients who didn't received DLI.

Conclusions: The treatment-related toxicity of Allo-HSCT in patients with acute lymphoblastic leukemia who had a history of CAR-T therapy was acceptable and clinical outcome was improved. Prophylactic DLI may further improve survival which should be further verified.

Disclosure: Nothing to declare.

7 - New Drugs and Cell-based Immune Therapies

O129

CAREFULLY ENGINEERED CD117 VARIANTS RESULT IN FULL PROTECTION OF SHIELDED HEMATOPOIETIC STEM AND PROGENITOR CELLS FROM A HIGHLY POTENT CD117-DIRECTED ANTIBODY DRUG CONJUGATE IN VIVO

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Background: Recent pre-clinical and early clinical data with monoclonal antibody (mAb)-based immunotherapies as conditioning regimens for hematopoietic stem cell transplantation (HSCT) suggest that targeting CD117 is safe and efficacious. However, CD117 expression on transplanted donor HSPCs requires a washout phase of the mAb before HSPCs can be transplanted. To overcome this limitation, we recently demonstrated that HSPCs engineered to be shielded from a CD117-targeted immunotherapy engraft and can be enriched through administration of an SCF blocking antibody. Since CD117-directed antibody drug conjugates (ADC) result in deeper HSPC depletion than SCF blockade alone, we aimed to test whether CD117 variants also shield from CD117-ADCs.

Methods: We coupled our recently developed, highly potent HSPC-depleting mAb (CIM058) to tesirine to form an anti-CD117 ADC. CIM058-tes potency was tested in vitro and in vivo in immunodeficient mice reconstituted with human HSPCs. We previously identified a series of CD117 variants (each a single amino acid substitution) that reduced CIM058 binding strongly (>500-fold) or completely, i.e., without any detectable residual binding. We engineered selected variants into human mobilized CD34+ HSPCs and engrafted the genome edited shielded HSPCs into immunodeficient mice. CIM058-tes was injected i.v. and the bone marrow was analyzed.

Results: CIM058-tes potently killed cell lines expressing high (KASUMI-1) or low CD117 (TF-1). In analogy to our studies with the SCF blocking mAb CIM058, TF-1 cells engineered to express specific, function-preserving single amino acid substitutions were shielded from CIM058-tes activity in vitro. To test the relevance of residual binding for HSPC shielding in vivo, we engineered HSPCs to express different CD117 variants. The selected CD117 variant-expressing HSPCs engrafted in immunodeficient NBSGW mice and contributed to multilineage hematopoiesis. In host mice receiving engineered variant HSPCs, CIM058 depleted non-edited CD117+ wildtype cells while shielded CD117+ cells persisted or were enriched. Similarly, CIM058-tes effectively depleted CD117 wt HSC. However, we observed variant-dependent shielding efficiency in vivo after administration of CIM058-tes. HSPC expressing variant 1.1 and variant 3.2, were enriched in the bone marrow as compared to unmodified HSPC after CIM058-tes treatment. However, CIM058-tes reduced the number of HSPC expressing variant 1.1 as compared to treatment with unconjugated CIM058, while such differences were not present in mice transplanted with variant 3.2 expressing HSPCs. The differential effect is likely explained by the residual binding of CIM058 to variant 1.1.

Conclusions: Our data demonstrate that HSPCs can be shielded from a highly potent CD117-targeting ADC. In addition, our data show that for highly potent agents such as CIM058-tes, even weak interaction with the immunotherapy can result in cell depletion. Therefore, for ADCs and other highly effective immunotherapies, variants that completely abolish binding to the depleting agent are preferrable over variants with residual binding. Collectively, our results suggest that CIM058-tes combined with engineered HSPCs expressing CD117 variant 3.2 may enable targeted posttransplant immunotherapy of $CD117^+$ malignancies.

Disclosure: Declaration of financial conflict of interest: Funding from Cimeio: LTJ; Employment by Cimeio or Ridgeline: RL, ETB, AC, LGP, EMG, MH, AK, CK, FL, VDS, SY, TW, SU; personal financial interest: all authors own Cimeio equity

7 - New Drugs and Cell-based Immune Therapies

O130

NOVEL IMMUNOTHERAPY FOR AML

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116

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Background: Acute Myeloid leukemia (AML) is unresponsive to immune checkpoint inhibitors. Vasoactive intestinal polypeptide (VIP) suppresses T cell activation via VPAC1 and VPAC2 receptors on T cells. Activated T cells up-regulate VIP and the VIP-receptors with kinetics similar to the up-regulation of PD1 and CTLA4. Since 30% of AML over-express VIP, we hypothesized that VIP could represent a targetable immune check-point pathway. Previous studies demonstrated that VIP-hybrid, a low-affinity antagonist of VIP-signaling, induced T cell-dependent anti-leukemic activity in murine allo-transplant models and promoted activation of T cells (Li et al., 2016, Cancer Res). We developed novel and more potent antagonists of VIP-receptor signaling based upon in silico screening of a library of peptides for high binding affinity to human VIP receptors VPAC1 and VPAC2 (Li et al., 2022, Blood). We hypothesized that VIP:VIP-receptor interactions represent a novel immune checkpoint pathway that limits anti-leukemia activity of T cells. We studied the anti-cancer potential of the VIP-receptor antagonists in murine models of C1498 myeloid leukemia and P815 myeloid mastocytoma models and mechanisms of anti-leukemia immune memory.

Methods: B6 VIP-WT (CD45.1, or albino) or VIP-KO mice were injected intravenously with 1 x 10^6 C1498 cells (AML), and DBA/2j mice were injected subcutaneously with 5 x 10^4 P815 cells (myeloid mastocytoma). Luciferase+ (C1498 or P815) tumor cells were detected by bioluminescence image, with quantitative measurements of C1498 by flow cytometry, and P815 tumors by caliper measurements. Leukemia-bearing mice were treated with subcutaneous injections of 10 ug of VIP-ANT or control scrambled peptides started six days after injection of cells when tumor was detectable or palpable.

Results: The survival of VIP-KO mice was significantly increased compared with VIP-WT B6 mice ($p = 0.028$. The survival of wild type -mice treated with ANT308 was markedly improved compared with wild-type mice not treated with VIP-receptor antagonists and mice treated with a control scrambled-sequence peptide, $p < 0.001$). Mice treated with the more potent VIP-receptor antagonists ANT300 and ANT308 had better survival ($p = 0.013$) compared to the less potent ANT002. Treatment with ANT308 significantly increased the numbers of activated CD8 + T-cells in splenocytes from leukemic mice and the percentage of blood CD8 + T cells expressing the AML-specific tetramer in the P815 mouse mastocytoma model. Treatment with ANT308 significantly increased survival in tumor-bearing mice in the mastocytoma tumor mouse model. Leukemic mice rendered tumor-free following treatment with ANT308 were resistant to subsequent rechallenge with leukemia cells, supporting the generation of protective immunological memory.

Conclusions: T cells activation following leukemic cell infusion is inhibited by paracrine and autocrine production of VIP from the tumor cells and the microenvironment including activated T cells. Inhibiting VIP-receptor signaling in T cells induces potent anti-leukemic activity, leading to robust and durable eradication of malignant cells in two mice models. Given the sequence identity of VIP between human and mice, and data showing activation of human T cells by VIP-receptor antagonists, clinical evaluation of VIP-receptor antagonists, such as ANT308, in patients with relapsed/refractory AML or high-grade MDS represents a novel immunotherapy approach.

Disclosure: Li, Jian-Ming and Waller, Edmund are inventors of patents describing VIP-receptor antagonists. Waller, Edmund and Owonikoko, Taofeek, are founders and shareholders of Cambium Oncology, and Emory start-up that has licensed intellectual property around VIP-receptor antagonists.

7 - New Drugs and Cell-based Immune Therapies

O131

REAL-WORLD OUTCOMES OF ADULT B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS TREATED WITH BLINATUMOMAB AND INOTUZUMAB: A RETROSPECTIVE SINGLE-CENTER ANALYSIS

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Background: Adults with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) who receive standard salvage chemotherapy have low complete remission (CR) rates of 18-45%. These remissions are often short-lived, with a median overall survival (mOS) of <6 months. Recently, immunotherapies, such as Inotuzumab (Ino) and Blinatumomab (Blina), have become available for treatment of R/R B-ALL. In phase 3 trials, Ino led to CR/CRi of 81%, with mOS 7.7 months, and Blina CR/CRi of 44% with mOS of 7.7 months.

However, few studies have investigated sequential use of Blina and Ino. We aimed to evaluate the outcomes of patients with R/R B-ALL treated with these immunotherapeutic agents in the real-world setting and make comparison to results reported in clinical trials and other centers.

Methods: This retrospective single center analysis included 51 consecutive adult B-ALL patients who received Blina and/or Ino in the L/BMT Program of BC in Vancouver, Canada from January 2016 to December 2021. Data pertaining to patient demographics, disease and treatment course, were collected from electronic medical records. Survival was estimated by Kaplan-Meier method (SPSS version 20) and comparison made using Log rank (Mantel-Cox) test.

Results: The distribution of our patient cohort by type of treatment and time when received, is shown in Figure 1. The median age was 42 years (range 21-80). The most common indication for Blina/Ino were relapse (74.5%), and CR with measurable residual disease (MRD + CR) (29.4%). Eight patients received both Blina and Ino, at separate time points during their treatment, with the majority receiving Ino for relapse, either post-Blina or post-transplant. Patients received a median of 2 cycles of Blina/Ino (range 1-6).

CR was achieved in 69% (29/42) and 41% (7/17) with Blina and Ino, respectively. 12/13 MRD + CR patients treated with Blina achieved MRD-CR after 1-2 cycles and 11 proceeded to transplant. One MRD + CR patient received Ino and achieved MRD negativity.

After median follow-up of 10.5 months (range 1-64.5), the mOS of the entire cohort was 14.5 months. The overall mOS was longer in the patients who received Blina (18.5 vs 4 months, $p = 0.001$); the mOS with Blina in the setting of relapse was shorter than when used for MRD + CR (11 vs 34.5 months, $p = 0.14$). Pre-transplant Blina led to mOS of 18.5 months vs post-transplant Blina 11 months ($p = 0.42$). The mOS for pre-transplant Ino vs post-transplant Ino were 3 vs 7 months ($p = 0.65$). The difference between relapse following Blina vs Ino was not statistically significant (median relapse free survival 9 vs 11 months, $p = 0.74$).

Table 1 Patient characteristics, treatment received, and outcomes

Morphological remission (CR) after 1st induction *(n = 51)*		43
Refractory after induction *(n = 51)*		10
MRD + CR1 post induction *(n = 38)*		22
Parameters prior to Blina or Ino initiation *(n = 51)*	Median WBC (x10^6/l)	4.75 (0.5–226)
	Median blasts in marrow (range) (%)	73.5 (1–100)
Patients who proceeded to transplant post Blina/Ino (%)		16
Patients who received Blina/Ino post-transplant (%)		11
Patients who received Blina/Ino only, without transplant		23
Patients who received either/both Blina/Ino both pre- and post-transplant		1
Patients who received Blina alone *(n = 34)*	Blina leading to CR in R/R B-ALL *(n = 21)* (%)	12 (57.14)
	Blina leading to MRD- in B-ALL *(n = 13)* (%)	12 (92.3)
	Patients proceeding to transplant after MRD- *(n = 12)* (%)	11 (91.7)
	Relapse following Blina *(n = 25)* (%)	11 (44)
Patients who received Ino alone *(n = 9)*	Ino leading to CR in R/R B-ALL *(n = 8)* (%)	5 (62.5)
	Ino leading to MRD- in B-ALL *(n = 1)*	1
	Relapse following Ino *(n = 6)* (%)	3 (50)
Patients who received both Blina and Ino *(n = 8)*	CR rate in group Blina, followed by Ino *(n = 6)* (%)	4 (66.7)
	CR rate in group Ino, followed by Blina *(n = 2)* (%)	1 (50)
Relapse (SE=Std. error, CI=Confidence interval)	Relapse Free Survival after Blina (months) *(n = 29)*	9 (SE 0.9, CI 7.16–10.8)
	Relapse Free Survival after Ino (months) *(n = 7)*	11 (SE 3.6, CI 3.7–18.2)

Conclusions: Response and survival rates in our real-world cohort of patients with R/R B-ALL are comparable to outcomes previously reported in clinical trials. A significant number of patients received both Blina and Ino during their treatment course of R/R B-ALL. The superiority of sequencing one agent before the other cannot be determined in this small cohort.

Clinical Trial Registry: No, but Local Ethics(REB) approval present.

Disclosure: Yasser Abou Mourad: Consulting and AD boards for Amgen and Pfizer; Shanee Chung: honoraria from Takeda, Astellas, Novartis;

Kevin Hay: Research funding - Janssen, Advisory boards - Kite/Gilead, BMS, Novartis, Janssen;

Heather Sutherland: consultancy funding from Amgen; rest: nothing to declare.

O132

MAINTENANCE OF SUPPRESSIVE POTENTIAL IN CRYOPRESERVED GMP-PURIFIED DONOR T REGULATORY (TREG) CELLS FOR INFUSION IN PATIENTS WITH STEROIDE-REFRACTORY CHRONIC GVHD

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Background: Infusion of donor Treg cells has shown activity in the prophylaxis and treatment of chronic GVHD both in in vivo models and in human patients. We designed a clinical trial of treatment of refractory chronic GVHD with multiple infusions of cryopreserved GMP-purified donor Treg cells. We therefore investigated whether the cryopreservation of purified Treg products negatvely affects Treg viability and function.

Methods: Treg cells were obtained from the original HSC donor (Treg DLI) by leukapheresis. Treg cells were purified utilizing the CliniMACS Plus Systems according to GMP procedure. Standard cryopreservation was performed in AB+ plasma containing 10% DMSO in a rate controlled fashion in liquid nitrogen. Treg cells were thawed in a 37C water bath without addition of solutions. The viability, purity and phenotype of thawed Treg cells was determined by flow cytometry, after gating on CD3 + CD4 + CD25+CD127neg cells. FOXP3 promoter demethylation analysis was perfomed on both fresh and thawed Treg cells by mass spectrometry. In vitro stimulation of thawed purified Treg cells was performed with antiCD3 and antiCD28 antibodies for three days, to evaluate the epression of Treg specific molecules. The required Treg dose was reached in 10/11 patients.

Results: Eleven Treg products were prepared during the course of the trial. The median yield of Treg production was 38,9% (IQ 33-44%). The median viability of the isolated cells, as measured by staining with 7AAD, was 88% (IQ 85-90), before cryopreservation as compared to 74% (IQ 65-82%) ($p = 0.002$) after thawing. The purity of the Treg products, based on the percentage of CD4 + CD25+CD127neg cells, was slightly but significantly reduced following cryopreservation and thawing of the Treg product (90% (IQ 90-94%) as compared to 87% (IQ 81-88%) ($p = 0.002$). However, the dose of effector T cells (CD4 + CD25 + CD127 +) and Th17 cells (CD196 + CD161 +) was <10e5/kg (median 2.8x10e4/kg e 3.9x10e3/kg, respectively). Treg cells were predominantly memory (central 43% (IQ 38-53), effector 32% (IQ 21-37), while naïve Treg cells were 20% (IQ 18-26). As previously described, cryopreservation and thawing was associated with downregulation of Foxp3 and CD62L expression on Treg cells, whereas the percentage of Treg cells expressing CD15s was similar. To investigate whether the Treg cells maintained the capacity to become activated once infused, we measured the methylation status of the Foxp3 locus in thawed Treg products. CpG methylation in thawed Treg cells was similar to freshly isolated 3rd party Treg cells from healthy donors suggesting that the Foxp3 locus of thawed Treg is potentially active. This was further confirmed by the observation that polyclonal stimulation of cryopreserved Treg cell products restored the expression of CD25 and Foxp3

and induced the Treg-spcific activation molcules CD39 and CD137.

Conclusions: The study confirms that cryopreservation of GMP-purified Treg cells may alter their viability, phenotype and function. However, Treg cells maintain the ability to become activated activate when stimulated. Infusion of cryopreserved Treg cells may be a feasible option in the context of a clinical trial.

Clinical Trial Registry: NCT02749084

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The authors have no conflict of interest to declare related to the study.

7 - New Drugs and Cell-based Immune Therapies

O133

NAVIRE, FRENCH REAL-LIFE OBSERVATORY OF EFFICACY AND RESISTANCE TO ANTI CMV MOLECULES IN STEM CELL RECIPIENTS. FIRST DATA ANALYSIS

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Background: Letermovir use in primary prophylaxis has considerably decreased early CMV infections rate. Its use in real-life was also extended by clinicians to secondary prophylaxis and sometimes to curative treatment. Also, some blips, breakthrough infections and resistances were reported. A post marketing survey was thus necessary. In this objective, we set up the NAViRe cohort (NCT04690933) of which we present herein a first preliminary analysis with a focus on blips and letermovir resistance.

Methods: NAViRe, is a real-life observatory of efficacy and resistance to anti-CMV molecules in hematopoietic stem cell transplanted (HSCT) recipients, in partnership between The French Society For Bone Marrow Transplantation (SFGM-TC) and the French Reference Center (FRC) for Herpesviruses. Patients are included before HSCT and monitored at D-8 (inclusion), D0 (transplantation), D20-25 (engraftment), D100 (+ /- 10 days) (end of prophylaxis)/M6 or D200 (+ /- 10 days), 1 and 2 years after HSCT, with whole blood collection. Genotyping is performed at the Reference Center in case of breakthrough or refractory infection. Data on virological follow-up, including CMV and other viruses, clinical data, major adverse events and outcomes are collected from both NAViRe e-CRF and EBMT Promise data base, upon agreement of all participants.

Results: Since September 2020, 266 patients were included: 118 women (44.4%), 148 men (55.6%), [56.5 + /- 13] years-old, 225 (88.6%) CMV-seropositive (R +); 120, 77 and 30 patients reached day 100, day 200, and 2 years post-HSCT, respectively.

Blips and infections were analyzed by collecting all the viral-loads from virology laboratories in 228 patients. Blips were defined as 1 or 2 weakly positive viral loads (VL) below 3logUI/mL with spontaneous negativation. Infections were defined as increasing VL up to or above 3logUI/mL in more than 2 samples. For 98 (42,9%) patients CMV viral-load remained undetectable, 81 (35,6%) experienced blips, 49 (21,5%) experienced CMV-infection among which 14 were treated (8 cases under letermovir prophylaxis). VL were not significantly different between blips (2,36 + /-0.66) and infections (2,69 + /-0,23). Blips occurred mostly in patients without letermovir (55/81,67,9% versus 26/81, 32,1%). Donor serological status was not clearly associated 34 (D + /R +), 34 (D-/R +), 6 (D + /R-), 7 missing data (different from Huntley et al., BBMT 2020).

Among 199 patients with declared prophylaxis, 143 (98,6%), were notified as receiving letermovir and were further studied. Serostatus available in 101/143 patients was mainly R+ (93%) (39 D-R + , 55 D + /R + , 7 D + /R-). Resistance genotyping was performed on all the "probable refractory" cases (Chemaly et al., 2017) (10/143, 6%, 8 under primary prophylaxis and 2 under secondary prophylaxis), all were R+ with a median viral load 1.77 + /- 1.35. Three patients were resistant to ?(3/143, 2,1%, 2 D-R + and 1 D + R +) harbouring C325Y (2) and L254F (1) UL56 mutations. A fourth patient had a new mutation on UL89 (S297V) currently explored by recombinant phenotyping at the FRC. Delay from transplant-to-breakthrough was 124.2 + /- 95.5 days.

Conclusions: Letermovir is largely use in our HSCT patients. Blips are not infrequent, and not clearly driven by the donor serostatus. To date, 2.1% of patients receiving letermovir have develop resistance, although this does not impair treatment with other antivirals.

Clinical Trial Registry: **NCT04690933, Clinicaltrials.gov**

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No specific authors disclosure to declare

7 - New Drugs and Cell-based Immune Therapies

O134

TARGETING FOLLICULAR HELPER T CELL OFFERS NOVEL APPROACH FOR DESENSIZATION OF PATIENTS BEFORE HLA-

MISMATCHED ALLOGRAFTING: AN IN VITRO AND IN VIVO STUDY

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Background: For allografting patients, the existence of Donor-specific antibodies (DSAs) may contribute not only to graft rejection in organ transplantation, but also to graft failure, including graft rejection, and poor graft function, after allogeneic stem cell transplantation (allo-SCT). Multiple desensitization strategies for DSA that targeting B cells and plasma cells have been used for transplant patients, but, a number of cases failed to the desensitization. In this study, we aimed to investigate whether targeting follicular helper T cell can offer novel approach for desensization of patients before HLA-mismatched allo-SCT.

Methods: Eighty-three haploidentical SCT candidates were classified as anti-HLA antibody positive patients (n = 40, group A) and negative ones (n = 43, group B), twenty healthy donors were used as control group. We found that the percentage of cTfh cells in $CD3^+CD4^+$ T cells ($P = 0.001$) and the absolute cTfh counts ($P<0.001$) in group A were higher than those of group B. The percentage of cTfh2 ($P = 0.032$) subset and cTfhem ($P = 0.013$) subset in the cTfh cells of group A was higher than that of group B. The percentages of either cTfhem subset or cTfh2 subset in the cTfh cells was positively correlated with MFI of anti-HLA antibody (P = 0.0118; P = 0.0365, respectively).

Results: To investigate the capacity of cTfh cells to help B cells in anti-HLA antibody production, the cTfh cells were sorted and cultured with autologous memory B cells. In vitro experiment showed that cTfh cells of patients with positive anti-HLA antibody could assist autologous memory B cells to produce a higher proportion of plasmablasts (P< 0.001) and IgG (P = 0.002) than that of patients with negative one. Then, anti-HLA antibodies were tested, we found that only supernatant of the co-culture system of anti-HLA antibody positive allo-SCT patients contains anti-HLA antibodies. In addition, the profiles of anti-HLA antibodies produced by memory B cells in vitro were consistent with to those of in vivo. We next to investigate the effects of drugs, including rusotinib, sirolimus and IL-21 blocking antibody (IL-21b), on the function of cTfh cells in assisting B cells in vitro. The sorted cTfh cells were treated with the drugs for 24h, respectively, the drugs were eluted and then the cTfh cells were incubated with autologous memory B cells. All three drugs were found to inhibit differentiation of B cell to plasmablast of five healthy donors and production of antibodies[CY1] . Sirolimus also reduced the level of DSA in two DSA positive patients in vitro.

Then, a pliot study was performed to investigate whether sirolimus could reduce DSA levels by suppressing cTfh cells in allo-SCT candidates. Twelve transplant candidate patients with positive DSA were enrolled. If a 50% reduction in a patient's DSA MFI is defined as effective for treatment, the effective rate of sirolimus was 50% for all patients.

Conclusions: In summary, in vitro and in vivo studies indicate that targeting Tfh cells can offer an alternative approach for desensitization of DSA in allografting cadidates.

Clinical Trial Registry: http://www.chictr.org.cn/ChiCTR-OPC-15006672

Disclosure: There is no conflict of interest in this study.

7 - New Drugs and Cell-based Immune Therapies

O135

ORAL COMPLEMENT FACTOR B INHIBITOR IPTACOPAN MONOTHERAPY IMPROVES HEMOGLOBIN TO NORMAL/NEAR-NORMAL LEVELS IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS NAÏVE TO COMPLEMENT INHIBITORS: PHASE III APPOINT-PNH TRIAL

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Background: First-line treatment for hemolytic paroxysmal nocturnal hemoglobinuria (PNH) patients comprises intravenous anti-C5 monoclonal antibodies. Recently, the first-in-class, oral, selective complement factor B inhibitor iptacopan demonstrated efficacy and safety in PNH patients with residual anemia despite anti-C5 treatment in the Phase III randomized APPLY-PNH trial. We report primary efficacy and safety data from the 24-week core treatment period of the single-arm, open-label, multicenter, Phase III APPOINT-PNH trial in complement inhibitor-naïve, hemolytic PNH patients (NCT04820530; data cut-off: 2 November 2022).

Methods: Complement inhibitor-naïve adult PNH patients with mean hemoglobin <10 g/dL and lactate dehydrogenase (LDH) >1.5 x upper limit of normal received iptacopan monotherapy 200 mg bid. The primary endpoint was response defined as a ≥2 g/dL hemoglobin increase from baseline in the absence of red blood cell transfusions (RBCTs); the response probability was described as proportions of responders with 95% confidence intervals (95% CIs) computed using bootstrap; missing data were accounted for

using Bayesian multiple imputation. Secondary efficacy endpoints (Table) and safety were also assessed.

Results: Forty patients were enrolled (mean age: 42.1 years); 42.5% were female. Mean time since diagnosis was 4.7 (standard deviation [SD] 5.5) years; RBCTs were received by 70% of patients in the 6 months prior to receiving iptacopan. At baseline, mean (SD) hemoglobin and LDH levels were 8.16 (1.09) g/dL and 1698.8 (683.3) U/L, respectively. The study met its prespecified success criterion with an estimated 92.2% of patients (95% CI 82.5, 100) achieving a ≥2 g/dL hemoglobin increase from baseline. Hemoglobin ≥12 g/dL and transfusion avoidance were achieved in an estimated 62.8% (95% CI 47.5, 77.5) and 97.6% (95%CI 92.5, 100) of patients, respectively. Adjusted mean hemoglobin change from baseline was +4.28 (95% CI 3.87, 4.70) g/dL; mean hemoglobin level at 24 weeks was 12.56 (SD 1.49) g/dL. Adjusted mean percentage LDH change from baseline was −83.55% (95%CI −84.90, −82.08); mean LDH at 24 weeks was 261.3 (SD 89.16) U/L. Adjusted mean change from baseline in Functional Assessment of Chronic Illness Therapy – Fatigue score was +10.75 (95%CI 8.66, 12.84). No clinical breakthrough hemolysis events or major adverse vascular events were observed. There were no deaths. Four serious adverse events were reported: bacterial pneumonia, COVID-19, cataract and type II diabetes mellitus. Infections/infestations (40.0% of patients, mainly COVID-19 [15.0%]), headache (27.5%) and diarrhea (7.5%) were the most frequent adverse events. No patients discontinued iptacopan. Notably, the estimated proportion of patients who achieved hemoglobin ≥12 g/dL was consistent with observations in the APPLY-PNH trial.

Table: Summary of efficacy and quality of life endpoints after the 24-week core treatment period of APPOINT-PNH

	Endpoints	Proportion of patients *n/M**	Summary statistic *Estimated proportion† (% [95%CI])*
Primary	Response defined as increase from baseline in hemoglobin of ≥2 g/dL‡ in the absence of RBCTs§	31/33	92.2 (82.5, 100)
Secondary	Response defined as hemoglobin level ≥12 g/dL‡ in the absence of RBCTs§	19/33	62.8 (47.5, 77.5)
	Transfusion avoidance§	40/40	97.6 (92.5, 100)
		M/N‖	*Adjusted mean change from baseline (95%CI)*
	Change from baseline in hemoglobin level (g/dL)‡,¶	40/40	+4.28 (3.87, 4.70)
	Change from baseline in FACIT-Fatigue score‡,**	40/40	+10.75 (8.66, 12.84)
	Change from baseline in ARC (10^9/L)‡,††	40/40	−82.48 (−89.33, −75.62)
		39/40	
	Percentage change from baseline in LDH level (U/L)‡,§§		−83.55 (−84.90, −82.08)
		n/N‡‡	*Adjusted annual rate (% [95%CI])*
	Rate of clinical breakthrough hemolysis‖‖	0/40	0 (0.00, 0.17)
	Rate of MAVEs	0/40	0 (0.00, 0.17)

*n=number of patients with response, M=number of patients with evaluable/non-missing data; †Estimated proportions reflect the population average probability of a patient meeting the endpoint criteria; ‡Assessed between D126–168 – evaluable if at least one value is non-missing; §Between D14–168; ‖M=number of patients with evaluable/non-missing data, N=overall number of patients; ¶Mean (SD) baseline hemoglobin level was 8.16 (1.09) g/dL; **Mean (SD) baseline FACIT-Fatigue score was 32.78 (10.17); ††Mean (SD) baseline ARC was 154.33 (63.67) x 10^9/L; §§Mean (SD) baseline LDH level was 1698.8 (683.3) U/L; ‡‡n=number of patients with at least one event, N=overall number of patients; ‖‖Events that met the protocol-specified criteria for clinical breakthrough hemolysis

95%CI, 95% confidence interval; ARC, absolute reticulocyte count; D, day; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; RBCT, red blood cell transfusion; SD, standard deviation

Conclusions: In this single-arm Phase III trial in complement inhibitor-naïve hemolytic PNH patients, oral iptacopan monotherapy resulted in clinically meaningful hemoglobin increases with good control of intravascular hemolysis in most patients; consequently, transfusion avoidance and patient-reported fatigue also improved. Iptacopan monotherapy demonstrated a favorable safety profile with no clinical breakthrough hemolysis events. APPOINT-PNH is the first study to report a mean increase from baseline in hemoglobin of such magnitude, leading to a majority of PNH patients achieving hemoglobin of ≥12 g/dL. Oral iptacopan monotherapy represents a potentially practice-changing outpatient treatment that could become a preferred therapeutic option for hemolytic PNH patients.

Clinical Trial Registry: NCT04820530: Study of Efficacy and Safety of Twice Daily Oral Iptacopan (LNP023) in Adult PNH Patients Who Are Naive to Complement Inhibitor Therapy (APPOINT-PNH)

https://clinicaltrials.gov/ct2/show/NCT04820530

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7 - New Drugs and Cell-based Immune Therapies

O136

PRE-CLINICAL MODELS OF ACUTE MYELOID LEUKEMIA DEMONSTRATE AFM28 EFFICIENTLY DIRECTS ALLOGENEIC NK CELLS TO CD123$^+$ LEUKEMIC BLASTS AND STEM CELLS

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Background: Acute myeloid leukemia (AML) is characterized by expansion of undifferentiated myeloid cells in the bone marrow (BM) and peripheral blood. Although AML can be treated with curative intent by allogeneic stem cell transplantation (aSCT), residual leukemic stem cells (LSCs) represent reservoirs for disease relapse. Novel treatments capable of eliminating LSCs to suppress measurable residual disease and prevent relapse are needed. Adoptive transfer of allogeneic natural killer (NK) cells has shown promise, and combination with an Innate Cell Engager (ICE®) could further enhance activity against LSCs. The tetravalent bispecific CD123/CD16A ICE®, AFM28, directs the cytotoxic activity of CD16A-expressing NK cells towards CD123-expressing AML blasts and LSCs. Here, the efficacy of AFM28 in pre-clinical AML models was assessed.

Methods: Antibody-dependent cell-mediated cytotoxicity (ADCC) was evaluated in 4-hour calcein-release assays using AML cell lines and primary human NK cells (effector to target ratio [E:T] 2.5:1) in the presence of titrated antibodies. CD123 and CD64 (a high-affinity IgG receptor) expression levels on AML cell lines and STAT5/pSTAT5 levels were evaluated by flow cytometry. Proliferation of TF-1 cells in presence of IL-3 or GM-CSF was measured via CellTiter Glo Assay. AFM28 activity against primary AML blasts and LSCs was tested using ADCC assays (BM mononuclear cells) and colony-forming unit assays (enriched $CD34^+$ cells) by using BM samples of AML patients ($n = 8$) and MDS patients ($n = 6$) combined with allogeneic NK cells (E:T 1:1) and treated with increasing concentrations of AFM28 or a non-targeting control engager for 24 hours. AFM28 anti-tumor activity was assessed in vivo using in-life imaging in a T cell-depleted huFcgR-C57BL6 transgenic mouse model against intravenously administered luciferase-transfected murine AML cells expressing human CD123.

Results: Efficacious ADCC against $CD123^+$ tumor cells by allogeneic NK cells in the presence of AFM28 was observed across a panel of AML cell lines. ADCC induction by AFM28 was independent of leukemic cell mutational profiles and occurred at low CD123 expression levels. Although expression of CD64 completely abolished ADCC induction with an Fc-enhanced anti-CD123 antibody, AFM28 showed high ADCC efficacy against all tested $CD64^+$ AML cell lines. In addition, AFM28 exerted an NK cell-independent inhibitory effect on the IL-3-induced phosphorylation of STAT5 and abolished proliferation of $CD123^+$ TF-1 cells. In ex vivo models using primary AML and MDS patient cells, AFM28 enhanced ADCC mediated by allogeneic NK cells. Patient-derived BM samples pre-treated with allogeneic NK cells and AFM28 showed significantly reduced numbers of outgrowing colonies, but not in absence of AFM28, indicating elimination of AML LSCs and progenitor cells. In vivo, treatment with AFM28 at 15 mg/kg b.w. for 42 days prevented tumor growth in 5/5 mice, whereas untreated mice (6/6) developed systemic disease.

Conclusions: AFM28 induced highly potent and selective lysis of $CD123^+$ leukemic cells, including LSCs and progenitor cells, by allogeneic NK cells. The capacity to eradicate LSCs could increase the frequency and durability of responses, induce long-term remission, and prevent disease relapse after conventional treatment or aSCT in patients with AML. A first-in-human clinical investigation of AFM28 is being initiated.

Disclosure: JJS, LW, N Schulze, TH, UR, JME, JE, TR, CM: Current employment and current equity holder in publicly traded company
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7 - New Drugs and Cell-based Immune Therapies

O137

ORAL IPTACOPAN MONOTHERAPY HAS SUPERIOR EFFICACY TO ANTI-C5 THERAPY IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA AND RESIDUAL ANEMIA: RESULTS FROM THE PHASE III APPLY-PNH STUDY

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Background: Intravenous (IV) anti-C5 therapies are the standard of care (SoC) for treating paroxysmal nocturnal hemoglobinuria (PNH) patients. However, residual anemia is common, secondary to C3-mediated extravascular hemolysis. Iptacopan is a first-in-class, oral, selective complement factor B inhibitor that showed promising safety and efficacy in Phase II trials enrolling anti-C5-treated and -naïve PNH patients. We report data from the 24-week randomized period of the open-label, multicenter, Phase III APPLY-PNH trial (NCT04558918; data cut-off: 26 September 2022; Peffault de Latour *et al*. ASH 2022).

Methods: Ninety-seven adult PNH patients with mean hemoglobin (Hb) <10 g/dL on stable SoC therapy (eculizumab/ravulizumab) for ≥6 months were randomized 8:5 to receive iptacopan monotherapy 200 mg twice daily (N = 62) or to continue their SoC regimen for 24 weeks (N = 35). Randomization was stratified by prior SoC therapy and red blood cell transfusions (RBCTs) in the preceding 6 months. Primary endpoints were response defined as a ≥2 g/dL Hb increase from baseline and response defined as Hb ≥12 g/dL, each in the absence of RBCTs. A prespecified testing procedure adjusted for multiplicity; two-sided, unadjusted *P* values are reported for significant endpoints.

Results: Baseline disease characteristics were balanced between arms. RBCTs were received by 57.7% of patients in the 6 months before randomization; 64.9% and 35.1% had received prior eculizumab and ravulizumab, respectively (mean duration: 4 years). Iptacopan monotherapy was superior for both primary endpoints vs. SoC (both *P*<0.0001; Table); 51/60 iptacopan-treated vs. 0/35 SoC-treated patients with evaluable/non-missing data had a ≥2 g/dL Hb increase from baseline and 42/60 vs. 0/35, respectively, achieved Hb ≥12 g/dL. Iptacopan monotherapy was superior for transfusion avoidance, changes from baseline in Hb level, Functional Assessment of Chronic Illness Therapy − Fatigue

Table: Summary of primary endpoints and secondary efficacy and QoL endpoints after the 24-week randomized treatment period of APPLY-PNH

	Endpoints	Arm	Proportion of patients	Summary statistic	Comparative statistic	Two-sided, unadjusted *P* value
			*n/M**	*Marginal proportion (% [95% CI])*	*Difference in marginal proportion (% [95% CI])*	
Primary	Response defined as increase from baseline in Hb of ≥2 g/dL[†] in the absence of RBCTs[‡]	Iptacopan SoC	51/60 0/35	82.3 (73.4, 90.2) 2.0 (1.1, 4.1)	80.3 (71.3, 87.6)	<0.0001
	Response defined as Hb level ≥12 g/dL[†] in the absence of RBCTs[‡]	Iptacopan SoC	42/60 0/35	68.8 (58.3, 78.9) 1.8 (0.9, 4.0)	67.0 (56.3, 76.9)	<0.0001
Secondary	Transfusion avoidance[‡]	Iptacopan SoC	60/62 14/35	96.4 (90.7, 100.0)[§] 26.1 (12.4, 42.7)[§]	70.3 (52.6, 84.9)[§]	<0.0001[§]
			M/N[‖]	*Adjusted mean change from baseline (95% CI)*	*Adjusted mean difference in change from baseline (95% CI)*	
	Change from baseline in Hb (g/dL)[†,¶]	Iptacopan SoC	62/62 30/35	+3.59 (3.32, 3.86) −0.04 (−0.42, 0.35)	+3.63 (3.18, 4.08)	<0.0001
	Change from baseline in FACIT-F score[†,**]	Iptacopan SoC	62/62 31/33	+8.59 (6.72, 10.47) + 0.31 (−2.20, 2.81)	+8.29 (5.28, 11.29)	<0.0001
	Change from baseline in ARC (10^9/L)[†,††]	Iptacopan SoC	62/62 35/35	−115.89 (−126.49, −105.30) + 0.37 (−13.03, 13.77)	−116.26 (−132.17, −100.36)	<0.0001
			M/N[‖]	*Geometric adjusted mean ratio to baseline*	*Reduction (% [95% CI])*	
	Ratio to baseline in log-transformed LDH (U/L)[†,‡‡]	Iptacopan SoC	62/62 35/35	0.96 (0.90, 1.03) 0.98 (0.89, 1.07)	1.15 (−10.18, 11.32)	No superiority
			n/N[§§]	*Adjusted annual rate (% [95% CI])*	*Rate ratio (95% CI)*	
	Rate of clinical breakthrough hemolysis[‖‖]	Iptacopan SoC	2/62 6/35	0.07 (0.02, 0.31) 0.67 (0.26, 1.72)	0.10 (0.02, 0.61)	0.0118
	Rate of MAVEs	Iptacopan SoC	1/62 0/35	0.03 (0.00, 0.25) 0	Not estimable	No superiority

*n=number of patients with response, M=number of patients with evaluable/non-missing data; [†]Assessed between D126–168; [‡]Between D14–168; [§]The prespecified methodology for handling of missing data may have underestimated transfusion avoidance in the SoC arm, so a *post hoc* sensitivity analysis was conducted using a different approach. In this analysis, marginal proportions (95% CI) were 96.7% (91.3, 100.0) vs. 38.9% (23.1, 55.8) for iptacopan and SoC, respectively (*P*<0.0001); [‖]M=number of patients with evaluable/non-missing data, N=overall number of patients; [¶]Excluding values within 30 days of RBCT. Mean (SD) baseline Hb levels were 8.93 (0.70) and 8.85 (0.90) g/dL in the iptacopan and SoC arms, respectively; **Mean (SD) baseline FACIT-F scores were 34.7 (9.8) and 30.8 (11.5) in the iptacopan and SoC arms, respectively; [††]Mean (SD) baseline ARCs were 193.2 (83.6) and 190.6 (80.9) x 10^9/L in the iptacopan and SoC arms, respectively; [‡‡]Mean (SD) baseline LDH levels were 269.1 (70.1) and 272.7 (84.8) U/L in the iptacopan and SoC arms, respectively; [§§]n=number of patients with at least one event, N=overall number of patients; [‖‖]Events that met the protocol-specified criteria for clinical breakthrough hemolysis

ARC, absolute reticulocyte count; CI, confidence interval; D, day; Hb, hemoglobin; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; QoL, quality of life; RBCT, red blood cell transfusion; SD, standard deviation; SoC, standard of care

score and absolute reticulocyte count, and rate of clinical breakthrough hemolysis (Table). Mean Hb levels (standard deviation) at 24 weeks, irrespective of RBCTs, were 12.6 (1.4) vs. 9.2 (1.4) g/dL with iptacopan vs. SoC. There were no deaths or serious encapsulated bacteria infections. One iptacopan-treated patient had a major adverse vascular event (transient ischemic attack; considered unrelated to iptacopan; iptacopan is ongoing). Headache (iptacopan: 16.1% vs. SoC: 2.9%) and diarrhea (14.5% vs. 5.7%) were more commonly reported with iptacopan, whereas COVID-19 (8.1% vs. 25.7%) and breakthrough hemolysis (3.2% vs. 17.1%) were more commonly observed with SoC. Two SoC-treated patients had serious adverse events of hemolysis vs. no iptacopan-treated patients. No patients discontinued study treatment because of adverse events.

Conclusions: In PNH patients with residual anemia on IV anti-C5 SoC therapy, single-agent, oral iptacopan resulted in a significant majority of patients achieving clinically meaningful Hb increases and Hb ≥12 g/dL via resolution of extravascular hemolysis and maintenance of intravascular hemolysis control. These hematological benefits were associated with transfusion independence in most patients and meaningful improvements in patient-reported fatigue. Iptacopan monotherapy was well tolerated with a favorable safety profile. Single-agent iptacopan may represent a practice-changing, oral, outpatient treatment for PNH patients who have an inadequate response to IV anti-C5 SoC therapy, potentially becoming a preferred treatment option for patients with hemolytic PNH.

Clinical Trial Registry: NCT04558918: Study of Efficacy and Safety of Twice Daily Oral LNP023 in Adult PNH Patients With Residual Anemia Despite Anti-C5 Antibody Treatment (APPLY-PNH) https://clinicaltrials.gov/ct2/show/NCT04558918

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Régis Peffault de Latour: reports consultancy and honoraria for Alexion, Amgen, MSD, Novartis, Pfizer and Sobi; and research funding for Alexion, Novartis and Pfizer

7 - New Drugs and Cell-based Immune Therapies

O138

LARGE NUMBERS OF HIGHLY POTENT CORD BLOOD-DERIVED REGULATORY T CELLS COULD BE ACQUIRED BY USING CULTURE PLATFORM OF CORD BLOOD-DERIVED MESENCHYMAL STEM CELLS

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Background: CD4 + CD25+ regulatory T cells (Tregs) are promising immunotherapeutic candidate for many immune disorders. Umbilical cord blood (UCB) is a more reliable and available source with enriched naïve T cells than peripheral blood (PB), however, therapeutic translation for clinical grade has been hampered by the difficult manufacturing of enough numbers of Treg. We compared the expansion potential of UCB-Tregs and PB-derived Tregs (PB-Tregs), and also tried to observe the additional effect of UCB derived-mesenchymal stem cell (UCB-MSC) for expansion of UCB-Tregs.

Methods: CD25+Treg isolated from UCB were incubated with or without UCB-MSC at a 10:1 ratio in the presence of exogenous interleukin (IL)-2 and anti-CD3/CD28 bead for 21 days. CD25+Treg derived from PB were also incubated in the presence of anti-CD3/CD28 microbead and IL-2. We assessed the expansion folds of Tregs as well as the functional assays including forkhead box P3 (FoxP3) Treg specific demethylated region (TSDR), T cell receptor (TCR) repertoire and suppressive index.

Results: The proliferation and yield of UCB-Treg on MSC platform (MSC-Treg) showed a two-fold increase compared to UCB-Treg ($p<0.05$), and showed a six-fold increase compared to PB-Treg ($p<0.001$) on day 21. MSC-Treg had significantly higher cumulative population doubling than UCB-Treg and PB-Treg ($p<0.01$). Specifically, UCB-/MSC-Treg and PB-Treg have no significant differences on purity markers defined as $CD4^+CD25^+CD127^-$ and $CD4^+CD25^+FoxP3^+$. MSC-Treg and UCB-Treg have been shown to be superior to PB-Treg in FoxP3 TSDR status and in immunosuppressive activity of Tregs against CD8+ cytotoxic T responder cells (Tc). Considering the importance of epigenetic control of Treg maturation, stability, and function, MSC-Treg (90%) and UCB-Treg (99%) had no significant difference on TSDR demethylation score. In contrast to expanded MSC-Treg and UCB-Treg, PB-Treg showed an epigenetically unstable FoxP3 locus (35%) because they mainly methylated at TSDR. Both MSC-Treg and UCB-Treg showed no significant difference in suppression index against Tc, with comparable IL-10 concentration. The diversity of the immune repertoire was expressed numerically through D50 values, tree maps and heat maps. The D50 of UCB-Treg was 29.5, that of MSC-Treg was 29.7, but that of PB-Treg was 17.5, indicating that UCB-Treg and MSC-Treg showed much higher TCR diversity. In addition, the tree map of UCB-Treg and MSC-Treg showed small boxes indicating low frequency, and greater diversity. On the other hand, PB-Treg showed large shape indicating high frequency or clonal expansion.

Conclusions: These data highlight the potential advantages of MSC platform to augment the number of UCB-Treg while maintaining their functions for adoptive transfer therapies.

Disclosure: Nothing to declare

7 - New Drugs and Cell-based Immune Therapies

O139

CURRENT USE OF FECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES: A SURVEY ON BEHALF OF THE CELLULAR THERAPY AND IMMUNOBIOLOGY WORKING-PARTY OF THE EBMT

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Background: Fecal microbiota transplantation (FMT) that is routinely used for treatment of Clostridioides difficile infection (CDI) is being investigated in patients with hematological malignancies. Nevertheless, access to FMT is variable between centers and there is no consensus harmonization regarding the indication, the route of administration or the type of FMT product used. We therefore conducted a survey within the EBMT to obtain an overview of the FMT activities in the Hematology departments.

Methods: The EBMT Cellular Therapy & Immunobiology Working Party (CTIWP) conducted a survey among EBMT centers to identify those performing FMT between January 2017 and December 2021. Number of FMT performed, indication, procedure and FMT characteristics were obtained. Descriptive statistics were utilized to analyze responses from participating centers and the distribution of responses according to the questionnaire.

Results: Responses were received from 132 participating EBMT centers active in 34 EBMT countries. 42%($n = 55$) of these have access to FMT either at their own center ($n = 30$) or through referral to another center ($n = 25$). Nevertheless, FMT was used for patients with hematological malignancies in only 32 centers ($n = 25$ in their own center, $n = 7$ through referral in another center). Among centers with no access to FMT, 71% were interested to participate through clinical trials.

FMT indication was available for adult patients for 22 centers that perform a median of 2 FMT (range, 0-25), totaling 139 FMT procedures between 2017 and 2021, including 51 in 2021, indicating important disparities in activity between centers and an increase in FMT use over the last year. The majority (65%) perform FMT as part of routine practice only (65%), while 35% also performed FMT within clinical trials. CDI was the most frequent indication ($n = 45$), followed by multidrug resistant bacteria eradication (MDRB, $n = 34$) and GVHD ($n = 22$). Ten patients received FMT for other indications while indication was unknown for 28 patients. For pediatric patients FMT indication was available from 5 centers with a median of 7 FMT (range, 0–14) performed between 2017 and 2021, for a total of 38 FMT.

52% of the centers performed FMT in the hematology department, and 60% reported outpatients FMT. To perform FMT 40% of the centers setup a minimum neutrophil threshold of 0.5 G/L and 32% a minimum platelet level (median 40G/L, range,20-100). 86% of the centers interrupt antibiotics at a median of 36 hours (range,12–72) before FMT. 68% of centers use third-party FMT from stool banks, 24% from related donor and 20% from a commercially available product. Regarding the route of administration, 40% used gastric tubes, 32% colonoscopy, 20% enema and 20% used pills. The majority (72%) of centers used only frozen FMT product, 16% used only fresh FMT and 12% used both.

Conclusions: Despite FMT has been increasingly used in patient with hematological malignancies over the last years, important disparities between centers exist for its availability. Main indications are treatment of CDI and MDRB eradication, but an increase in the FMT activity observed with development of new indications such as GVHD. Finally, most centers wished to develop FMT, particularly, through clinical trials.

Disclosure: Nothing to declare

14 - Non-infectious Early Complications

O140

THE SIMPLIFIED COMORBIDITY INDEX STRATIFIES NON-RELAPSE MORTALITY IN PATIENTS RECEIVING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT AFTER REDUCED-INTENSITY CONDITIONING: A CIBMTR VALIDATION STUDY

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Background: Comorbidity assessment is integral for determining the risk for non-relapse mortality (NRM) in candidates for allogeneic hematopoietic cell transplantation (alloHCT). We previously developed the Simplified Comorbidity Index (SCI), which captures a small number of "high-yield" comorbidities and older age (**Table 1**) to predict NRM, using a single-center development cohort of myeloablative CD34-selected alloHCT (Blood Adv 2022). Here we validate the score in a multicenter cohort of patients (pts) receiving reduced-intensity conditioning (RIC) and unmanipulated alloHCT.

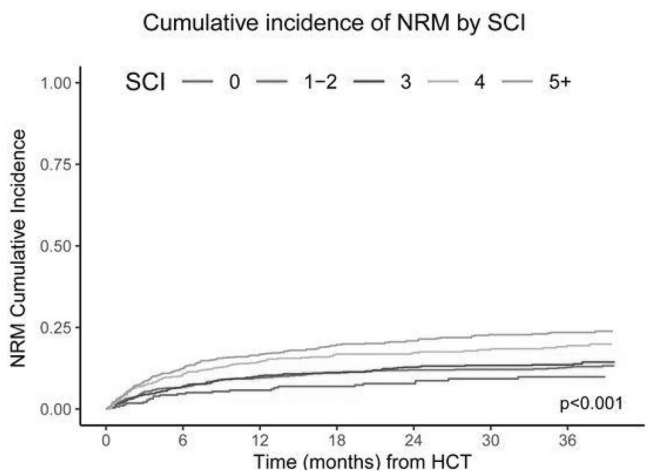
Table 1: The Simplified Comorbidity Index

SCI Score Features	Points
Composite cardiac comorbidity (cardiac comorbidity, arrhythmia, or valvular disorder)	1
Moderate pulmonary dysfunction (identical to the HCT-CI)	1
Age ≥ 60	1
Severe pulmonary dysfunction(identical to the HCT-CI)	2
Moderate or severe hepatic disease (identical to the HCT-CI)	2
Mild renal impairment (eGFR 60-90 ml/minute/1.73 m^2)	2
Moderate or severe renal impairment (eGFR < 60 ml/minute/1.73m^2)	3

Methods: The study population included adult RIC alloHCT recipients with HLA-matched related and unrelated donors utilizing the Center for International Blood and Marrow Transplant Research (CIBMTR) database. Univariable and multivariable cause-specific Cox models were constructed to evaluate the relationship between the SCI and NRM.

Results: Among 3197 pts included, 70% were ≥60 years and 52% had high-performance status (PS, Karnofsky ≥90). Myelodysplastic syndrome (42%) and acute myeloid leukemia (28%) were the leading diagnoses. Most pts had an 8/8 HLA-matched unrelated donor (66%). Of the comorbidities included in the SCI, mild renal impairment (estimated glomerular filtration rate [eGFR] of 60-90 ml/minute/1.73 m^2), severe pulmonary disease (per the HCT-CI definition), and composite cardiac (capturing one or more cardiac disorders), were the most common (46%, 28%, and 23%).

The SCI ranged from 0-9, with 9%, 29%, 24%, 17%, and 21% pts having a score of 0, 1-2, 3, 4, ≥5. Corresponding 1-year cumulative incidence of NRM was 5.8%, 9.5%, 10%, 15%, and 17%, respectively ($p < 0.001$; **Figure 1**). Corresponding median overall survival (95%CI) was 62 (39, not reached), 37 (34, 49), 38 (33, 50), 28 (18, 49), and 8 (14, 23) months. Using the HCT-CI with the same score groups as SCI, 1-year NRM was 8%, 12%, 10%, 12%, and 16%. In univariable Cox model, compared to an SCI score of 0, scores of 1-2, 3, 4, and ≥5, were associated with a hazard ratio (HR [95%CI]) for NRM of 1.42, 1.54, 2.16, 2.85 ($p < 0.001$). Associations remained consistent in a multivariable Cox regression model, adjusting for age, sex, PS, disease risk, and donor type.



Conclusions: This registry analysis demonstrates that the SCI is a valid tool for NRM risk assessment in patients undergoing reduced intensity conditioning allogeneic HCT from matched donors.

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Shouval: *Medexus:* Consultancy, Ended employment in the past 24 months; *MyBiotics:* Consultancy.

Pasquini: *Novartis:* Research Funding; *Bristol Myers Squibb:* Consultancy, Research Funding; *Kite:* Research Funding; *Janssen:* Research Funding.

14 - Non-infectious Early Complications

O141

OUTCOMES OF DEFIBROTIDE-TREATED PATIENTS WITH VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION (VOD/SOS) FOLLOWING ALLOGENEIC-HAEMATOPOIETIC CELL TRANSPLANTATION (HCT): RESULTS FROM THE DEFIFRANCE REGISTRY

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Background: VOD/SOS is a potentially fatal complication of HCT, with a higher incidence in patients receiving allogeneic-HCT compared to those receiving autologous HCT. Defibrotide is approved for severe hepatic VOD/SOS post-HCT in patients aged >1 month in the EU and VOD/SOS with renal or pulmonary dysfunction post-HCT in adult and paediatric patients in the US. The DEFIFrance registry collected real-world data of defibrotide use in France. This analysis presents the outcomes of patients treated with defibrotide for VOD/SOS after allogeneic-HCT by donor type.

Methods: DEFIFrance collected retrospective and prospective data on defibrotide-treated patients from 53 HCT centres in France. VOD/SOS diagnosis was at the investigator's discretion and severity was categorised using adult European Society for Blood and Marrow Transplantation (EBMT) criteria in patients ≥18 years and paediatric EBMT criteria in patients <18 years. Primary endpoints were Kaplan-Meier (KM)–estimated Day 100 post-HCT survival and complete response (CR; total serum bilirubin <2 mg/dL and multiorgan failure resolution per the investigators' assessment). A secondary endpoint was the incidence of treatment-emergent serious adverse events (SAEs) of interest: haemorrhages, coagulopathies, injection-site reactions, infections and thromboembolic events.

Results: In total, 288 patients were treated with defibrotide for VOD/SOS after allogeneic-HCT, including those with human leukocyte antigen (HLA)-matched sibling (n = 86), matched unrelated (n = 92), mismatched unrelated (n = 41) and haploidentical donors (n = 50). Patient baseline characteristics at the time of diagnosis are summarised in Table 1. Overall, the median (range) age was 46 years (0, 74), and most patients (76.9%) had severe or very severe VOD/SOS.

Overall, the KM-estimated Day 100 post-HCT survival rate was 63.9% (95% CI: 58.1%, 69.1%). Patients with matched sibling donors generally had higher Day 100 survival rates than those with mismatched unrelated donors (Figure 1). The highest survival

Table. Demographic and baseline characteristics of patients treated with defibrotide post allogeneic-HCT.

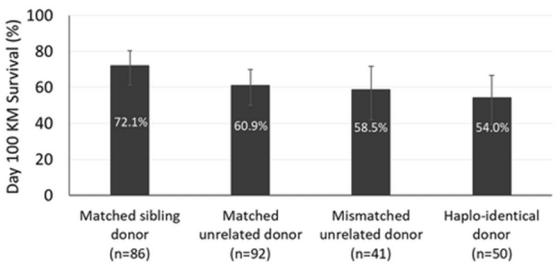
	Matched sibling donor $n = 86$	Matched unrelated donor $n = 92$	Mismatched unrelated donor $n = 41$	Haplo-identical donor $n = 50$	All allograft[a] $n = 288$
Age (year)					
Median (Min, Max)	48 (1, 69)	47 (1, 71)	38 (2, 68)	50 (9, 74)	46 (0, 74)
Age group, n (%)					
Age <18 years	15 (17.4)	17 (18.5)	14 (34.1)	2 (4.0)	62 (21.5)
Age ≥18 years	71 (82.6)	75 (81.5)	27 (65.9)	48 (96.0)	226 (78.5)
Sex					
(%) Male	57 (66.3)	52 (56.5)	25 (61.0)	26 (52.0)	169 (58.7)
VOD/SOS severity[b]					
Mild/Moderate	20 (23.3)	19 (20.9)	15 (36.6)	8 (16.3)	66 (23.1)
Severe	36 (41.9)	30 (33.0)	14 (34.1)	18 (36.7)	101 (35.3)
Very severe	30 (34.9)	42 (46.2)	12 (29.3)	23 (46.9)	119 (41.6)
Primary disease, n (%)[c]					
ALL	11 (12.8)	27 (29.3)	10 (24.4)	10 (20.0)	65 (22.6)
AML	31 (36.0)	20 (21.7)	16 (39.0)	18 (36.0)	88 (30.6)
MDS	8 (9.3)	14 (15.2)	9 (22.0)	9 (18.0)	38 (13.2)
Lymphoma	17 (19.8)	11 (12.0)	0 (0.0)	7 (14.0)	42 (14.6)

[a]18 patients had umbilical cord blood donors; one patient had non-HLA matching data was missing from one non-parent donor.
[b]VOD severity data was missing from two adults (one with matched unrelated donor, one with haplo-identical donor). The denominators used to calculate the percentage of severity were 91 for patients with matched unrelated donor and 49 for patients with haplo-identical donor.
[c]Primary disease occurred in ≥10.0% of patients in any group.

rate (72.1% [95% CI: 61.3%, 80.3%]) was observed in patients with matched sibling donors. Patients with haplo-identical donors had similar Day 100 survival rates as the unrelated donor groups (Figure 1); however, 81.6% of haplo-transplant patients had severe or very severe VOD/SOS and nearly all (96%) were adults. Overall, the Day 100 survival rate ranged from 85.7%–100% in the paediatric population across donor types. The CR rate by Day 100 was similar across the donor types (66.0%–70.7%) in the overall population. Treatment-emergent SAEs of interest occurred in 29.9% (86/288) of patients; the most common categories were haemorrhage and infection, with an incidence of 17.0% and 16.7%, respectively.

Conclusions: Day 100 survival tended to be higher in patients with HLA-matched donors compared with those with mismatched and/or unrelated donors. Patients with haplo-identical donors, which have increased in recent years, had Day 100 survival similar to those with unrelated donors. The safety profile of defibrotide observed in this analysis from the DEFIFrance registry was consistent with previous studies. The favourable benefit-risk profile supports the use of defibrotide in patients with VOD/SOS following allogeneic-HCT regardless of donor type.

Figure 1. The KM–estimated Day 100 post-HCT survival rate by donor type



HCT, haematopoietic cell transplantation; KM, Kaplan-Meier.

Clinical Trial Registry: N/A

Disclosure: M Mohty has received research funding and honoraria from Jazz Pharmaceuticals.

A Huynh, R Peffault de Latour, C Jubert, and D Blaise have received honoraria from Jazz Pharmaceuticals.

D Gutierrez and N Dronamraju are employees of Jazz Pharmaceuticals and hold stock and/or stock options in Jazz Pharmaceuticals.

C Renard has received research funding from Jazz Pharmaceuticals.

14 - Non-infectious Early Complications

O142

OUTCOMES IN OLDER AND YOUNGER ADULT DEFIBROTIDE-TREATED PATIENTS WITH VENO-OCCLUSIVE DISEASE/ SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) AFTER ALLOGENEIC-HAEMATOPOIETIC CELL TRANSPLANTATION (HCT): RESULTS FROM THE DEFIFRANCE REGISTRY

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Background: VOD/SOS is a potentially fatal complication following HCT, with higher incidence of VOD/SOS occurring in patients receiving allogeneic-HCT vs those receiving autologous-HCT. Older patients may be more susceptible to developing VOD/SOS and older patients with VOD/SOS tend to have poorer outcomes. Defibrotide is approved for the treatment of severe VOD/SOS in patients post-HCT aged >1 month in the EU and VOD/SOS with renal or pulmonary dysfunction post-HCT in the US. This analysis examined adult patients who received defibrotide for VOD/SOS treatment following allogeneic-HCT in the real-world DEFIFrance registry to evaluate the duration of defibrotide treatment, day 100 survival post-HCT and resolution of VOD/SOS.

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 the adult European Blood and Marrow Transplantation (EBMT) criteria in adults (≥18 years), and paediatric patients (<18 years) were retrospectively/prospectively categorised using paediatric EBMT criteria. Primary endpoints were Kaplan-Meier (KM) estimated day 100 survival post-HCT and complete response (CR; per the investigators). A secondary endpoint was incidence of serious treatment-emergent adverse

events of interest at day 100. Here, we present data from adult patients overall and by age subgroup (≤60 years or >60 years).

Results: A total of 226 adult patients (aged ≤60 years, n = 167; aged >60 years, n = 59) were included in this analysis. Patient characteristics are listed in Table 1. The median (range) age of patients ≤60 years was 47 (18–60) years and patients >60 years was 65 (60–74) years. The majority of patients in both age subgroups had severe or very severe VOD/SOS (≤60 years: 81.4%; >60 years: 72.9%). The median duration of defibrotide treatment was similar for patients ≤60 years (15.0 [IQR: 10.0, 21.0] days) and patients >60 years (16.0 [IQR: 10.0, 22.0] days). The KM-estimated survival rate at day 100 was 56.6% (95% CI: 49.9%, 62.8%) for the overall population, and was higher in patients ≤60 years (61.1% [95% CI: 53.2%, 68.0%]) vs patients >60 years (44.1% [95% CI: 31.2%, 56.2%]). The CR rate in the overall population was 61.5% (95% CI: 54.8%, 67.9%), with higher CR rates in patients ≤60 years (65.9% [95% CI: 58.1%, 73.0%]) vs patients >60 years (49.2% [95% CI: 35.9%, 62.5%]). In the overall population, 33.6% of patients had at least one serious treatment-emergent adverse event of special interest. Patients ≤60 years had higher rates of haemorrhage (19.2%) than patients >60 years (16.9%). Patients aged >60 years had higher rates of infection (23.7%) than patients ≤60 years (16.8%).

Conclusions: Adults ≤60 years tended to have higher survival and VOD/SOS resolution than older adults by day 100 following allogeneic-HCT. Overall, older adults exhibited higher rates of serious treatment-emergent adverse events of special interest than younger adults. Considering the high proportions of patients with severe or very severe VOD/SOS, the overall outcomes in DEFIFrance support the utility of defibrotide treatment for VOD/SOS in the real-world setting and the risk-benefit profile for defibrotide in DEFIFrance is consistent with prior studies.

Table 1. Demographics and characteristics of adult patients with VOD/SOS treated with defibrotide

	Patients aged ≤60 years *n* = 167	Patients aged >60 years *n* = 59[a,b]	Overall *N* = 226[a,b]
Age (year)			
Median (Min, Max)	47 (18–60)	65 (60–74)	53 (18–74)
Sex, n (%)			
Male	98 (58.7)	40 (67.8)	138 (61.1)
VOD/SOS severity, n (%)			
Mild/moderate	31 (18.6)	14 (23.7)	45 (19.9)
Severe	64 (38.3)	23 (39.0)	87 (38.5)
Very severe	72 (43.1)	20 (33.9)	92 (40.7)
Donor type[a]			
Sibling donor (HLA-matched)	55 (32.9)	16 (27.1)	71 (31.4)
Nonparent donor (HLA-matched)	53 (31.7)	22 (37.3)	75 (33.2)
Nonparent donor (HLA-mismatched)	22 (13.2)	5 (8.5)	27 (11.9)
Haplo-identical	34 (20.4)	14 (23.7)	48 (21.2)
Umbilical cord blood	3 (1.8)	1 (1.7)	4 (1.8)
Primary disease in DEFIFrance, n (%)[c]			
AML	63 (37.7)	16 (27.1)	79 (35.0)
ALL	36 (21.6)	5 (8.5)	41 (18.1)
MDS	17 (10.2)	22 (37.3)	39 (17.3)
Lymphoma	29 (17.4)	4 (6.8)	33 (14.6)
Treatment Duration (days)	15.0	16.0	15.5
Median (IQR)	(10.0, 21.0)	(10.0, 22.0)	(10.0, 22.0)
Any serious TEAEs of special interest	54 (32.3)	22 (37.3)	76 (33.6)
Haemorrhage	32 (19.2)	10 (17.0)	42 (18.6)
Infection	28 (16.8)	14 (23.7)	42 (18.6)

[a]Donor type missing for one patient; [b]Severity data missing for two patients; [c]Primary diseases in ≤10% of patients not shown.
ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; HLA, human leukocyte antigen; IQR, interquartile range; MDS, myelodysplastic syndrome; SOS, sinusoidal obstruction syndrome; TEAE, treatment-emergent adverse event; VOD, veno-occlusive disease.

Clinical Trial Registry: N/A

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14 - Non-infectious Early Complications

O143

THE CHICKEN AND THE EGG: UNRAVELLING THE FACTORS THAT SHAPE GUT DYSBIOSIS IN HSCT RECIPIENTS

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Background: Haematopoeitic stem cell transplantation (HSCT) is associated with significant changes in the composition and functionality of the gut microbiota. These changes are increasingly linked to life-threatening complications including blood stream infection, graft-versus host disease, pulmonary infections, perturbed immune reconstitution, relapse and death. Despite intensive efforts characterising the gut microbiota composition, it is not known what causes microbial disruption. Without this knowledge, it is challenging to rationally design interventions to support microbial stability. We therefore aimed to describe the temporal dynamics of the gut microbiota and decipher the most influential factors that shape its composition in HSCT recipients.

Methods: This study was performed as an exploratory, secondary analysis of biospecimens collected from N = 37 auto-HSCT recipients (60 years (44-69), 28M:9F) enrolled into a randomised clinical trial conducted at Radboud University Medical Centre (Nijmegen, the Netherlands) investigating the clinical

benefit of enteral nutrition versus parenteral feeding. All patients were diagnosed with multiple myeloma, and treated with high dose chemotherapy (BEAM/HDM) prior to auto-HSCT. No differences were observed in clinical outcomes based on the dietary intervention, and thus, all data were aggregated into a single cohort for this study. 16S rRNA gene sequencing was used to characterise the gut microbiota composition in N = 249 faecal samples collected between day -3 and +90. GC-MS was used to quantify short chain fatty acid concentrations (in faeces) and plasma citrulline concentrations (a biomarker of mucositis) in N = 249 matched blood samples. All other data (antibiotics, diet, conditioning therapy, age, sex, treatment day) were accessed through the clinical data collected as part of the trial.

Results: Rapid and significant changes were observed in the diversity ($P < 0.0001$), richness ($P < 0.0001$) and composition ($P = 0.0006$) of the gut microbiota of all patients after auto-HSCT. This was accompanied by a loss of microbial metabolites, in particular butyrate ($P<0.0001$), acetate ($P < 0.0001$) and propionate ($P = 0.0002$). Both butyrate and acetate remained significantly decreased at +30 days ($P = 0.04$). To understand the proportional impact of various parameters on the composition of the faecal microbiota, PERMANOVA was performed. This analysis evaluated the impact of antibiotics, plasma citrulline, dietary intake, age, sex, conditioning therapy and treatment day on the faecal microbiota composition. Plasma citrulline was the most dominant factor shaping the composition of the faecal microbiota, identified to explain 14.8% of the variation in its composition ($P = 0.001$). Accordingly, plasma citrulline and alpha diversity dynamics were significantly correlated ($r^2 = 0.48$, $P<0.0001$). Of all microbial taxa, the most significant correlations with citrulline were identified for *Faecalibacterium* ($r^2 = 0.63$, $P<0.0001$), *Roseburia* ($r^2 = 0.63$, $P<0.0001$) and *Enterococcus* ($r^2 = -0.39$, $P < 0.0001$). Temporal analysis showed that citrulline nadir occurred 9 days prior to microbial disruption.

Conclusions: Given its use as a biomarker of intestinal mucositis, the integrity and/or hostility of the intestinal mucosa is the most dominant factor shaping gut microbiota composition in auto-HSCT recipients. As such, efforts to support microbial resilience must consider the impact of mucosa-microbe interactions. Critically, our temporal analyses indicate that intestinal mucositis precedes dysbiosis in auto-HSCT recipients providing an opportunity to predict consequences of gut dysbiosis (i.e., infection) by monitoring plasma citrulline concentrations.

Clinical Trial Registry: www.trialregister.nl: NL3937

Disclosure: Nothing to declare.

14 - Non-infectious Early Complications

O144

NON-GVHD ENTEROCOLITIS FOLLOWING CORD BLOOD TRANSPLANT IS REAL, WITH POORLY UNDERSTOOD PATHOPHYSIOLOGY, AND REQUIRES DISTINCT MANAGEMENT FROM GVHD, WITH EVENTUAL RESOLUTION WITHOUT IMMUNE SUPPRESSION

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Background: Cord blood transplant (CBT) has specific utility in both malignant and non-malignant disease. In malignant disease, we have shown that CBT reduces relapse and improves leukaemia-free survival compared to other cell sources. The superior chimerism achieved after CBT might improve long-term outcomes in metabolic haematopoietic stem cell transplant (HSCT) for lysosomal storage disorders and other non-malignant diseases. The high transplant related mortality with CBT frequently serves as a barrier to its use, with gastrointestinal (GI) complications a particular challenge. We evaluate the GI pathology associated with CBT over 11-years at Royal Manchester Children's Hospital (RMCH), a large UK paediatric CBT centre.

Methods: All patients that received a CBT at RMCH between July 2011-July 2022 were identified from our database and screened against histopathology records to identify those who underwent post-transplant GI endoscopy. Histology reports were reviewed by expert histopathologists to classify as GVHD or non-GVHD enterocolitis based on the presence of GVHD diagnostic criteria (apoptosis, crypt dropout and ulceration). Statistical analysis was carried out using Prism.

Results: Over the 11-year period, 131 children underwent CBT at RMCH. 27 patients (21%) experienced GI failure (persistent diarrhoea with weight loss and/or intolerance of enteral feeding without an infective cause), necessitating endoscopy. 4 patients were excluded from final analysis as their GI issues were deemed unrelated to CBT (3 had undergone endoscopy following previous non-cord HCT and 1 had histological changes consistent with underlying Wolman disease), leaving a cohort of 23 patients for analysis.

10/23 patients (43%) had histopathology findings of non-GVHD enterocolitis ('cord colitis') and 13 (57%) with GI acute GVHD. 0/23 patients (0%) had histological evidence of infection. Table 1 details patient and transplant demographics. There were no significant confounding variables between groups.

The cord colitis (CC) cohort had better overall survival, 89% vs 58% ($p = 0.17$) (Figure 1) but a longer dependence on parenteral nutrition (mean 168 vs 114 days, $p = 0.15$), with 4 requiring home parenteral nutrition. Despite 50% of CC patients having associated acute skin GVHD (≤ grade 2), the cohort had a significantly shorter duration of immune suppression, mean 116 vs 211 days ($p = 0.05$). All CC patients had a trial of ciprofloxacin and metronidazole with limited response (change in stool frequency or enteral feed tolerance) and all had eventual resolution of symptoms with return to full enteral nutrition following wean of immune suppression. 1 death in the CC group occurred 7 months post HSCT due to AML relapse.

Table 1: Patient and transplant demographics

	CORD COLITIS (10 patients)	**GVHD (13 patients)**	
Age (years)	**Mean 5.6** **Range 1.9–14.3**	**Mean 7.7** **Range 0.7–16.8**	***p* = 0.3**
Transplant indication	Malignant disease 80% •4x AML •3x ALL •1x lymphoma Metabolic (MPS1) 10% Immune (RALS) 10%	Malignant disease 69% •9x AML Metabolic 31% •2x MPS1 •2x other	p = 0.58
Cord HLA-match (/8)	Fully matched (8/8) = 20% 7/8 HLA-matched= 40% 6/8 HLA-matched= 40%	Fully matched (8/8) = 15% 7/8 HLA-matched= 46% 6/8 HLA-matched= 23% 5/8 HLA-	p = 0.6

	CORD COLITIS (10 patients)	GVHD (13 patients)	
Age (years)	**Mean 5.6** **Range 1.9–14.3**	**Mean 7.7** **Range 0.7–16.8**	**$p = 0.3$**
		matched= 15%	
Conditioning	80% myeloablative 20% reduced intensity	85% myeloablative 15% reduced intensity	$p = 0.78$
No of patients who had previous BMT	2 (20%)	2 (15%)	$p = 0.78$
Associated GVHD	50%- all skin	n/a	

Figure 1: Overall survival cord colitis vs GVHD

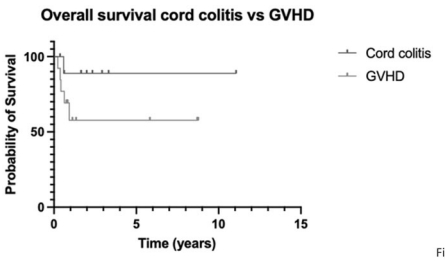

Figure 1: Overall survival cord colitis vs

Conclusions: Non-GVHD enterocolitis, so called "cord colitis", is a significant and unique complication of CBT that occurred in 7.6% of CBT patients at RMCH during the study period. CC requires a different treatment strategy to GVHD and infectious enterocolitis which underlines the importance of prompt histopathological examination to inform management. In the absence of histopathological changes of acute GVHD, immune suppression should be promptly weaned to support immune recovery to reduce relapse and infection risk. Our data support that non-GVHD enterocolitis resolves without immune suppression and with supportive care.

Disclosure: none of the authors have any relevant disclosures related to this abstract

14 - Non-infectious Early Complications

O145

ENDOTHELIAL GLYCOCALYX: A MORPHOLOGICAL SUBSTRATE FOR EASIX

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Background: Endothelial Activation and Stress Index (EASIX) predicts mortality and endothelial complications after allogeneic stem cell transplantation (alloSCT) and also prognosis of a growing number of malignant and non-malignant diseases. The endothelial substrate for EASIX is still undefined.

To test the hypothesis that EASIX reflects endothelial Glycocalyx integrity, we applied sublingual microscopy using Glycocheck®. This device measures perfused boundary regions (PBR) in capillaries of defined vessel diameters. Low PBR values directly reflect a normal and functional endothelial glycocalyx, whereas high PBR values indicate damaged glycocalyx. Here we report an interim analysis of a prospective observational study (NCT05502887).

Methods: Sublingual microscopy was performed in 40 healthy volunteers (11 male, 29 female, median age 39 (21-66) years), and in 47 patients (29 male, 18 female, median age 62 (24-76) years) within 7 days before starting conditioning for alloSCT or lymphodepletion for CART therapy. Diagnoses were AML 36%, lymphoma 28%, myeloproliferative neoplasia 6%, myelodysplastic syndrome 9%, multiple myeloma 8%, ALL 6%, and other diseases 6%. Of the 47 patients, 22 were in CR (47%, including 4 patients with MRD positive disease), 6 (13%) achieved partial remission (13%) and 10 (21%) had progressive disease at the time of Glycocheck analysis. 46/47 patients had a high disease risk profile (either initial high risk or relapsed/refractory disease).

24 repetitive sublingual measurements (minimum 15) per individual were recorded for calculation of mean values for PBR, vascular density, and red blood cell (RBC) velocity separately for any vessel diameter between 4µm and 25µm. EASIX values were measured on the day of the Glycocheck analysis.

Results: Healthy individuals had lower PBRs (i.e., better Glycocalyx) and a higher density of small sublingual vessels than patients. In 14 patients we repeated the analysis on day+28 after alloSCT and found that the individual PBRs did not change significantly within this period.

EASIX significantly correlated with PBRs in all vessels with diameters >7 µm with a maximum Pearson correlation coefficient >0.4 in 15-17µm diameters. Interestingly, increased PBR values were confined to EASIX values above 2.32, which is the validated cut-off predicting a >13-fold increased hazard ratio of early sepsis. Patients with EASIX>2.32 also had significantly lower sublingual vascular densities. In multivariable binary logistic regression analyses including age, gender, and CRP, EASIX significantly associated with a high PBR>3µm (for continuous EASIX per log2 increase: OR 3.2 (1.7-5.9), p<0.001; for EASIX>2.32: OR 13.2 (2.9-51.2), p<0.001.

Conclusions: The strong correlation between PBR and EASIX score observed here provides first direct evidence for endothelial damage being a major driver of EASIX. Continuation of the study will provide further impact on the relations of Glycocheck-assessed Glyococalyx dysfunction, biomarkers and cellular therapy outcomes.

Clinical Trial Registry: NCT05502887

Disclosure: nothing to disclose

14 - Non-infectious Early Complications

O146

IMPACT OF TACROLIMUS TIME IN THERAPEUTIC RANGE (TTR) IN TRANSPLANT OUTCOMES

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Background: Tacrolimus is the backbone of allogeneic stem cell transplant (AlloSCT) immunosuppression. Adequate target-through level is usually affected by different metabolisms and drug interactions. Although a proper time in therapeutic range (TTR) is a goal in post-transplant, there is no gold standard.

Moreover, no analysis have been published regarding tacrolimus TTR and graft-versus-host disease/relapse free survival (GRFS).

Methods: We performed a retrospective cohort analysis of adults AlloSCT from jan/2012 till dec/2019. Second transplant were excluded, as well as patients without tacrolimus for at least 5 consecutive days. We defined adequate TTR (aTTR) when at least 75% of the measurements were in target (5-15ng/mL). Statistical analysis were performed with Easy R 1.33. Non-relapse Mortality (NRM), relapse incidence (RI), acute and chronic GVHD and graft failure were calculated with Gray test; Overall Survival (OS) and GRFS with log-rank.

Results: A total of 186 patients were included, with a median follow up time of 3.0 years. Main cohort characteristics are listed in table 1, 105 patients were in aTTR group (57%) compared to 81 patients (43%) that were more than 25% of measurements above or below target. Primary graft failure was significantly lower in aTTR (2% vs. 10%, $p = 0.01$). No differences in acute and chronic GVHD nor RI were observed. NRM was significantly reduced in aTTR (100 days and 3 years 9% and 18% vs. 24% and 37%, $p = 0.004$). Regarding cause of death, infections were higher in non aTTR (22 vs 9% $p = 0.07$). No significant differences were observed in OS and GRFS. NRM multivariate analysis showed an independent impact of TTR and HCT-CI/age (expressed as HR 95% CI: 0.41 [0.20-0.81], HCT-CI/age intermediate-high risk HR 2.99 [1.27-7.05]). No significant impact was observed when we compared supra-therapeutic vs. others (aTTR + sub-therapeutic). When we analysed sub-therapeutic (14%, 26 patients) vs. others (supra-therapeutic + aTTR), although no impact on GVHD incidence, a significant impact was found in other transplant outcomes. Graft failure was significantly higher (27% vs 2%, $p<0.001$), as well as NRM (day 100 and 3 years 50% and 54% vs. 10% and 22%, $p<0.001$) and a significant reduction in OS (3 years 30% vs. 51%, $p = 0.009$) and GRFS (3 years 17% vs. 33%, p = 0.01). We performed a MVA for OS and GRFS for sub-therapeutic vs others and both outcomes remained independently associated with tacrolimus TTR (OS 2.33, 1.33-4.06 and GRFS 2.10, 1.26-3.48).

Table 1. Cohort characteristics

	Full Cohort *N* (%)	aTTR (*N* = 102)	non aTTR (*N* = 84)	*p* value
Patient age (mean)	38.7 years	37.1 years	40.6 years	$p = 0.10$
Donor age (mean)	36.1 years	33.8 years	38.6 years	$p = 0.02$
Disease AML/ MDS	84 (46)	44 (43)	40 (48)	$p = 0.67$
ALL	49 (26)	24 (23)	25 (30)	
Lymph/MM	28 (15)	17 (17)	11 (13)	
Others	25 (13)	17 (17)	7 (10)	
HCT-CI/Age Score 0	59 (32)	35 (34)	24 (29)	p = 0.15
Score 1-2	90 (48)	43 (42)	47 (56)	
Score ≥3	37 (20)	24 (24)	13 (15)	
DRI Low (+ benign)	19 (10)	13 (13)	6 (7)	$p = 0.08$
Intermediate	131 (71)	70 (68)	61 (73)	
High-Very High	36 (19)	19 (19)	17 (20)	
	84 (45)	43 (42)	41 (49)	$p = 0.67$
Donor Match Sibling				
Haploidentical	59 (32)	34 (33)	25 (30)	
Unrelated	43 (23)	25 (25)	18 (21)	
Myeloablative conditioning	122 (66)	63 (62)	59 (70)	$p = 0.28$
Disease Status (advance)	108 (58)	60 (59)	51 (61)	$p = 0.88$

Conclusions: These findings emphasised the relevance of adequate tacrolimus TTR, and defines that sub-therapeutic levels are more dangerous for our patients than supra-therapeutic levels, with significant impact in graft failure, NRM, OS and GRFS. We aimed to validate our findings with an independent cohort from Huntsman Cancer Institute Transplant Program. Institutional protocols needs to be standardized to meet adequate tacrolimus TTR, especially in the first 30 days post-transplant.

Clinical Trial Registry: NA

Disclosure: No conflict of interest to disclose

15 - Non-infectious Late Effects, Quality of Life and Fertility

O147

ACCELERATED COGNITIVE AGEING AMONG SURVIVORS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION COMPARED WITH A MATCHED GENERAL POPULATION SAMPLE – THE MOSA STUDY

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Background: Although cognitive problems can recover over time, a subgroup of hematopoietic stem cell transplantation (HCT) survivors experiences persistent cognitive problems in the long-term which is a major concern by those affected. Despite these implications, studies assessing cognitive functioning in HCT survivors are limited. The aim of the present study was (1) to quantify the prevalence of cognitive impairment in patients treated with HCT who survived at least 2 years, and to compare these with a matched reference group representing the general population; (2) to identify potential determinants of cognitive functioning within the HCT survivor group.

Methods: Within the single-centre Maastricht Observational study of late effects after Stem cell trAnsplantation (MOSA) cognitive performance was assessed by a neuropsychological test battery. A total of 115 HCT survivors were group-matched on a 1:4 ratio to the reference group by age, sex, and level of education. Regression analyses adjusted for different sets of covariates were used to test for differences in cognition between HCT survivors and the reference group resembling the general population. Cognitive impairment was defined as scores in the cognitive domains < -1.5 SD from what can be expected based on someone's age, sex, and education.

Results: Transplantation characteristics were summarized in table 1. The mean age at time of transplant was 50.2 (SD 11.2)

years, and the mean number of years of survivorship was 8.7 (SD 5.7) years. The majority of HCT survivors were treated with autologous HCT (N = 73; 64%). Most HCT survivors were diagnosed with lymphoid malignancies (N = 40; 35%), multiple myeloma (N = 28; 24%), and acute leukemia (N = 25; 22%). The prevalence of cognitive dysfunction in HCT survivors was 34.8%, and 21.3% in the reference group (p = .002.) When adjusted for age, sex, and level of education HCT survivors had a worse overall cognition score (b = -.35, 95%CI = -.55, -.16, p<0.001), translating into 9.0 years of higher cognitive age. Analyses of specific cognitive domain scores showed that HCT survivors scored worse on memory (b = -.43, 95%CI = -.73, -.13, p = .005), information processing speed (b = -.33, 95%CI = -.55, -.11, p = .003), and executive function & attention (b = -.29, 95%CI = -.55, -.03, p = .031) than the reference group. The odds of cognitive impairment were on average 2.4 times higher among HCT survivors than the reference group (OR = 2.44, 95%CI = 1.47, 4.07, p = .001).

Transplantation characteristics	HCT-total % (*N*)	AutoHCT %(*N*)	AlloHCT %(*N*)
Type of transplant	115	64% (73)	36% (42)
Sex/men	57% (65)	58% (42)	55% (23)
Mean (±SD) age at time of transplant in years	50.2 (±11.2)	51.4 (±10.7)	48.4 (±11.9)
Mean (±SD) *year of transplant*	2007 (±6.1)	2007 (±6.0)	2008 (±6.1)
Mean (±SD) years after transplant (survivorship)	8.7 (±5.7)	8.9 (±5.4)	8.2 (±5.7)
2-5	36% (41)	33% (24)	41% (17)
6-10	34% (39)	37% (28)	29% (12)
11-15	18% (21)	16% (12)	21% (9)
>15	12% (14)	14% (9)	10% (4)
Disease category			
Lymphoma	35% (40)	48% (35)	12% (5)
Multiple myeloma	24% (28)	37% (26)	5% (2)
Acute leukemia	22% (25)	6% (4)	50% (21)
Chronic leukemia	6% (7)	-	17% (7)
Myeloproliferative neoplasm/ MDS	5% (6)	-	14% (6)
Solid tumor	7% (8)	11% (8)	-
Other (aplastic anemia)	1% (1)	-	2% (1)
Conditioning regimen with total body irradiation	23% (26)	4% (3)	55% (23)

Conclusions: The prevalence of cognitive dysfunction in HCT survivors is higher compared to the general population (respectively 34.8% and 21.3%), and HCT survivors had, on average, a 2.4 times higher odds of cognitive impairment. Furthermore, HCT survivors had a worse overall cognition score and lower scores on all three cognitive domains respectively memory, information processing speed, and executive function & attention compared to the general population suggesting nine years of accelerated cognitive aging in HCT survivors. This study shows convincing evidence for worse cognitive functioning in HCT survivors. It is important to increase awareness for neurocognitive dysfunction after HCT in clinicians and HCT survivors.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

O148

PROGNOSTIC IMPACT OF PSYCHOSOCIAL FACTORS IN PATIENTS UNDERGOING AN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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***Background**: Assessment of a candidate for allogeneic hematopoietic stem cell transplantation (HSCT) is a complex process, which requires the evaluation of underlying disease factors, patient comorbidities, age, performance status and donor and graft source availability. Socioeconomic circumstances of the candidate may also impact on procedure outcome and must be considered*

Methods: A retrospective unicentric study was performed in patients who underwent a first allogeneic-HSCT between January 2012 and July 2022. Baseline patients characteristics, HSCT data and pre-HSCT scores (HCT-CI and EBMT) were collected. Race/ethnicity and three variables from the psychosocial pre-HSCT evaluation were collected and categorized into favorable or unfavorable: presence of communication difficulties, economic situation and cohabitation nucleus. The main objective of this study was to check if an unfavorable social situation has an impact on allogeneic-HSCT outcome.

Results: Two-hundred and eighty-six patients were included, with a median time of follow-up of 3.6 [range 0.2 - 10.5] years. Patients' characteristics are summarized according to the presence or absence of ≥1 unfavorable social factors (*Table 1*). Interestingly, patients with ≥1 unfavorable social factors were younger, mostly non-caucasian, and with a higher EBMT score. In the univariable analysis, age, diagnosis, disease status, donor type and conditioning regimen had an impact on overall survival (OS) and on non-relapse mortality (NRM), with lower OS and higher NRM probabilities for the patients with higher age, myeloproliferative disorders, non-first complete response (CR), haploidentical donors or UCB source, and non-myeloablative conditioning regimens. Higher scores in HCT-CI and EBMT were also significantly associated with lower OS and higher NRM probabilities. Regarding social variables, communication barriers, economic difficulties and living alone were significantly associated with a negative impact on OS and NRM. Moreover, the presence of ≥1 of these unfavorable social factors was associated with lower OS (p<0.001) and higher NRM probabilities (p<0.001). Race/ethnicity had no impact on OS or NRM. In the final multivariable model for OS and NRM three variables

were considered: EBMT score -which includes age, disease status and donor type- (0-4 vs >4 points), HCT-CI (0-2 vs >2 points) and the number of unfavorable social factors (0 vs ≥1). In OS and NRM models, the three variables emerged as significant, with an independent prognostic value. The presence of ≥1 of the three unfavorable social factors was directly associated with worse OS and NRM after an allogeneic-HSCT, with hazard ratios (HR) (95%CI) of 1.746 (1.259 – 2.419) and 1.981 (1.352 - 2.903), respectively.

Table 1. Patients' characteristics.

	Non-unfavorable social factors ($n = 216$)	≥1 unfavorable social factors ($n = 70$)	*p*
Age, years	53 (16–69)	44 (18–70)	0.006
Gender			0.222
Male	126 (58%)	35 (50%)	
Female	90 (42%)	35 (50%)	
Race/Ethnicity			<0.001
Caucasian	203 (94%)	41 (59%)	
African-American	1 (0.5%)	2 (3%)	
Arabic	3 (1.5%)	11 (16%)	
Asian	0	3 (4%)	
Hispanic	9 (4%)	13 (19%)	
HCT-CI			0.952
0-2	138 (64%)	45 (64%)	
≥ 3	78 (36%)	25 (36%)	
EBMT score			0.028
0-4	170 (79%)	46 (66%)	
≥ 5	46 (21%)	24 (34%)	
Diagnosis			0.166
Acute Leukemia	139 (64%)	35 (50%)	
MDS	26 (12%)	9 (13%)	
Lymphoprol. Sd	33 (15%)	14 (20%)	
Myeloprol. Sd	10 (5%)	7 (10%)	
Others	8 (3%)	5 (7%)	
Disease status			0.209
First CR	105 (49%)	28 (40%)	
Others	111 (51%)	42 (60%)	
Donor type			0.332
Related-Donor	83 (38%)	29 (41%)	
Haploidentical Donor	41 (19%)	13 (19%)	
Unrelated-Donor	86 (40%)	23 (33%)	
UCB	6 (3%)	5 (7%)	
Conditioning			
Myeloablative	114 (53%)	30 (43%)	0.149
Others	102 (47%)	40 (57%)	

The group with ≥1 unfavorable social factors showed a 5-year OS probability of 45% (38-52%) versus 19% (10-29%) for the group with non-unfavorable social factors. The group with ≥1 unfavorable social factors showed a 5-year cumulative incidence of NRM of 60% (47-70%) versus 35% (28-42%) for the group with non-unfavorable social factors.

Conclusions: Poor social circumstances in allogeneic-HSCT candidates are associated with worse prognosis of the procedure, and a psychosocial evaluation before the transplantation could help to detect them. Social and economic support and effective communication are measures that could have a positive impact on allogeneic-HSCT results.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

O149

THE VALUE OF USING PATIENT-REPORTED OUTCOMES FOR HEALTH SCREENING DURING LONG-TERM FOLLOW-UP AFTER PEDIATRIC STEM CELL TRANSPLANTATION FOR NONMALIGNANT DISEASES

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Background: The value of using patient-reported outcomes (PROs) in routine care has been primarily assessed in patients with active disease symptoms, but its value in a comprehensive care follow-up program has not been assessed yet.

Methods: Patient-reported outcomes measures (PROMs) were implemented in our long-term comprehensive care program after pediatric hematopoietic stem cell transplantation (HSCT) for nonmalignant disease. The program focuses solely on screening of physical and mental health. PROMs were completed in advance of the consultation and results were discussed during the consultation. Semi-structured interviews were held to explore the patients', caregivers', and healthcare providers' (HCP) perspectives on PRO use in the comprehensive care program and were thematically analyzed. Additionally, two patient-reported experience measures (PREMs) were used in a pretest-posttest design to assess if PROM implementation was accompanied by more patient-centered care.

Results: Fifteen patients, or their caregivers, were interviewed on experiences with PROs and patients' median age was 17 years (range, 8-37). Median age at HSCT was 3 years (range, 1-15) and underlying disease were inborn errors of immunity (N = 5), hemoglobinopathies (N = 5), and bone marrow failure syndromes (*N* = 5). Four themes on experiences with PROs emerged from the data from the patients' perspective. First, use of PROs helped to discuss topics and facilitate the conversations at the

comprehensive care program. Discussing the PROs started the conversation and guided an efficient consultation with a focus on the topics perceived as most relevant to the individual patient. Second, evaluating PROs made the patients feel understood and supported. The patient and HCP noticed mutual preparation prior to the consultation, resulting in more tailored follow-up questions. Third, completing the PROMs created a moment of self-reflection for patients. Completing the PROMs facilitated a conversation at home and made the patient and caregiver reflect on the treatment, which can have an impact. Fourth, use of PROs made the consultation more efficient due to better preparation and a direct transfer of the PRO results into the patient's electronic medical file. Table 1 presents illustrative quotations.

HCPs' reported an improved equality and reciprocity in their doctor-patient interaction and improved shared-decision making after PRO implementation. PROs improved insight into patients overall well-being and helped to recognize and prepare topics needing attention during consultation.

Evaluation using PREMs indicated no difference in patient-centeredness after PRO implementation, which is in line with the findings from the interview data from the patients' perspective.

Table 1. Illustrative quotations

Subtheme	Sex	Age	Quotation
Use of PROs help to discuss topics	♂	11	*[About discussing PROs] "I think it provides [name doctor] the right tools to start a conversation, so that you don't have to start asking questions out of the blue."*
	♀	17	*"I thought it was better, because with the questionnaires you can really think clearly about everything beforehand and if you're at the appointment, well then you'll also forget half of it."*
Completing the PROMs create a moment of self-reflection	♂	17	*"He filled in the questionnaires two days beforehand and well, then you talk about it, you talk about the whole process, and about how his friends dealt with it and well, you get to have a moment in which you talk extensively about it."*
	♀	17	*[About filling in the PROMs] "I thought it was better, because with the help of the questionnaires you can really think clearly about everything."*
Evaluating the PROs make the patients feel understood	♀	12	*[About discussing PROs] "… and then such an answer will fall in a different context and then it is all much more reasonable and justified instead of, well if you have to answer something in two little sentences, it can appear extreme pretty fast."*

Conclusions: To our knowledge, this is the first multiple methods study on the value of use of PROs where the aim of the consultation is screening for health status instead of symptom control or cure. Our results show that PRO use for screening purposes in the long-term follow-up program after pediatric HSCT is of added value both from a patient's and HCP's perspective. Completing the PROMs should not replace a routine consultation since providing context to results is desired by patients as well as HCPs. With the active use of PROs patients are empowered to deliberatively assess their health status.

Disclosure: Nothing to declare.

15 - Non-infectious Late Effects, Quality of Life and Fertility

O150

RISK FACTORS FOR CHRONIC DISEASE FOLLOWING ALLOGENEIC HAEMOPOIETIC STEM CELL TRANSPLANTATION

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Background: This study presents an analysis of the risk factors for chronic disease in a cohort of individuals in Australia surviving at least 2 years following allogeneic haemopoietic stem cell transplantation (alloHSCT).

The World Health Organisation (WHO) classifies chronic disease risk factors into behavioural and metabolic. The Australian Institute of Health and Welfare (AIHW) through the National Health Survey (NHS) and Australian Diabetes Obesity and Lifestyle Study (Aus Diab) consistently report these same risk factor classifications for chronic disease in the Australian population.

To provide optimal long-term care for individual following alloHSCT, understanding, identifying, and managing chronic disease and risk factors is required. Applying population specific public health programs ensures optimal care is delivered within the local health system.

Methods: Individuals attending Long Term Follow Up (LTFU) clinics after alloHSCT at two tertiary health services in Melbourne Australia were enrolled in the Victorian alloHSCT Survivorship Study (VaHSS).

At each annual LTFU clinic attendance prospective measures of chronic disease risk factors tobacco smoking, alcohol, physical activity, body mass and physical measurements, blood pressure, and lipid levels and evidence two chronic diseases ischaemic heart disease (IHD) and type II diabetes mellitus (T2DM) associated with these risk factors were collected.

Standardized Incidence Ratio(SIR) were calculated from Australian population data from NHS and AusDiab studies by age and gender and presented as percentages (SIR%).

Results: Data was analysed from 591 individuals, 321(54%) males, attending the most recent LTFU clinic enrolled in the VaHSS between May 2008 and February 2019.

Median age at clinic was 48 years, at alloHSCT 40 year, 61% underwent myeloablative conditioning, 55% sibling donor and the most common indication for alloHSCT was acute leukaemia (52%).

The table summarises ISR% for IHD, T2DM and their risk factors.

Compared to Australian population the VAHSS cohort for both males and females had significantly higher incidence of IHD and T2DM in females.

The chronic disease risk factors hypertension, dyslipidaemia and metabolic syndrome were significantly higher in both genders in the VaHSS cohort compared to Australian population data.

		Male			Female		
		SIR%	95%CI	p	SIR%	95%CI	p
Disease	IHD	263.6,	186.4 – 331.4	<0.0001	222.2	102.9,341.5	0.04
	T2DM	122.1	81.9-162.3	0.3	173.2	125.3, 221.14	0.002
Modifiable risk factors	hypertension	534.5	499.0, 570.0	<0.0001	550.7	507.4, 594.0	<0.001
	dyslipidaemia	928.7	881.2, 976.2	<0.0001	1156.0	1090.3, 121.7	<0.001
	Metabolic syndrome	125.6	106, 145.3	0.01	149.3	129.9, 170.8	<0.001
	BMI > 25	60.7	48.2,73.3	<0.0001	90.3	75, 105.6	0.2
	Increase waist measurement (>94cm men, >80cm women	80	65.7,94.2	0.006	97	83, 114	0.7
Behavioural risk factors	smoking	33.4	4.1-62.6	<0.001	49.6	11.3, 87.9	0.01
	Meets recommended physical activity guidelines	163.8	141.5,186.2	<0.001	157.9	131.2, 184.7	< 0.001

The rate of prescribed antihypertensive medication was 30.4% in males and 18.6% females whilst the crude rate of hypertension in the VaHSS cohort was 50.8% and 49.2% respectively.

The rate of prescribed lipid lowering medication was 16.7% in males and 18.3% females whilst the crude rate of dyslipidaemia in the VaHSS cohort was 49.2% and 38.1% respectively.

In males there was a significantly lower incidence of BMI >25 and waist measurement greater than 90cm in the VaHSS cohort, females were equivalent to the Australian population on these measures.

Males and females in the VaHSS cohort had significantly lower rates of smoking and significantly higher rates of recommended levels of exercise compared to the Australian cohort.

Conclusions: Increased rates of chronic disease and sub optimally managed modifiable risk factors were identified in the VaHSS cohort. High rates of positive health behaviours indicate this is a group of individuals motivated to achieve optimal health outcomes. They should be supported by strong population specific public health programs that enhance long term follow up programs.

Disclosure: no conflict of interest

15 - Non-infectious Late Effects, Quality of Life and Fertility

O151

PERSONALIZED NUTRITIONAL MANAGEMENT AND NUTRITIONAL SUPPORT AFTER ALLOGENEIC STEM CELL TRANSPLANTATION SIGNIFICANTLY DECREASE MALNUTRITION AND IMPROVE QUALITY OF LIFE: RESULTS OF THE ALLONUT TRIAL

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Background: Malnutrition significantly increases the risk of non-relapse mortality after allogeneic stem cell transplantation (aHSCT).[1] Despite these concerning data, only few clinical trials have tackled the essential question of nutritional management and support following aHSCT, with most studies focusing on the impact of nutritional support during the early phase of transplantation. We report here the first results of the ALLONUT clinical trial (*ClinicalTrials.gov Identifier*: NCT03829072) designed to improve the nutritional outcome of patients receiving aHSCT.

Methods: The ALLONUT trial is a prospective phase 2 clinical trial assessing the efficacy of a close tailored nutritional support and management with traditional (enteral and parenteral nutrition) and original solutions (cooking classes) to improve patients nutritional status following aHSCT. All patients were to follow a personalized nutrition program, that included visits with a board-certified dietitian who performed a nutritional status evaluation and implemented corrective measures to prevent and treat malnutrition. All patients were given cooking classes by a one-star Michelin chef with recipes following the cooking guidelines for transplanted patients' food. The primary endpoint was the severe malnutrition rate at day 100. Malnutrition was diagnosed using the French nutrition evaluation recommendations.[4] Severe malnutrition diagnosis was based on the decrease of the Body mass index and the severity was based on the albumin level. Secondary endpoints included severe malnutrition incidence at day 0, 30, and 360, albumin and transthyretin (TTR) levels, the Subjective Global Assessment (SGA) score, the Simple Evaluation of Food Intake (SEFI) score, and the QLQ-C30 score to assess the Quality of life.

Results: The study enrolled 70 consecutive patients who received an aHSCT at Nice University Hospital. The patients' characteristics are displayed in Table 1. All patients completed the nutritional assessment visits and the cooking classes. At the time of admission for transplantation, 10% of the patients presented with a moderate or severe malnutrition. The proportion of patients suffering from severe malnutrition reached 26.9% at day 30. The patients' nutritional status started to improve from there with the cooking classes and the outpatient personalized nutrition program. At day 100 after transplantation 23 % were still experiencing malnutrition while only 10.8 % of them meet the severe malnutrition criteria at one year after aHSCT. Regarding the secondary endpoints, with a median follow up of 12 months the median overall survival was not reached in our cohort. Albumin and TTR levels were at the lowest point at day 0, and were back to normal at day 100The QLQ-C30 calculation revealed that the quality of life decreased after transplantation and was the lowest at day 30, after what it slowly corrected to meet the pre-transplant level at day 100 before exceeding it at day 360.

Table 1. Population characteristics

	***N* = 70**
Sex M/F	34/36
Median Age (range	55 (18–73)
Disease	
•AML	39 56.5%)
•CML	3 (4.3%)
•Lymphoma	9 (13%)
•Bone marrow failure	2 (2.8%)

	N = 70
•MDS/MPN	16 (23.1%)
HLA matching	
•Identical sibling	12 (17.3%)
•Unrelated 10/10	44 (63.7%)
•Mismatched unrelated	13 (18.8%)
Acute GVHD	
•Grade I	16 (23.1%)
•Grade II	21 (30.4%)
•Grade III	17 (24.6 %)
•Grade IV	10 (14.4%)
Chronic GVHD	33 (47.8%)
CMV status	
Positive	37 (53.6%)
negative	32 (46.3 %)
Median BMI (range)	23.9 (16–44.9)
Median SGA (range)	2 (0–22)
Median Albuminemia (range)	43 (28–54)
Median Préalbuminemia (range)	0.282 (0.165–0.499)
Median Handsgrip (range)	30 (14–54)
Median brachial circonference (range)	30 (21–40)
Median EVA appetit (range)	10 (2–10)

Conclusions: The results of our trial confirmed that despite most transplanted patients suffering from moderate or severe malnutrition following transplantation, a close and personalized nutrition program combining standard and original measures led to the correction of both nutritional status and quality of life.

Clinical Trial Registry: NCT03829072

Disclosure: Nothing to declare

15 - Non-infectious Late Effects, Quality of Life and Fertility

O152

ALTERATIONS OF SERUM CYTOKINES IN RESPONSE TO PHYSICAL TRAINING PROGRAMME IN ADULT PATIENTS POST BLOOD AND MARROW TRANSPLANT (BMT)

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Background: It is well recognized that post-BMT patients (pBp) suffer from significantly higher chronic disorders and reduced quality of life (QoL). Physical training especially regular, moderate-to-high intensity activities has been shown to be effective non-pharmacological interventions in reducing some of these post-transplant complications. Studies on alterations in cytokines and growth factors (GFs) in response to physical training that have been postulated to underlie their beneficial effects in cancer patients especially in pBp are sparse. The aim of this study is to assess the changes in serum cytokines and GFs in pBp who are >6 months post-transplant. The hypothesis is that regular moderate-to-high intensity activities in pBp may lead to beneficial changes in serum cytokines (biomarkers and drivers of inflammation, tissue repair/regeneration and cancer) resulting in improved health outcomes.

Methods: Fifty-one pBp enrolled in a multi-centre trial (registered on the ANZCTR (ACTRN12615000570583) who completed their exercise practice log and provided blood samples at baseline and at various time points over 12 months were included in this study. Sera were frozen and thawed on the day of the cytokine assays. A total of 27 cytokines including GFs were quantified using 4 panels of Millipore magnetic bead multiplex assays (Cat # HCYTOMAG-60K, Cat# HMYOMAG-56K, Cat# HNDG3MAG-36K, Cat # HIGFMAG-52K) per our recent report (Hendrawan K et al 2022). The repeated measure correlation method was used to explore the intra-individual association between objective physical functional measures including sit-to-stand (STS), hand-grip-strength (HGS) and 6-minute walk-test (6-MWT), and the cytokine concentrations across multiple time points (baseline and follow-up). Log transformation was applied where appropriate. The significance level of 0.01 was used for specific contrasts of primary and secondary outcomes and the exploration of serum cytokines, due to the type I error inflation from multiple testing.

Results: Six cytokines were found to significantly correlate with objective physical measures. sICAM-1 (biomarker of vascular inflammation and atherosclerosis) negatively correlated with STS ($r = -0.47$, $p = 5.4 \times 10^{-6}$). IGF-2 (mitogenic and anti-apoptotic factor and a possible neuro-protective protein/memory enhancer) negatively correlated with STS ($r = -0.45$, $p = 6.5 \times 10^{-5}$) and 6-MWT ($r = -0.33$, $p = 4.5 \times 10^{-3}$). Oncostatin M (tumour growth inhibitor) positively correlated with STS ($r = 0.32$, $p = 2.9 \times 10^{-3}$) and HGS ($r = 0.27$, $p = 0.01$). IL-8 (pro-inflammatory) positively correlated with STS ($r = 0.42$, $p = 6.2 \times 10^{-5}$) and, Osteonectin (pro-fibrosis) negatively correlated with HGS ($r = -0.31$, $p = 3.5 \times 10^{-3}$).

Conclusions: STS and HGS performances decrease with increasing age in both men and women with low HGS, for example, being a predictor of increased mortality from cardiovascular disease and cancer in men. The observed correlation of sICAM-1, IGF-2 and Oncostatin M with regular exercise may provide biological mechanisms on how regular moderate intensity exercise may have long-term benefit on cardiovascular, pulmonary and metabolic diseases and cancer in HCT survivors. Reduced Osteonectin may decrease the risk of fibrosis associated with graft versus host disease. Increased IL-8 level may promote anti-tumour T cells. However, the anti-cancer role of IL-8 and Osteonectin remains controversial. To our knowledge, this study is the first report to provide evidence to support the role of cytokines in response to the benefit of regular physical training.

Clinical Trial Registry: ANZCTR (ACTRN12615000570583)

Disclosure: Nothing to declare

15 - Non-infectious Late Effects, Quality of Life and Fertility

O153

A PARTIALLY SUPERVISED EXERCISE PROGRAM FOLLOWING ALLOGENEIC STEM CELL TRANSPLANT IMPROVES EARLY POST-TRANSPLANT QUALITY OF LIFE AND PHYSICAL

136

FUNCTIONING: RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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Background: Exercise may be one supportive care intervention that can improve quality of life (QoL), physical functioning and other health-related outcomes in allogeneic stem-cell transplant (alloHSCT) survivors.

Methods: From 2016-2021, we conducted a 1:1 randomized controlled trial to investigate whether a partially-supervised progressive exercise intervention in alloHSCT patients improved change in EORTC-QLQ-C30 global health-related QoL (HRQoL) score from baseline to Day (D) 100 compared to an unsupervised self-directed exercise program. Outcomes were assessed at baseline, D60, and D100. Multivariable linear regression models were conducted to adjust for confounders, including transplant age, sex, disease (acute leukemia or other) and baseline global QoL score.

Results: Of 245 consecutive alloHSCT patients assessed for eligibility, 121 (49%) were enrolled (74 inclusion criteria not met; 48 declined; 2 withdrew consent). 108 were randomized (9 HSCT cancelled, 4 excluded for co-morbidities) with 54 patients/arm. Baseline characteristics were not significantly different between groups except for an increased diagnosis of acute leukemia in the control group (54% vs 22%, p = 0.001). Overall, there was no significant difference in global HRQoL score at baseline, D60, or D100 between intervention and control groups (p = 0.83). There was a trend towards improvement at D60 ($p = 0.06$), which then leveled by D100 (Fig.1). There was no significant difference in change in global HRQoL score from baseline to D100 when comparing groups, after adjusting for confounders (score change:-2.04 [95% CI:−9.29–5.21], p = 0.58). Similar patterns were observed for the EORTC QLQ-C30 functional subscales.

There was a significant decline in global QoL score from baseline to D60 in the control group (-6.17 [95%CI:12.36-0.01], p = 0.05), which was not observed in the intervention group ($p = 0.48$). In addition, there was a significant improvement in score from discharge to D60 in the intervention group (8.69 [95%CI:3.44-13.94], p<0.01) which was not observed in the control group (p = 0.38). This same trend of improvement in global HRQoL from discharge to D60 in the intervention but not control group was seen for physical functioning (p<0.01) and role functioning (p = 0.03). Symptom subscales including nausea/vomiting (p = 0.02) and appetite loss (p = 0.04) showed significant improvement at D60, and constipation improved from baseline to D100 in the intervention group (p = 0.02). Muscle strength, measured as grip strength (p = 0.04) and 30-second chair stand (p = 0.03), improved at D60 and D100 respectively (Table 1).

In the intervention arm, attendance for aerobic supervised and unsupervised sessions was 62% and 85%, respectively, and for resistance sessions, 71% and 72% respectively. Attendance of supervised sessions decreased over time, with overall attendance 84% pre-alloHSCT, 67% weeks 1-3, 66% weeks 4-9 (D60), and 52% weeks 10-15 (D100). Patient reported symptoms and logistics, including patients returning home in the late post-HSCT period, were the most common reasons for non-attendance.

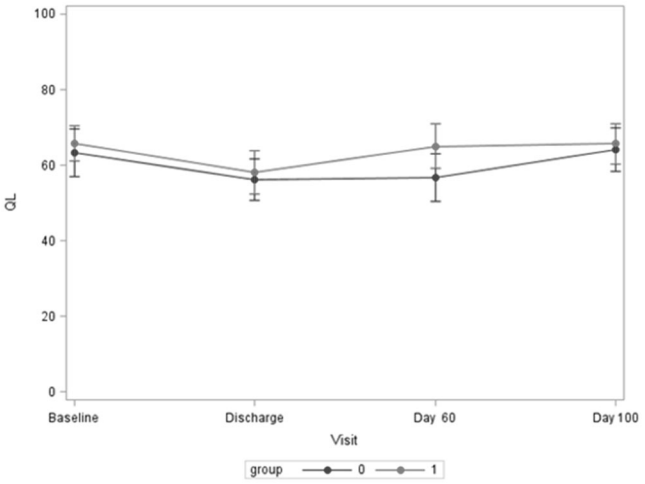

Table 1.

Measurement	D/C	D60	D100
30-sec chair stand[1]	1.09 [0.92, 1.28], p = .32	1.07 [0.91, 13.25], p = .41	**1.18 [1.02, 1.36], p = .03**
Grip strength – L[2]	1.46 [-0.52, 3.44], p = .15	**2.19 [0.09, 4.30], p = .04**	1.88 [-0.58, 4.34], p = .13
Timed up and go[2]	-0.10 [-0.78, 0.58] p = .77	-0.30 [-0.77, 0.17] p = .21	-0.36 [-0.86, 0.14], p = .15
6MWT[2]	-8.26 [-48.16, 31.65], p = .68	1.75 [-33.51, 37], p = .92	3.42 [-34.36, 41.20], p = .86

Adjusted estimates: adjusted for age at transplant, gender, disease (acute leukemia vs other) and baseline score.
[1]Estimated by generalized linear mixed effect Poisson model; estimates shown are rate ratios (intervention vs control).
[2]Estimated by linear mixed effect model; estimates shown are differences (intervention – control).

Conclusions: Results of this randomized-controlled trial of a partially supervised exercise program post-alloHSCT demonstrate early improvements in global HRQoL, physical functioning, and symptoms at D60, which were not maintained at D100. Adherence to the intervention decreased over time. Future efforts should focus on approaches to optimize delivery methods and adherence to exercise interventions in the post-alloHSCT period to sustain improvements in outcomes.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT02900768

Disclosure: The authors have no relevant conflicts of interest to disclose.

15 - Non-infectious Late Effects, Quality of Life and Fertility

O154

PATIENTS REPORTED OUTCOMES (PROS) IN ROUTINE PRACTICE SUPPORT THE IMPACT OF GVHD ON LONG-TERM WORSENING OF QUALITY OF LIFE: ANALYSIS ON 105 PROSPECTIVE PATIENTS

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is a standard for the cure of several hematological diseases. Improvement of overall survival has been a major achievement. Unfortunately, graft-versus-host disease (GvHD) still represents the main complication affecting HSCT, increasing transplant related mortality and worsening quality of life (QoL). While mortality and morbidity impact of GvHD are well recognized, the impact on QoL is still poorly characterized. The collection of patients reported outcomes (PROs) in routine practice is limited. The most common PRO measures used are the Lee chronic GvHD (cGvHD) symptom scale, the FACT-BMT and the NIH Form B.

We aimed to analyze the perception of QoL in long-term survivors after HSCT according to the FACT-BMT scale, in particular we aimed to quantify the detrimental impact of GvHD beside signs of clinical activity.

Methods: Our analysis consisted of a prospective single-centre study among long-term survivors treated with HSCT between January 2004 and December 2020 at our Institute. Data were censored December 1st, 2022. The follow-up was performed according with our comprehensive Long Term Follow Up institutional program.

Required inclusion criteria were follow-up >/= 2 years post HSCT, disease complete remission, complete information about GvHD, second solid cancer, infectious complications.

The FACT-BMT questionnaire was administered as a paper questionnaire. A written consent was given in accordance with the Declaration of Helsinki.

Results: Overall, 105 patients alive and in complete remission at last follow-up completed the questionnaire. Forty-four patients were female, 61 male. According to age, 23 patients were between 20 and 40-year at time of questionnaire, 35 between 40 and 60-years, while 47 were over 60. According to donor source, 3 patients received a cord blood transplant, 30 a mismatch related transplant, 22 a match related and 50 a match unrelated transplant. All the patients interviewed through the paper questionnaire at the moment of the follow-up visit, agreed to fill the questionnaire. PROs analysis confirmed a better perception of QoL for patients that did not experience cGvHD. No difference emerged according to donor source. At increasing age, patients reported an increased concern about work (p 0.0178). Female patients reported less satisfaction about the appearance of their body (p 0.02).

Of note, patients who experienced cGvHD showed worst functional well-being (p <0.0001) and worst physical well-being due to side effects (p <0.0001). Overall, among patients without cGvHD, other HSCT-related side effects were not perceived worse than they had imagined, while among those experiencing cGvHD, most patients complained about this perception (p 0.0023). Among patients with GvHD, patients still under immunosuppressive therapy reported less satisfaction about the appearance of their body (p 0.0319).

Conclusions: QoL in patients cured by HSCT is still far from being satisfactory, most of all among patients with history of cGvHD, irrespective of activity. Dedicated counselling and support to address QoL is a relevant unmet medical need. Systematic evaluation of PROs in standard practice will optimize the care of HSCT survivors, potentially enhancing patient-provider communication and allowing the development of measure for both prevention and treatment of GvHD.

Disclosure: Nothing to declare

18 - Paediatric Issues

O155

LOW TOXICITY WITH MYELOABLATIVE CHEMO-BASED CONDITIONING FOR CHILDREN WITH ALL BELOW 4 YEARS OF AGE. RESULTS FROM THE PROSPECTIVE MULTINATIONAL FORUM-TRIAL

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Background: Relapse and non-relapse mortality (NRM) are the major causes of treatment failure in infants and young children with high-risk ALL undergoing HSCT. The optimal chemotherapeutic approach aiming improved EFS and low NRM is not yet defined.

Methods: The prospective FORUM trial used two myeloablative chemo-conditioning regimens for children below 4 years of age: fludarabine (FLU), thiotepa (THIO) and either intravenous busulfan (BU) or treosulfan (TREO) (Peters et al., JCO 2021). This report includes 194/202 from 26 countries enrolled in FORUM. Median age at HSCT was 2.2 yrs.Stem cell source was BM in 132 (68%) pts, PBSC in 37 (19%), and UMCB in 24 (13%). Donors were HLA-matched siblings (MSD) in 39 (20%) pts and 9 or 10/10 HLA allele-matched UD in 155 (80%) pts. Clonal genetic abnormalities included 9 pts with BCR-ABL, 13 pts with TEL-AML, and 53 pts with KMT2A r-rearrangements; all pts underwent HSCT in complete morphological remission (CR) (142 pts CR1; 50 pts CR2, 2 pts CR3). FLU/THIO/BU and FLU/THIO/TREO were used in 101, and 93 HSCTs, respectively. GvHD-prophylaxis was Cyclosporin-A-based in 90%; recipients of MUD-grafts also received ATG (Grafalon or ATG Thymo, respectively) and methotrexate.

Results: At data cut-off, median follow-up was 3 yrs (range, 3 months – 7.2 yrs).3-yrs OS was 0.69±0.04, 3-yrs EFS was 0.52±0.04; 3-yrs CIR was 0.44 + 0.04, and 3-yrs NRM was 0.05 ± 0.02. OS and EFS did not differ between pts below 2 and 2-4 yrs of age at HSCT. Pts transplanted in CR 1 had significantly better EFS (0.58±0.04) as compared to >CR-pts (0.36±0.07, p = 0.01); due to a higher CIR. OS was worse for the 53 pts with KMT2A-

rearrangements (3-yrs OS 0.56±0.08 vs. 0.73±0.04, p = 0.040). EFS for pts below 1 yr of age at diagnosis was significantly inferior as compared to older pts (3-yrs EFS 0.40±0.05 vs. 0.63±0.05, p = 0.002). At 3-yrs, OS was 0.63±0.05 and 0.76±0.05; EFS was 0.52±0.05 and 0.51±0.06 (p = 0.794) for the FLU/THIO/BU and FLU/THIO/TREO-group, respectively (p = 0.075). However, pts who relapsed post-HSCT had a better 3-yr post-relapse OS after FLU/THIO/TREO compared to FLU/THIO/BU (0.38±0.11; 0.16±0.07. p = 0.012) respectively. 3-yrs cGVHD/relapse-free survival for FLU/THIO/BU was 0.44±0.05 and for FLU/THIO/TREO 0.41±0.06 (p = 0.943). In multivariate analysis, remission > CR1 and KMT2A, negatively influence OS while EFS was worse for patients who underwent HSCT > CR1 or had ALL-diagnosis below 1 yr of age. Donor type, stem cell source, age between 1 and 4 yrs at HSCT, conditioning regimen, and PCR-MRD positivity pre-HSCT did not significantly influence outcome. 1-yr TRM was low for both conditioning regimens (0.06±0.02 for FLU/THIO/BU and 0.03±0.02 after FLU/THIO/TREO.

Conclusions: Within the FORUM-trial, infants and young children receiving HSCT after conditioning with either BU- or TREO containing regimens have a lower OS and EFS as compared to children above the age of 4 yrs due to a higher CIR. Because of decreased NRM, these results represent an improvement as compared to previously reported series; however, KMT2A-rearrangement continues to be an obstacle to successful HSCT.

Clinical Trial Registry: EudraCT No. 2012-003032-22
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18 - Paediatric Issues

O156

THE IMPACT OF PRE-TRANSPLANT EXTRAMEDULLARY DISEASE ON THE OUTCOME OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA IN CHILDREN - ON BEHALF OF PDWP/EBMT

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Background: Extramedullary disease (EMD) is a rare presentation in Acute Myeloid Leukemia (AML). We studied the effect of EMD (CNS involvement only and other EMD ± CNS) compared to isolated BM involvement in the outcomes following hematopoietic stem cell transplantation for AML in children.

Methods: An EBMT registry-based retrospective study to assess the impact of extramedullary disease (EMD) in children (de novo AML, age <18y at transplant, period 2008-2016) with AML who underwent a first allogeneic hematopoietic cell transplant (allo-HCT) with non-TBI conditioning regimen. Outcomes of interest included: leukemia-free survival (LFS), overall survival (OS), relapse incidence (RI) and non-relapse mortality (NRM). Patients were grouped into three categories: BM involvement only (Group A), BM + CNS involvement only (Group B) and BM+ other EMD ± CNS (Group C). Patients with Down syndrome related AML and t(15:17) AML were excluded.

Results: A total of 958 (529 males) patients met study criteria, including 685 (71.5%) Group A, 135 (14.1%) Group B and 138 (14.4%) Group C patients. Group C patients were transplanted at a younger age (median age at transplant 4.8y vs 9.2y and 6.6y for Group A, B respectively, p <0.001). A higher proportion of Group A patients were in CR1 (70.8%) compared to Group B (63.7%) and C (60.1%) patients. The three groups were comparable regarding the distribution of standard and high risk cytogenetics. Fifty seven percent of the patients received an

unrelated donor and 35% a matched sibling/family donor. The median post HCT follow-up was 5.4 years (IQR: 5.2-5.7y). Five years LFS, OS, RI and NRM were 62%, 68.4%, 26.4% and 11.6%, respectively in the entire cohort. Multivariate analysis showed higher RI in Group C compared to Group A (HR = 1.45 (1.01-2.06) p = 0.04) and a non-significantly different NRM (HR: 0.61 (0.29-1.29), p = 0.2). There was no difference in RI in Group B compared to Group A (Hazard Ratio (HR) : 1.12 (0.76-1.64). In the multivariate analysis patients with EMD (CNS only or EMD + /- CNS) had no significant difference in LFS, OS and NRM. The Hazard ratio of LFS, OS and NRM for Group B and C compared to Group A was: HR = 1.13, p = 0.46; HR = 0.96, p = 0.82; HR = 1.09, p = 0.76 and HR = 1.19, p = 0.28; HR = 0.96, p = 0.82; HR = 0.61, p = 0.2, respectively.Further 116 patients underwent hematopoietic stem cell transplantation with active disease. Eighty-nine patients had BM involvement only (group A), 12 patients had BM and CNS disease (Group B) and 15 patients had BM and other sites of EMD + /- CNS (Group C). In this cohort, the 4y-OS was 37% in Group A, 25% in Group B of and 38% in Group C. Four-year LFS was 31%, 25% and 39% in Group A, Groups B and Group C respectively.

Conclusions: Our findings suggest that children with AML and BM with EMD ± CNS involvement (group C) have a higher incidence of relapse after HCT compared to those with BM only or BM + CNS only disease. However, the presence of EMD with CNS involvement or other extramedullary disease did not have a statistically significant impact on overall survival, leukemia-free survival or non-relapse mortality.

Disclosure: Nothing to declare

18 - Paediatric Issues

O157

OFF-LABEL USE OF LETERMOVIR FOR CMV PROPHYLAXIS IN VERY HIGH-RISK PEDIATRIC HSCT RECIPIENTS

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Background: CMV infection is the leading viral cause of morbidity and mortality among HSCT recipients, in particular in patients with primary immunodeficiencies (PIDs). Letermovir was shown to be well tolerated and highly efficient to prevent CMV reactivation in adult CMV-seropositive HSCT recipients (R +). Published data about letermovir use in children under the age of 12 years are scarce.

Methods: Since Nov 2020, off-label use of letermovir was started in Necker children Hospital in pediatric HSCT recipients with high-risk of CMV infection/disease defined as i) group 1: recipients having experienced CMV viremia within 3 weeks before HCST regardless on donor compatibility ii) group 2: R+ or D + R- in transplant with MMRD or MUD. In group 2, letermovir was initiated no later than on D0. In all cases, CMV PCR in blood was negative at the time of letermovir initiation. The dose in mg was BSAx240/1.73 in patients with Ciclosporin comedication, or BSAx480/1.73 without.

Between Nov 2020 and Aug 2022, letermovir was initiated in 27 patients, recipients of 32 transplants, at a median age of 4 years (range: 0.25-16), with notably 10 patients below the age of 1. HSCT indications were mostly PIDs in 24 patients (SCID (3), CID (9), HLH (4), defect of phagocyte (7), agammaglobulinemia (1)) hemoglobinopathy (2), and osteopetrosis (1). There were 20 transplants from MMRD, 5 MUD, 2 MMUD and 5 from HLA-identical intra-familial donors. Conditioning regimen was myeloablative in all with serotherapy. 12 patients in group 1 had received a curative treatment before letermovir was started. CMV PCR was performed in whole blood weekly until M3 then every 2 other weeks until M6. Failure of prophylaxis was defined as positive blood CMV PCR requiring curative treatment based on clinician judgment. Letermovir was stopped based on immune reconstitution data.

Results: Letermovir was initiated at D0 of HSCT (median, range: D-37-D + 34). The tolerance was good with only 1 premature stop due to iterative vomiting. Among the 32 HSCT, 5 prophylaxis failures were noticed (16%). CMV reactivations occurred at a median of 7 days (range: 4-14) after HSCT, the highest PCR values were <3log copies/mL in 2 patients and between 3 and 4log copies/mL in 3 occasions. Treatment with foscavir (n = 2) or ganciclovir *plus* foscavir (n = 3) was given for a median of 21 days (range: 7-64) followed by letermovir resume after CMV negativation. No emergence of resistance mutation was observed in children with virological failure. At last follow up, 3 patients are still under letermovir, 2 patients died of VOD and adenovirus disease while receiving letermovir and 22 patients stopped at D147 post-HSCT (median; range: 47-389) with 8 of them (33%) experiencing then transient untreated CMV replication. Median count of CD4 T-cells at withdrawal of letermovir was 269/ml (range: 8-1000).

Conclusions: Letermovir was safe and efficient in preventing CMV reactivation in high-risk PIDs recipients of HSCT, even in very young children. Criteria defining prophylaxis failure need to be better defined in order to avoid both unnecessary interruption of letermovir and selection of resistance-associated mutations. Therapeutic drug monitoring in children urgently need to be assessed.

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The others authors have no conflict of interest to declare.

10 - Stem Cell Donor

O158

HLA-DP PERMISSIVE MISMATCH SUBSETS CONFER REDUCED GVHD RISKS AND IMPROVED DISEASE CONTROL AFTER HCT FOR ACUTE LEUKEMIA AND MDS: A STUDY BY THE EBMT CTIWP

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Background: Permissive HLA-DPB1 mismatches defined by the T-cell epitope (TCE) model are an established criterion for selection of unrelated donors in allogeneic hematopoietic cell transplantation (alloHCT). We have recently demonstrated that frequent permissive mismatches can be stratified according to their immunopeptidome divergence into core vs non-core subgroups, which are differentially associated with alloHCT outcomes (Arrieta-Bolanos *et al. Blood* 2022). Here, we sought to refine the definition of these permissive subsets and explore how their directionality affects their impact on clinical outcomes in a large contemporary cohort of predominantly European transplants collected by the EBMT Cellular Therapy and Immunobiology Working Party.

Methods: HLA-DP matching status was scored in a cohort of 8420 adult patients who received a first alloHCT from a high-resolution 10/10-matched unrelated donor for AML, ALL, or MDS between 2005-2020. TCE group 3 (TCE3) permissive pairs (N = 3178) were stratified into core and non-core mismatched, and compared with allele-matched (N = 2390) and non-permissively mismatched (N = 2598) pairs. The original TCE3 core allele definition was compared to an extended model including alleles with 0-5 exon 2 amino acid differences with the 4 high-frequency core alleles (i.e., DPB1*02:01, 04:01, 04:02, 23:01). These models were tested in parallel to the standard TCE model considering permissive mismatches (N = 3432) as a whole, and including graft-versus-host (GvH) and host-versus-graft (HvG) directions to determine their association with transplant outcomes in multivariable regression models.

Results: Using the standard TCE model, we confirmed previous data that non-relapse mortality (NRM) risks were significantly increased for non-permissive (HR 1.3 [99% confidence interval: 1.0-1.5]; p = 0.0011) but not for permissive (HR 1.1 [0.9-1.3]; p = 0.08) HLA-DPB1 mismatches, compared to allele matches. Both permissive and non-permissive mismatches were associated with increased grades II-IV acute GvH disease (aGvHD) and lower relapse compared to allele matches, with stronger associations for the GvH non-permissive group. When permissive pairs were stratified into core and non-core mismatches, only non-core permissive pairs showed significantly increased risks of aGvHD (HR 1.4 [1.2-1.6]; p<0.0001) and reduced risks of relapse (HR 0.83 [0.71-0.97]; p = 0.0027) compared to allele-matched pairs. These associations were driven by non-core permissive mismatches in the GvH and not in the HvG direction. Importantly, none of the permissive subsets associated with significantly increased risks of NRM compared to the allele-matched pairs. This resulted in an advantageous relapse-free survival for non-core GvH mismatches compared to allele-matched pairs (HR 0.86[0.74-1.0]; p=0.0121).

Conclusions: Our results confirm the clinical relevance of the refined definition of core vs non-core HLA-DP permissive mismatches, and identify non-core permissive mismatches in the GvH direction as a subset associated with improved disease control. These findings highlight the potential for tailored permissive donor selection according to individualized clinical goals (e.g., reduction of relapse with non-core permissive mismatches vs reduction of aGvHD with core permissive mismatches) in alloHCT for acute leukemia and MDS.

Disclosure: Nothing to declare

10 - Stem Cell Donor

O159

OPTIMIZING HAPLOIDENTICAL DONOR SELECTION FOR PEDIATRIC HEMATOPOIETIC CELL TRANSPLANT

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Background: The selection of hematopoietic cell transplant (HCT) donors is integral to the HCT process as it correlates with complications and outcomes. In recent years, haploidentical donors, including mothers, fathers, siblings, aunts, uncles, and cousins, have been used increasingly. However, there is little data to help guide pediatric physicians in identifying the optimal haploidentical donor.

Methods: The Center for International Blood & Marrow Transplant Research database was used to assess our hypothesis that use of younger age or sibling donors would be associated with less acute (aGVHD) and chronic (cGVHD) graft-versus-host-disease (GVHD). Graft failure and relapse were evaluated, stratified by donor age or relationship, compared by Gray's Test for Equality. Two-year overall survival was determined using Kaplan-Meier curves, stratified by donor age or relationship, compared by log-rank testing. Multivariable analysis was performed using logistic regression for aGVHD and Cox regression for the remaining outcomes, adjusting for significant co-variates.

Results: 1069 patients ≤18yo received haploidentical HCT in the US from 2013-2019. Indication for transplant was malignancy in 58%. The majority received myeloablative conditioning (67%). GVHD prophylaxis was post-transplant Cyclophosphamide in 36% and ex-vivo T-cell depletion strategies in 57% (7% other).

Donors were stratified by age: <18 years ($n = 138$), 18-35y ($n = 440$), and >35y ($n = 491$). Frequency of Grade II-IV aGVHD at 100 days post-HCT was highest with older age donors: 31% for donors >35y, 23% for 18-35y, and 15% for <18y ($p < 0.001$). The cumulative incidence of cGVHD at 2 years was also higher with older age donors: 30% (95% CI 28-32%) with >35y donors, 26% (95% CI 23–29%), and 16% (95% CI 12–20%) with <18y donors ($p = 0.025$). Multivariable analysis confirmed increased risk of aGVHD (grade II-IV) with donors >35y compared to donors age 18-35y (OR 1.46, $p = 0.02$) and donors age <18y (OR 2.24, $p = 0.003$) and increased risk of cGVHD with donors >18y (18–35: HR 1.78, $p = 0.014$) (>35: HR 1.88, $p = 0.009$).

Donor relationship was analyzed as mother ($n = 382$, median age 36), father ($n = 386$, median age 39) and sibling ($n = 244$, median age 16) donors. Use of parental donors had an increased risk of aGVHD (II-IV) compared to sibling donors

(mother: OR 1.63, $p = 0.024$, father: OR 1.57, $p = 0.034$). The use of mothers had a significantly increased risk of cGVHD compared to both father and sibling donors (HR 2.33, $p = <0.001$). There were no differences in aGVHD (grade III-IV), relapse, or survival by donor age or donor relationship, however, graft failure was highest when donors were ≥18y (22% with 18–35y, 13% with >35y) compared to donors <18y (10%, $p = 0.0013$).

Conclusions: Our data shows GVHD outcomes are correlated with haploidentical donor selection – use of donors <18y has decreased incidence of aGHVD, cGVHD, and graft failure. The use of a sibling donor confers a lower risk for acute GVHD while the use of a maternal donor increases risk of chronic GVHD. For pediatric patients receiving haploidentical HCT, the use of sibling donors should be considered to decrease the risk of acute and chronic GVHD.

Disclosure: Nothing to declare.

10 - Stem Cell Donor

O160

COMPARABLE OUTCOMES FOLLOWING NON-FIRST-DEGREE AND FIRST-DEGREE RELATED DONOR HAPLO-HCT FOR ACUTE LEUKEMIA PATIENTS IN CR: A STUDY FROM THE GLOBAL COMMITTEE AND ALWP OF EBMT

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Background: Non-first-degree (NFD) related donors can be considered as alternatives for first-degree (FD) related donors in haploidentical hematopoietic cell transplantation (haplo-HCT), but the efficacy of these transplants remains uncertain. We therefore compared the outcomes of NFD and FD related haplo-HCTs for acute leukemia patients in complete remission (CR).

Methods: We retrospectively analyzed 2703 acute myeloid leukemia (AML: n = 2047) and acute lymphoblastic leukemia (ALL: n = 656) patients in CR who received a haplo-HCT from 2010-2021 in 177 EBMT centers participating in the study. Exact matching and propensity score (PS) matching was used for pair-matching. The following variables were used for exact matching: diagnosis, status at transplant, patient age per 5 years, GVHD prophylaxis. The propensity score was based on patient sex and conditioning intensity. The NFD-to-FD ratio was 1:3, but patients with only 1 or 2 controls were included in the analysis.

Results: One hundred and twenty-three NFD were matched with 324 FD. The patients were well matched with standardized mean difference estimates of less than 5% for all matched parameters. Myeloablative conditioning was used in 65% and 69% of FD and NFD patients, respectively. The source of stem cells was peripheral blood (PB) alone in 46% and 68%, respectively. Both cohorts reached good engraftment rates (FD: 95.6% vs. NFD: 96.7%, p = 0.78). The 180-day cumulative incidence (CI) of grade II-IV acute graft-versus-host disease (GVHD) (FD: 29.1% vs. NFD: 24%, p = 0.31), and the 2-year CI of extensive chronic GVHD (FD: 9.9% vs. NFD: 15.3%, p = 0.2) were comparable between the two cohorts. No differences were observed between the two cohorts in 2-year CIs of relapse (FD: 22.6% vs. NFD: 22.1%, p = 0.84) and non-relapse mortality (NRM) (FD: 17.7% vs. NFD: 13.2%, p = 0.33). The 2-year probabilities of overall survival (OS) (FD: 68.3% vs. NFD: 71.8%, p = 0.56), leukemia-free survival (LFS) (FD: 59.7% vs. NFD: 65.7%, p = 0.6), and GVHD-free, relapse-free survival (GRFS) (FD: 47.8% vs. NFD: 50.9%, p = 0.69) were similar between the two cohorts (Table 1). The three major causes of death in FD and NFD were relapse (41% and 46%), GVHD (13% and 29%), and infection (30% and 15%), respectively.

Conclusions: No significant differences were observed in outcomes following haplo-HCT using NFD or FD donors in this retrospective matched-pair analysis. Our findings support the consideration of NFD donors for haplo-HCT when there is no available FD donor. If both donor types are available, an additional question may be to identify other important factors such as donor age and cytomegalovirus (CMV) status where the NFD donor might be a better choice than a FD donor.

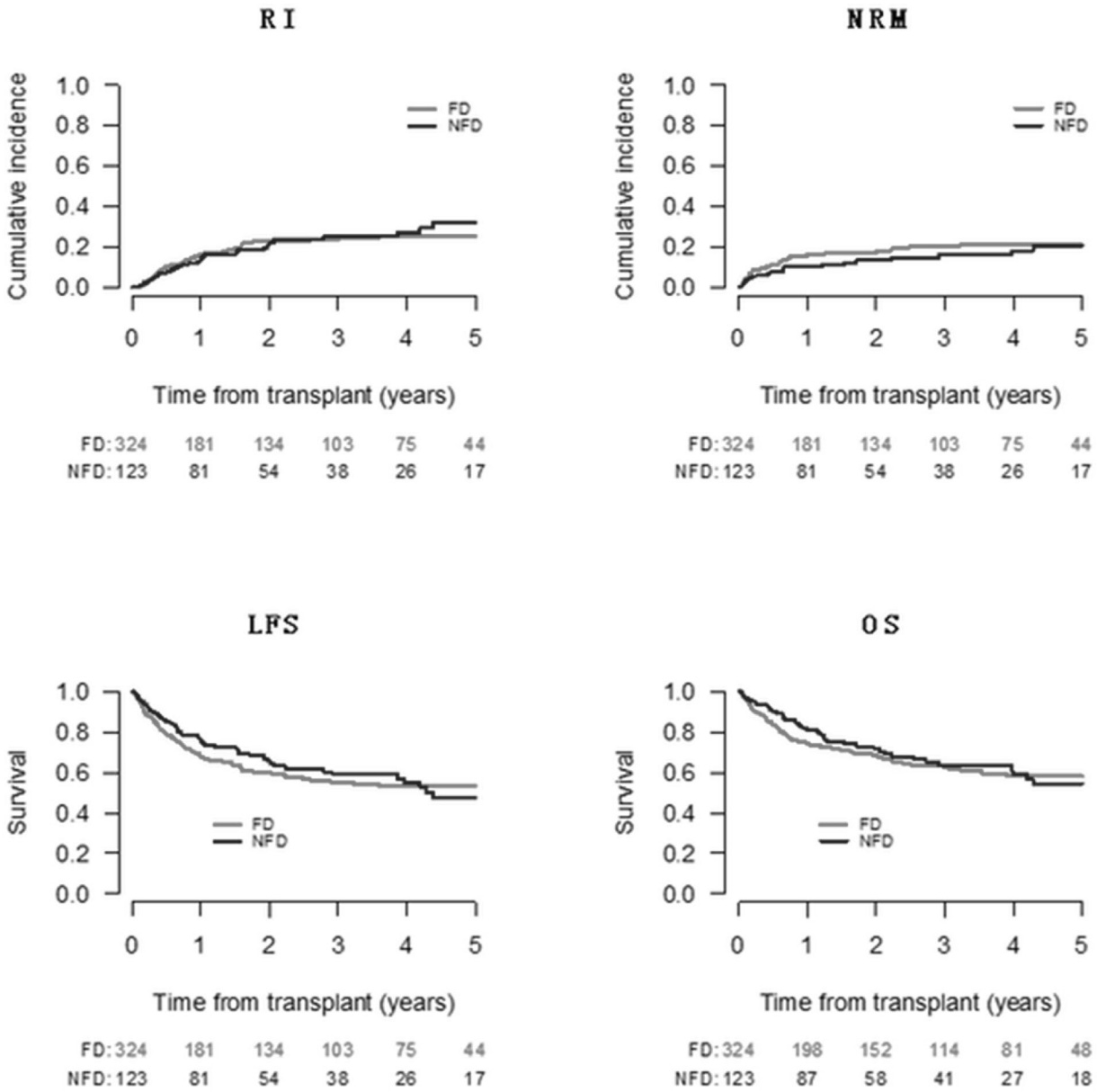
Disclosure: Nothing to declare.

Table 1. Outcomes post haplo-HCT with FD and NFD donors. Matched-pair analysis.

	2 years	180 days						2 years	
	Relapse	NRM	LFS	OS	GRFS	Acute GVHD II-IV	Acute GVHD III-IV	chronic GVHD	ext. chronic GVHD
FD	22.6%[17.8-27.7]	17.7% [13.5-22.3]	59.7%[53.7-65.3]	68.3%[62.5-73.5]	47.8%[41.8-53.6]	29.1%[24-34.4]	9.1%[6.2-12.7]	31%[25.6-36.6]	9.9%[6.6-13.9]
NFD	21.1%[13.9-29.3]	13.2% [7.7-20.2]	65.7%[55.9-73.9]	71.8%[62.3-79.4]	50.9%[41-60]	24%[16.8-31.9]	10.7%[6-17]	38.9%[29.4-48.3]	15.3%[9.1-22.9]
HR (95% CI)	1.04 (0.69-1.58)	0.77 (0.45-1.31)	0.92 (0.66-1.27)	0.9 (0.63-1.28)	0.95 (0.72-1.25)	0.8 (0.52-1.23)	1.28 (0.68-2.4)	1.17 (0.81-1.69)	1.44 (0.82-2.52)
p value	0.84	0.33	0.6	0.56	0.69	0.31	0.44	0.41	0.2

Abbreviations: NRM, non-relapse mortality; LFS, leukemia-free survival; OS, overall survival; GRFS, GVHD-free, relapse-free survival;

Figure 1: Outcomes following haplo-HCT with an FD or an NFD donor



Disclosure: Nothing to declare.

10 - Stem Cell Donor

O161

SERIOUS ADVERSE EVENTS OR REACTIONS IN RELATED DONORS AFTER HPC DONATION. A REPORT FROM THE EBMT DONOR OUTCOME REGISTRY

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Background: In 2013, the Donor Outcome Registry was added to the ProMISe database of the EBMT.

Methods: The intention is to collect data on the haematopoietic progenitor cell (HPC) collection procedure itself (i.e., comprising the period from start of bone marrow (BM) collection or first G-CSF injection for peripheral blood (PB) HPC collection until day 30) as well as on long term follow-up after 1 year, 2 years followed by biannual reports until 10 years post-donation (minimum after 5 and 10 years). The main aim of the registry is to collect data on severe adverse events or reactions (SAER) due to the donation process. Both related and unrelated donor data can be registered. Here, we report the data from registered related donors.

Results: Since the opening of the EBMT Donor Outcome Registry in 2013, 4114 related donors (HLA identical siblings n = 3033, syngeneic n = 23, matched other relative n = 100, partially matched relative n = 958) have been registered from 78 centers in 25 countries. Donors comprised of 1118 BM and 2990 PB donors (unknown n = 6). For HPC mobilization prior to apheresis, both filgrastim and lenograstim originals and biosimilars were frequently used. Use of cell binding inhibitors (e.g., plerixafor) was reported in 66/2990 (2.2%) PB donors. SAEs associated with the donation procedure were reported in 23/3690 (0.6%) donors, whereas data are unknown in 14 and not reported in 567 donors. These SAEs occurred in 11 HLA identical siblings and 12 partially matched relatives. SAEs included (amongst others) haemothorax (n = 2), autoimmune thyroiditis (n = 1), thrombophlebitis (n = 1), hypertension (n = 3), malignant hyperthermia (n = 1). After donation, donors were also asked if they would donate again. Responses are available for 1486 (36%) donors showing that 1368 (92%) would donate again, whereas 118 (7.9%) would refuse to donate another time. In total, 6930 follow up records were reported. Of them, 4039 records relate to the period 1 year or later including information on long term outcome of 1940 donors. During long term follow up (i.e., 1 year to 10 years), 9 haematological malignancies (Hodgkin's disease n = 1, multiple myeloma n = 1, chronic myeloid leukemia n = 3, myeloid sarcoma n = 1, acute promyelocytic leukemia n = 1, not defined n = 2), 9 non-haematological malignancies (cancer of the prostate n = 4, ovary =1, bladder n = 1, not defined n = 3), and 8 autoimmune diseases (ulcerative colitis n = 1, rheumatoid arthritis n = 2, ankylosing spondylitis n = 1, not defined n = 4) have been reported. This seems not increased compared to the general population.

Conclusions: The EBMT donor outcome database represents a unique platform to analyze the outcome of a large number of donors on short and long-term encompassing a remarkable number of countries. Overall, donor outcome of related donors is still extremely underreported. However, these data showing 0.6% SAE rate are nevertheless reassuring and comparable to unrelated donor studies. For the future it would be important to gather data on donors who are younger (<18 years) or older (>60years) than unrelated donors. Sustained efforts are necessary to increase numbers of reports and avoid reporting bias. This could be achieved by making the reporting of donor outcome data mandatory.

Disclosure: The authors have no potential conflict of interest and source of funding related to this abstract to disclose.

10 - Stem Cell Donor

O162

ASSOCIATIONS BETWEEN HLA EVOLUTIONARY DIVERGENCE AND OUTCOME OF MATCHED RELATED OR UNRELATED HCT: A STUDY FROM THE EBMT CELLULAR THERAPY AND IMMUNOBIOLOGY WORKING PARTY

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Background: HLA Evolutionary Divergence (HED) is a numerical metric calculated from the amino acid variability in the peptide binding pocket of HLA allotypes, representing the predicted diversity of immunopeptidomes presented by those allotypes..

Increasing HED scores have been associated with improved response to immune checkpoint inhibition in solid tumor patients, and more recently with outcome of allogeneic hematopoietic cell transplantation (HCT) from different donor types. Exploration of HED scores as continuous variables in the uniform setting of HLA-matched HCT, not confounded by the impact of HLA mismatches or cohort-specific mean cut-off values, has not been performed so far and was the scope of the present study.

Methods: We analyzed 17,525 adult patients who had received a first allogeneic HCT for acute leukemia or myelodysplastic/myeloproliferative disease between 2010 and 2019 from a 10/10 HLA-A, -B, -C, DRB1, DQB1 matched related (N = 3,682) or unrelated (N = 13,843) donor, with 2nd field HLA typing data in the EBMT database. HED scores were calculated as described (Pierini & Lenz, *Mol Biol Evol* 2018) for HLA-A, -B, -C, DRB1, DQB1. (Cause-specific) proportional hazards models including common predictors were used to investigate the association of locus-specific HED scores as continuous variables with a linear effect, with the endpoints overall survival (OS), relapse-free survival (RFS), non-relapse mortality (NRM), relapse, acute and chronic GvHD.

Results: The distribution of HED scores was similar in related and unrelated transplants (0-15 for HLA-A, -B, -C; 0-20 for HLA-DR, -DQ). Patients in the unrelated compared with the related donor group were more likely to have received in-vivo T-cell depletion (82% vs 43%), and transplants from donors mismatched for HLA-DPB1 (73% vs 3%) and not older than 35 years (54% vs 16%). The 5-year probability of RFS was not significantly different between related and unrelated transplants (48.0% vs 45.4%, P = 0.08), and associated with similar non-HLA variables including patient age and performance status, diagnosis and disease status at transplant. No significant associations were found between HED scores at any locus and any of the outcome endpoints studied after related donor HCT. In contrast, in the unrelated donor setting, increasing HED scores at the HLA-B locus (HED-B) were associated with improved OS (hazard ratio [HR] 0.99 per unit difference, P = 0.004) and RFS (HR 0.99, P<0.001), as well as lower NRM (HR 0.98, P = 0.004) and and aGvHD(grade 2-4 (HR = 0.99, P = 0.014), while no significant associations were found with the other endpoints. For RFS, we observed a significant interaction between HED-B and B-Leader status, in which the protective HED-B associations appeared to be strongest for patients with B-Leader status MM.

Conclusions: Our results hint to a weak but consistent protective association of increasing HED-B scores as continuous variable, with improved survival after HLA-matched unrelated but not related HCT for malignant disease. Possible mechanistic explanations include HED-B effects on T-cell reconstitution, as well as interaction with B-Leader related mechanisms. The findings will be of aid in patient risk stratification after allogeneic HCT.

Disclosure: Tobias Lenz is co-inventor on a patent application to use HED in predicting cancer immunotherapy treatment success. The other authors have no conflict of interest to declare for this study.

2 - Stem Cell Mobilization, Collection and Engineering

O163

DONOR GRAFTS WITH ABUNDANT HAEMOPOIETIC STEM CELLS AND MONOCYTES, BUT FEWER T CELLS, INDEPENDENTLY PREDICT CLINICAL OUTCOME FOLLOWING REDUCED INTENSITY CONDITIONED ALLOGENEIC STEM CELL TRANSPLANTATION

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Background: A potent allogeneic immune response is central to the curative potential of allogeneic stem cell transplant (SCT). However, this also results in detrimental Graft versus Host Disease (GvHD). Individual immune cell subsets in peripheral blood stem cell (PBSC) grafts have been correlated with clinical outcome, but the combinatorial impact of these on transplant outcome, and the composition of an 'ideal graft', remains unclear.

Methods: High dimensional mass cytometry described the composition of 155 PBSC grafts from HLA matched donors used in patients undergoing reduced intensity conditioned SCT incorporating in vivo T cell depletion at University Hospitals Birmingham between 2009-2017. Algorithm-based clustering described cell clusters within grafts, and Gaussian mixture modelling defined graft groups based on cellular composition. The impact of grouping and lineage composition on survival events (OS, GRFS) was assessed using Cox proportional hazard models, and Fine and Gray models for time to event analyses (GvHD, relapse, TRM) with competing risks.

Results: On average, monocytes comprised 36% of PBSC grafts (IQR 20-51%), T cells 29% (7-39%), and B cells 18% (10-23%). Dendritic cells comprised 4% (2-5%), NK cells 4% (1-4%) and HSCs 3% (1-4%). 6% were monocytoid/DC cells, common myeloid or DNAM+ lymphoid progenitors. Considerable graft variation was noted, but 3 distinct groups were identified according to lineage composition.

Group A (n = 80) was characterised by an abundance of monocytes and HSCs, with lower T cell content. Group B (n = 41) had higher proportions of B and T cells, whilst group C (n = 34) had the highest proportion of T cells and the fewest monocytes.

2 year OS and GRFS for the whole cohort was 62% and 32% respectively. OS for patients receiving a group A graft was higher than those receiving a group B or C graft (p 0.027* group A, 74%, group B 50% HR 2.43, group C 49% HR 2.1). Higher GRFS was associated with group A grafts (p 0.005** group A 40%, group B 27% HR 1.48, group C 12.5% HR 2.20). There were no significant differences in the rates of acute GvHD or relapse, and reduced survival in patients receiving Group B grafts related to non-GvHD related TRM (HR_{SD} 3.45; P 0.01*). Time dependent effects limited the analysis of graft impact on chronic GvHD, but an increase in the proportion of T cells relative to HSCs (characteristic of group C) was associated with increased cGvHD (HR_{SD} 2.01; P 0.05), where the proportion of double negative (CD4- CD8-) T cells had the largest effect on the incidence of cGvHD (HR_{SD} 1.29).

Conclusions: PBSC graft composition is highly variable. We defined three graft groups according to overall composition. Receipt of a graft abundant in monocytes and HSCs, with lower T cell content, had superior GRFS and OS. Understanding the impact of donor grafts on clinical outcome may influence future studies in GvHD prophylaxis, whilst methods to deplete high risk cell subsets, such as double negative T cells, might decrease the risk of chronic GvHD.

Disclosure: FK has received research funding from Gilead, and honoraria from Therakos, neither of which are in conflict with this abstract. The other authors have nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

O164

RATIONAL USE OF PLERIXAFOR USING A COMBINED ALGORITHM OF CD34 COUNT IN PERIPHERAL BLOOD AND PREDICTED BLOOD VOLUMES TO PROCESS ACCORDING TO COLLECTION EFFICIENCY COEFFICIENT

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Background: Poor mobilization is an increasingly encountered problem as older and heavily treated patients become candidates for stem cell transplantation (SCT). Plerixafor can rescue these patients but its high cost forces to adapt its use. Since June 2020 we use pre-emptive plerixafor based on a combined algorithm of CD34 count in peripheral blood (PB) before apheresis procedure and predicted blood volumes to process according to our center collection efficiency coefficient (CE_2).

Methods: We retrospectively analyzed in our center the use of plerixafor in autologous apheresis between January 2019 and August 2022, comparing outcomes before (Period 1) and since June 2020 (Period 2). We performed 297 apheresis in 225 patients. All patients received G-CSF 5 µg/Kg/12h for at least 4 days. 81 (36%) patients received plerixafor (0.24 mg/Kg). Our CD34 minimum target was ≥2 x10^6/Kg (except for some patients with Multiple Myeloma (MM) whose target was ≥4 x10^6/Kg).

Results: The patients' characteristics are summarized in Table 1. There were no statistically significant differences on age or diagnosis between both periods. During Period 1, 24 patients (32%) required plerixafor, whereas in Period 2, 57 patients (38%) required pre-emptive plerixafor. The patients who required more than one apheresis procedures were 14 (58%) in Period 1 and 14 (25%) in Period 2. Patients requiring two doses of plerixafor were 9 (37%) in Period 1 and 12 (21%) in Period 2. There were no adverse events grade 3-4 related to plerixafor use.

Median yield CD34 cells were 2.49 x10^6/Kg (Q1-Q3: 2.03-3.07) during Period 1 and 3.34 x10^6/Kg (Q1-Q3: 2.20-5.03) during Period 2. Patients with MM and other Plasma Cell Dyscrasia (PCD) yield more median CD34 (4.25 and 4.40 respectively) than Non-Hodgkin Lymphoma (NHL) (2.20) and Hodgkin Lymphoma (HL) (2.55) in both periods.

Mobilization with plerixafor failed in 5 (6.17%) patients: 2 MM (who did not stop lenalidomide treatment) and 3 NHL. CD34/µL count in PB postplerixafor in these patients were 5.37, 6.02, 6.38, 7.42, 13.41. All patients who did not fail mobilization had >10 CD34/µL in PB postplerixafor.

	Period 1	Period 2	*p*
Apherised patients	75	150	
Patients who required >1 procedure (%)	30 (40%)	30 (20%)	*0.002*
Patiets who received plerixafor	<24 (32%)	57 (38%)	*0.377*
Apheresis procedures required			*0.010*
1 (%)	10 (42%)	41 (72%)	
2	12	14	
3	2	0	
Doses of plerixafor			*0.166*
1	15 patients	45 patients	
2 (%)	9 patients (37%)	12 patients (21%)	
Total	33 doses	69 doses	
Age, median (Q1-Q3)	60 (42-65)	61 (55-66)	*0.153*
Diagnosis			*0.416*
HL (%)	3 (13%)	3 (5%)	
NHL (%)	7 (29%)	19 (33%)	
MM (%)	11 (46%)	29 (51%)	
Other PCD (%)	2 (8%)	6 (11%)	
Others (%)	1 (4%)	0	

Conclusions: Since the application of our combined algorithm, we have not statistically significantly increased the use of plerixafor. Further, we have reduced the number of apheresis procedures per patient and the number of patients who required a second dose of plerixafor. This algorithm guides us to a better use of plerixafor leading to an optimal utilization of our resources and improving the efficiency of the mobilization process with less exposure to the patients to treatments and apheresis procedures.

Besides, the combined mobilization with G-CSF ± plerixafor achieved CD34 harvest in 97.8% of patients. Less than 10 CD34/µL in PB postplerixafor seems to be a good predictor of mobilization failure.

Disclosure: Nothing to declare

2 - Stem Cell Mobilization, Collection and Engineering

O165

HIGH-DOSE CYCLOPHOSPHAMIDE 4 GR/M^2 AND STEM-CELL COLLECTION AFTER DARATUMUMAB-BASED QUADRUPLET INDUCTION IN NEWLY DIAGNOSED TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA PATIENTS: A SINGLE-CENTER EXPERIENCE

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Background: Quadruplet induction with Daratumumab/Bortezomib/Thalidomide/Dexamethasone (Dara-VTd) has become the standard treatment for transplant-eligible newly diagnosed multiple myeloma patients (NDMM). Despite improved response rates, concerns with stem-cell mobilization and collection emerged in

CASSIOPEIA trial. Greater use of Plerixafor as well as lower total number of CD34+cells/Kg collected per patient compared to VTd were reported.

Methods: After Dara-VTd induction, NDMM received inpatient high-dose cyclophosphamide 4 gr/m^2 (HD-CTX) followed by granulocyte colony-stimulating factor (G-CSF) 5 µg/kg/day starting on day +2 from HD-CTX until last day of collection, as per institutional practice. Plerixafor was administered on demand in patients with <20 CD34+cells/µl on day of planned leukapheresis or in those predicted as poor mobilizer per institutional practice. Main parameters considered on first day of leukapheresis were: patient body weight (kg) / CD34+cells/µl ratio as well as peripheral white blood cells/µl / CD34+cells/µl ratio. Pre-planned total target dose was 10x10^6CD34+cells/Kg for multiple autologous stem-cell transplantation (ASCT).

Results: From December 2021 to data cut-off (15th December 2022) 41 NDMM received Dara-VTd at our institution. Twenty patients completed induction and were included in this analysis. At diagnosis median age was 61 years (range: 39-70), 20% were ISS III, 5% were R-ISS III and 50% were R2-ISS III-IV. Fourteen patients (70%) had high-risk cytogenetic abnormalities as del17p13, gain1q21, t(4;14), t(14;16) and t(14;20). After a median of 4 Dara-VTd cycle (range: 4-6) overall response rate (ORR) was 95%, with 35% VGPR and 40% sCR. One patient progressed after 4th cycle. Thalidomide and Bortezomib dosage were reduced in 65% and 20% of patients, respectively. After a median of 131 days (range: 12-51) from start of induction, 19 patients received HD-CTX. After HD-CTX ORR was 95% with improved VGPR (45%). No relevant grade 3-4 adverse events were reported. After a median of 11 days (range: 9-13) 18/19 patients underwent leukapheresis; 50% received Plerixafor. Seventeen patients completed stem-cell collection, harvesting a mean total amount of 10,03 x10^6 CD34+cells/kg (range: 7,6-14,8) (Table 1). One patient progressed soon after HD-CTX whereas one patient discontinued mobilization due to concomitant Sars-Cov2 infection. Unfortunately both subsequent rescue attempts with chemo-free G-CSF 10 µg/kg/day + Plerixafor and cyclophosphamide 2 gr/m^2 + G-CSF 10 µg/kg/day + Plerixafor failed. After a median of 201 days from start of induction (range: 144-283), 15/20 (75%) NDMM patients and 15/17 (88%) of those who completed leukapheresis already underwent ASCT. Mean number of infused CD34+cells was 5,16 x10^6/kg (range: 3,59-9,86). All patient obtained stable neutrophils and platelets engraftments after a median of 12 days (range: 9-14) and 16 days (range: 13-19), respectively. No relevant toxicities were reported. At last follow up, all patients were alive.

Table 1. Characteristics of stem-cell mobilization and harvesting.

Days from start of induction to HD-CTX: median (range)	131 (90-190)
Days from last daratumumab to HD-CTX: median (range)	32 (12-51)
Days from HD-CTX to first day of leukapheresis: median (range)	11 (9-13)
Peripheral white blood cells/µl on first day of leukapheresis: median (range)	60.700(8.000-153.000)
Peripheral CD34+cells/µl on first day of leukapheresis: median (range)	17.7 (3.6-67)
Total number of leukapheresis days: median (range)	2 (1-2)
Plerixafor use: number (%)	10 (50%)
Body weight (kg) / CD34+cells/µl ratio in patients who received Plerixafor: median (range)	5,09 (1,04-9,39)
Peripheral white blood cells/µl / CD34+cells/µl ratio in patients who received Plerixafor: median (range)	1896,55 (996,49-21308,39)
Amount of CD34+cells x10^6/kg collected per patient: mean (range)	
•Day 1	6,24 (1,4-12,9)
•Day 2	5,43 (3,2-10)
•Total	10,03 (7,6-14-8)
Collection efficiency: mean (range)	
•Day 1	58% (18-83)
•Day 2	71% (43-100)
Total blood volume processed (liter): mean (range)	5,19 (2,5-9,6)

Conclusions: In real-life setting, mobilization with HD-CTX 4 gr/m^2 and G-CSF 5 µg/kg/day following Dara-VTd induction proved feasible and effective in NDMM. High incidence of poor mobilizers in Daratumumab-exposed patients was confirmed in our experience. Nonetheless, HD-CTX 4 gr/m^2 together with on-demand and patient-tailored usage of Plerixafor allowed high number of stem-cell collection per patient sufficient for multiple ASCT and favorable transplantation outcomes.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

O166

VALIDATION OF AN APPLICABLE PREDICTION MODEL BASED ON COLLECTION EFFICIENCY (CE_2) FOR PERIPHERAL BLOOD STEM CELL COLLECTION IN CANDIDATES FOR AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Prediction models for apheresis procedures are a useful approach to optimize the CD34+cell collection yield. The aim of this study is to validate in real life the proposed prediction model and analyze the impact on number of procedures and adverse event(AE) incidence.

Methods: We conducted an unicentric retrospective study enrolling 129 patients diagnosed of multiple myeloma(MM) (n = 82) and non Hodgkin lymphoma(NHL)(n = 47) who underwent apheresis procedures between May/2021 and September/2022. All procedures were performed by *Optia-Spectra*. The blood volumes to process were obtained from the following formula: (CD34+ objective dose/CE_2) / (Pre-CD34 + /µL x10^3/Blood volume patient). The CE_2(Mean-1SD) was based on a retrospective series: 0.37 for MM without plerixafor(107 cases), 0.24 for MM with plerixafor(28 cases) and 0.33 for NHL(71 cases). We establish the threshold CE_2(Mean-1SD) so that statistically 84% of procedures achieved our objective CD34 + /Kg. According to our current protocol, procedures should begin on day+4 if pre-harvest peripheral blood CD34+cell count is between 10-17/µL and predicted blood volume needed is less than 4.5. Intravenous prophylactic calcium is administered from the second blood volume onwards. In the previous protocol, apheresis was started on day+4 when the CD34 + /µL count was >20, processing a maximum of 3 blood volumes; prophylactic oral calcium was administered to all patients.

Results: Our model was precise in 87.59%(113/129) of the procedures: 85.11%(40/47) for patients diagnosed of NHL(87.50%(28/32) NHL without plerixafor; 80.00%(12/15)NHL

Table 1. Specific data depending on the pathology and administration of plerixafor.

Pathology	N patients (%)	>1 apheresis procedure (%)	Reduction in second apheresis procedures (%)	Mean blood volumes (range)	Procedures >3 blood volumes (%)	Adverse effects (%)	CE_2 (Mean-1SD)
NHL	47/129 (36.43)	11/47 (23.40)	8/47 (17.03)	3,38 (1.67-4.40)	31/47 (65.96)	2/47 (4.26)	0,31 (0.46-0.15)
NHL without plerixafor	32/129 (24.81)	4/32 (12.50)	6/32 (18.75)	3,24 (1.67-4.40)	17/32 (53.13)	2/32 (6.25)	0,31 (0.43-0.12)
NHL with plerixafor	15/129 (11.62)	7/15 (46.67)	2/15 (13.33)	3,67 (2.8-4.23)	12/15 (80.00)	0/15 (0.00)	0,30 (0.48-0.18)
MM without plerixafor	52/129 (40.31)	10/52 (19.23)	8/52 (15.38)	3,32 (1.87-4.14)	35/52 (67.31)	4/52 (7.69)	0,35 (0.47-0.12)
MM with plerixafor	30/129 (23.26)	3/30 (10.00)	3/30 (10.00)	3,34 (2.47-4.19)	17/30 (56.67)	2/30 (6.67)	0,32 (0.45-0.13)

with plerixafor), 84.62%(44/52) for MM without plerixafor and 96.67%(29/30) for MM with plerixafor administration. Furthermore, the predictive CD34+cell yield showed a reasonable correlation with the real CD34+cell dose obtained (Pearson correlation 0.843,p 0.000).

The mean number of blood volumes performed was 3.35(range: 1.67-4.40). In 64.34%(83/129) of the first procedures performed, the number of blood volumes processed was greater than 3. The incidence of AEs was 3.88%(5/129), all of them mild symptomatic hypocalcaemia, not related to the mean number of blood volumes processed (AE:3.06 blood volumes; non-AE:3.36 blood volumes).

In our study we found that 18.60%(24/129) patients required second procedures. Of these, 70.83%(17/24) were due to a prediction of blood volume greater than 4.5 and the remaining 29.3%(7/24) were related to an underestimation of the model.

We calculated that if we had followed the previous protocol, 33.33% (43/129) patients would not have reached the cellular dose in a single procedure, avoiding second procedures in 14.73%(19/129) of patients.

Specific data depending on the pathology and administration of plerixafor appear in *Table-1*.

Conclusions: Our prediction model for apheresis procedures in patients with MM and NHL, compared to the previous protocol, seem to be a useful approach to optimize CD34+cell collection, avoiding second procedures in a significant number of patients and maintaining a low AE rate.

Moreover, the model we used seems applicable in our center, confirming prospectively that the CE_2 used in the prediction model are adjusted to our reality and showing an adequate correlation between the predicted CD34+cell count and the cellular dose we actually reached.

Disclosure: Nothing to declare.

2 - Stem Cell Mobilization, Collection and Engineering

O167

TCRA/B DEPLETION USING CLINIMACS PRODIGY VS. CLINIMACS PLUS SYSTEMS: A HEAD TO HEAD COMPARISON

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Background: Depletion of TCRα/β + T (and B) cells using the CliniMACS Plus (CP) has been used for a decade as an ex-vivo graft manipulation method for haploidentical hematopoietic stem cell transplantation (HSCT). Despite excellent clinical results, use of the procedure has been limited as it requires a highly trained staff, is time consuming, and its efficiency is user dependent. An automated platform, using the CliniMACS Prodigy device launched few years ago, overcomes these obstacles, but data regarding its efficiency and clinical outcome is scarce. Here, we report the first head to head comparison between the two methods including clinical outcome, performed by the same staff at our center.

Methods: Donors were prepared by 4 daily doses of Granulocyte-Colony Stimulating Factor (G-CSF) (10mcg/kg/day). If donor CD34+ cell count was < 40/ ul 12 hours after the third dose of G-CSF, a single dose of plerixafor (0.24 mg/kg) was administered after the 4th dose of G-CSF, 6 hours before apheresis. Graft procurement was performed using the Spectra Optia (TerumoBCT), using the CMNC program, on the morning of the 5th day.

When using CP, the apheresis product was stored overnight at room temperature (RT), and manipulation started the following day. Grafts undergoing depletion using Prodigy were loaded on the device at the end of the apheresis. Prodigy was programmed to perform all pre- enrichment stages on the same day and pause the process prior to the enrichment stage in order to permit removal of a Quality Check (QC) sample in the morning of the following day, followed immediately by the separation stage. Procedures were performed using manuals and reagents purchased from Miltenyi Biotec, Germany. All procedures were performed in a Class D clean room.

Additional GVHD prophylaxis with mycophenolic acid (MMF) until post-transplant d + 28 was administered only if TCRab > 5*10^4/ kg.

Results: We performed 18 procedures for 17 patients using CP between 2015-2021, and 8 procedures for 8 patients using Prodigy between 2021-2022, Results are shown in table 1. No significant difference was found in CD34 % recovery, though when comparing to starting material, the CD34% recovery is close to reach a statistical significance (with better recovery

using the Prodidy), suggesting more cell loss in the pre-separation stages using the CP . The TCRαβ log depletion was significantly higher using Prodigy, reflecting a better efficacy and resulted in less patients requiring additional GVHD prophylaxis.

	Clinimacs Plus (N = 18)	Clinimacs prodigy (N = 8)	P value
Technical:			
Infusion time : Average (range)	21:45 (17:15–02:00)	16:20 (14:05–18:00)	1.000
Starting material %CD34 (median, range)	0.855 (0.612–2.7)	1.077 (0.945–1.497)	0.600
Starting material %TCRab (median, range)	34.9 (20.8–67)	32.6 (27.8–44.5)	0.83
CD34 %(target/QC) recovery (median, range)	76.86 (54.5–100)	80.9 (63.8–100)	0.56
CD34% (target/ starting material) recovery (median, range)	62.05 (39.4–90.7)	80.846 (55–89.9)	0.097
TCRαβ Log depletion (median, range)	3.707 (3.06–4.533)	4.605 (3.80–5.01)	<0.01
TCRab/kg>5*10^4 (requiring additional GVHD prophylaxis)	13 (72%)	3(37%)	0.18
Clinical:			
Disease type : Malignant/Non Malignant	6/12	5/3	0.218
Donor type :Haplo/MUD/ MSD	15/2/1	7/0/1	0.68 8
HSCT number :1st /2nd/ 3rd	10/6/2	7/1/0	0.108
Neutrophil engraftment: Median (range)	11 (9-16)	9 (8–16)	0.049
Platelet engraftment: Median (range)	12 (8-35)	11 (10–16)	0.09
Acute rejection / non engraftment	3	1	1
Poor graft function	1	1	1
Malignancy relapse	5	0	0.015
Acute skin GVHD :Grade 1/ Grade 2–4	4/0	2/0	1

Conclusions: We found TCRαβ depletion using the CliniMACS Prodigy more efficient than procedures using Clinimacs Plus, with comparable clinical outcome. The elimination of operator-related variables produces a reliable product with a substantial reduction of work-load for the laboratory staff.

Disclosure: Nothing to Declare

2 - Stem Cell Mobilization, Collection and Engineering

O168

IN HOUSE BONE MARROW COLLECTION SET: THE CATALAN BONE MARROW TRANSPLANTATION GROUP EXPERIENCE

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Background: Bone marrow (BM) harvesting represents one of the essential sources of stem cells for hematopoietic stem cell transplantation. In 2019, a supply stoppage of commercial BM collection set was communicated in Europe. Therefore, an in house BM collection set was created as alternative by the Catalan Bone Marrow Transplantation Group.

Methods: A prospectively validation protocol of the in house BM collection set was done by seven collection centres and one cell processing laboratory in Catalonia, Spain. All consecutive BM donors between June 2022 to November 2022, and the subsequent recipients, were prospectively included in the study. The following predefined acceptance criteria were made: absence of serious technical issue and clumping, >70% viability in $CD45^+/CD34^+$ cell population, > 0.4/μL colony-forming units granulocyte/macrophage. The components for the in house collection BM set were: 1000 ml parenteral nutrition bag, safety valve, Transfusion set including 200 μm filter connected to a 1000 ml transfer bag with a sterile tubing welder and tube clamp.

Results: A total of 16 donors underwent BM harvest with the in house collection set. Nine (56%) donors were pediatric (<18 years old) and the half were females.Regarding BM harvest, in five cases (31%), the harvested volume was higher than 1000 ml and therefore two collection bags were needed. Standard anticoagulation was 10% ACD-A and 4-20 UI Heparin/mL. All the predefined acceptance criteria were met. Regarding main patients' characteristics that received the BM collected with the in house collection set, 13 (81%) were pediatric and 12 (75%) males. Nine (56%) had nonmalignant disease.Ten (63%) recipients received BM in fresh or after manipulation with more than $3x10^8$ TNC/kg and 6 (38%) with more than 4 $x10^8$ TNC/kg). The median (range) of CD34/kg received was $2.1x10^6$ (0.4–6.7). The median (range) days of neutrophil and platelet engraftment was 21 (13-32) and 28 (14–177), respectively. Five (31%) harvest products were contaminated by bacteria flora of normal skin, but no adverse reactions were reported after stem cell infusion. Three BM harvest (19%) required to exchange a new transfusion set because of filter clogging. However, no impact was observed in quality control and hematologic engraftment. No assembling issues were recorded.

Conclusions: In summary, to the best of our knowledge, this is the first study to assess an in house BM collection set. All the predefined acceptance criteria in the validation protocol were met and all patients engrafted. Therefore, the in house BM collection set is a real approach to solve the diminished supply of commercial sets. Higher risk of filter clogging were observed in compare than commercial sets due to the lack of 850 and 500 μm filters. More BM harvest procedures using this in house BM collection set are needed to confirm these results.

Disclosure: The authors state that they have no conflict of interest regarding this article.

Table displays the mobilization outcomes for each diagnosis by mobilisation regimen.

	G-CSF	Cyclo-G	Other chemotherapy + G-CSF	G-CSF vs Cyclo-G (*p* value)	G-CSF vs other-G (*p* value)	Cyclo-Gvsother-G (*p* value)
Multiple Myeloma						
Number of patients	438	319	45			
Pre-CD34+ count ($x10^6$/kg) Median (Q1-Q3)	29 (18–54)	40 (21–75)	23 (15–53)	<0.0001	ns	<0.0001
CD34+ yield per procedure ($x10^6$/kg) Median (Q1-Q3)	2.01 (1.16–3.30)	3.65 (1.87–6.23)	2.01 (1.20–5.04)	<0.0001	ns	<0.0001
CD34+ yield per patient ($x10^6$/kg) Median (Q1-Q3)	4.75 (3.47–6.3)	7.44 (5.44–9.61)	5.75 (3.72–7.84)	<0.0001	ns	<0.0001
Plerixafor use N (%)	41 (9.3%)	11 (3.4%)	15 (33%)	<0.001	<0.00001	<0.00001
NHL						
Number of patients	142	47	189			
Pre-CD34+ count ($x10^6$/kg) Median (Q1-Q3)	23 (14–43)	19 (11–30)	28 (15–72)	NS	NS	0.0055
CD34+ yield per procedure ($x10^6$/kg) Median (Q1-Q3)	1.53 (0.89–3.19)	1.19 (0.80-3.04)	2.93 (1.30-5.87)	NS	<0.00001	<0.00001
CD34+ yield per patient ($x10^6$/kg) Median (Q1-Q3)	3.70 (2.65–5.89)	3.69 (2.60–6.50)	5.98 (3.85–8.93)	NS	<0.00001	<0.00001
Plerixafor use N (%)	37 (26%)	4 (9%)	37 (20%)	0.011	NS	NS
Hodgkin's Lymphoma						
Number of patients	44	16	30			
Pre-CD34+ count ($x10^6$/kg) Median (Q1-Q3)	33 (16–63)	35 (18–64)	37 (16–63)	NS	NS	NS
CD34+ yield per procedure ($x10^6$/kg) Median (Q1-Q3)	1.94 (0.97–4.78)	3.02 (1.61–6.85)	2.10 0/96–4.38)	NS	NS	NS
CD34 yield per patient Median (Q1-Q3)	4.53 (2.99–7.44)	5.52 (3.02–5.52)	4.32 (2.99–8.05)	NS	NS	NS
Plerixafor use N (%)	6 (14%)	2 (9 %)	8 (27%)	NS	NS	NS

2 - Stem Cell Mobilization, Collection and Engineering

O169

G-CSF ONLY VS CHEMOTHERAPY PLUS G-CSF MOBILISATION FOR AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANT – ASSESSING A CHANGE IN REGIME DUE TO THE COVID-19 PANDEMIC

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Background: At the start of the COVID-19 pandemic professional societies in UK and across the world recommended switch to Granulocyte Colony Stimulating Factor (G-CSF) alone mobilization regimens for autologous haematopoietic stem cell transplant (ASCT) candidates to reduce the risk to COVID -19 exposure due to possible inpatient admissions and frequent day to day visits associated to Cyclophosphamide and other chemotherapy based, regimens.

The purpose of this study is to assess the impact of this change on apheresis outcomes for ASCT in England.

Methods: 1270 patients aged ≥16 undergoing 2431 apheresis procedures for ASCT between 1st January 2019 and 31st December 2021 were analysed retrospectively using data from the NHS Blood and Transplant (NHSBT) Stem Cell Collection Registry. These represent approximately 43% of ASCT mobilized in England during the study period.

Analysis was by diagnosis (multiple myeloma (MM), Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL)) and mobilisation regimen (G-CSF alone, Cyclophosphamide plus G-CSF (Cyclo-G) and other chemotherapy plus G-CSF (other-G). The outcomes measured were pre-CD34 count, CD34 yield per procedure, CD34 yield per patient, plerixafor use and number of apheresis procedures required to achieve CD34 target. Qualitive variables were analysed with chi square test while non-parametric quantitative variables with Kruskal-Wallis test.

Results: 802 of patients in the study population were undergone mobilization for MM (63%), 378 for NHL (23%) an 90 for HL (7%).

In patients with any diagnosis the use of G-CSF alone significantly increased, from 32% pre COVID-19 to 62% in 2021.

This is reflected in the decrease at the same period of the use of Cyclo-G from 43% to 23% while the use of alternative chemotherapy plus G-CSF did not change.

The trend towards preferential use of G-CSF was more prominent in MM (from 36% to 73%) followed by HL (35% to 57%) and NHL (23% to 50%).

Patients with MM mobilized with G-CSF alone collected the target CD34 dose with more procedures compared to those mobilized with Cyclo-G (1 procedure 35%, 2 procedures 47% vs 1 procedure 43%, 2 procedures 35%). For patients with NHS, HL the number of procedures required to achiwve the target dose did not differ amongst mobilization regimens.

Conclusions: Our real time data show that the use of G-CSF only mobilisation in all patients groups increased after the start of the COVID-19 pandemic.

For patients with MM, mobilization with G-CSF alone is inferior compared to Cyclo-G resulting in significantly lower CD34 yields per procedure and total CD34 collected per patient, greater number of procedures required to achieve the target CD34 dose and higher use of plerixafor.

Patients with NHL were more effectively mobilized with chemotherapy based +G-CSF regimens while for HL patients the three mobilization regimens were equal for all outcomes.

Clinical Trial Registry: N/A

Disclosure: None

9 - Stem Cell Source

O170

THE EFFECT OF HUMAN LEUKOCYTE ANTIGEN EPITOPE MATCHING ON OUTCOMES AFTER HAPLOIDENTICAL TRANSPLANTATION DEPENDS ON GRAFT-VERSUS-HOST DISEASE PROPHYLAXIS AND PRETRANSPLANT DISEASE STATUS

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Background: Graft-versus-host disease (GVHD) prophylaxis using posttransplant cyclophosphamide (PTCy) has contributed to the extensive use of haploidentical donors as alternative options for allogeneic hematopoietic stem cell transplantation (HSCT). We aimed to study, using human leukocyte antigen (HLA) epitope, the effect of HLA mismatch on the outcomes of patients who underwent haploidentical HSCT in association with GVHD prophylaxis and pretransplant disease risk.

Methods: This retrospective study included 1037 patients who underwent their first HSCT for hematologic malignancies from haploidentical peripheral blood donors in the Transplant Registry Unified Management Program between 2011 and 2020. We included patients transplanted with HLA 4/8 to 6/8 allele-matched donors. A total of 542 patients received PTCy and 495 patients received anti-thymocyte globulin-based GVHD prophylaxis (ATG). Overall survival (OS) was defined as the primary endpoint and relapse as the secondary endpoint. We quantified Predicted Indirectly ReCognizable HLA-Epitopes in the graft-versus-host (GVH) direction presented on HLA class I (PIRCHE-I). The mean PIRCHE-I value was used to define low and high PIRCHE-I. We defined the following diseases as standard risk: acute leukemia in complete remission, myelodysplastic syndrome without excess blasts, chronic myelogenous leukemia in the chronic and accelerated phases, and lymphoma in complete/partial remission. Other conditions were defined as high risk. The Cox proportional-hazards model was used to evaluate OS. The competing-risks regression model was used to evaluate relapse. Patient age, donor relationship, sex, disease stage, and performance status were included in the final multivariate model analysis.

Results: The median age of the patients was 50 years (range, 16 to 77 years). The PIRCHE-I values ranged from zero to 58 (mean, 12.2). As compared to the PTCy group, the ATG group contained a higher percentage of patients with high-risk diseases (73% vs. 47%, $p < 0.001$).

In patients with high-risk diseases who received PTCy, higher PIRCHE-I were associated with a significantly lower risk of relapse, leading to a higher OS (high PIRCHE-I patients compared with low PIRCHE-I patients: relapse: HR 0.68, 95% CI 0.41–0.99, $p = 0.050$; mortality: HR 0.69, 95% CI 0.49–0.99, $p = 0.042$). In patients with high-risk diseases who received ATG, higher PIRCHE-I were associated with a significantly higher risk of relapse but were not associated with OS (high PIRCHE-I patients compared with low PIRCHE-I patients: relapse: HR 1.50, 95% CI 1.13–2.00, p = 0.005; mortality: HR 1.01, 95% CI 0.80–1.28, $p = 0.918$). In patients with low-risk diseases, PIRCHE-I did not show a significant effect on OS or relapse regardless of the GVHD prophylaxis (high PIRCHE-I patients compared with low PIRCHE-I patients in the PTCy group: relapse: HR 0.99, 95% CI 0.57–1.69, $p = 0.959$; mortality: HR 1.03, 95% CI 0.65–1.61, $p = 0.913$; high PIRCHE-I patients compared with low PIRCHE-I patients in the ATG group: relapse: HR 1,23, 95% CI 0.58–2.63, $p = 0.589$; mortality: HR 1.01, 95% CI 0.60–1.70, $p = 0.042$).

Conclusions: These findings suggest differential effects of T-cell epitope matching, based on GVHD prophylaxis, after haploidentical HSCT. Pre-transplant disease status might also be important for understanding the GVL effect of mismatched HLA in haploidentical HSCT using PTCy.

Disclosure: All authors have no COI to disclose.

9 - Stem Cell Source

O171

A NOVEL DONOR SEARCH AND SELECTION ALGORITHM FACILITATES A COMPARABLE INCIDENCE OF TRANSPLANT FOR PATIENTS REGARDLESS OF BASELINE SEARCH PROGNOSIS: REPORT FROM BMTCTN 1702 TRIAL

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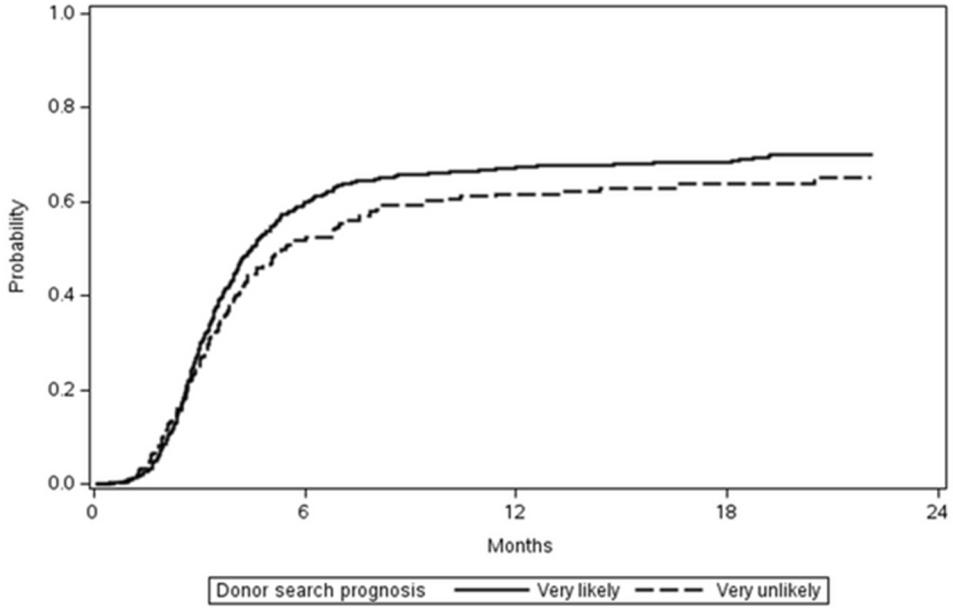
Figure 1: Adjusted Cumulative Incidence of Transplant by Search Prognosis



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Background: Patients requiring allogeneic transplantation (HCT) have variable likelihood of identifying an 8/8 HLA-matched unrelated donor (MUD) and prolonged search for a MUD may increase the risk of disease progression/death. A search prognosis calculator using recipient HLA estimates the likelihood of 8/8 MUD, but has not been used as a selection algorithm in a large prospective national trial.

Methods: The pre-specified secondary objectives of this large BMT CTN 1702 study were (1) estimate and compare the cumulative incidence of HCT by search prognosis category and (2) describe barriers to achieving HCT. In this prospective trial, centers committed to following the recommended donor search and selection strategy based on patient search prognosis: Those with >90% 8/8 MUD probability (very likely) were instructed to identify 8/8 MUD donors, while those with <10% 8/8 MUD probability (very unlikely) were to utilize alternative donors (mismatched unrelated, haploidentical, umbilical cord blood) as their first approach, with prioritization of alternative donor type per investigator discretion. Those with intermediate 8/8 MUD probability (less likely) were searched per individual/institutional standard. Patients of all ages with no available matched sibling donor, intended to have a HCT within 6 months, and had a diagnosis of AML/ALL/MDS/NHL/HL/SAA/SCD were eligible. The cumulative incidence of HCT according to search prognosis category was modeled using a covariate-adjusted Fine-Gray model.

Results: Total evaluable patient cohort was 1755 from 51 centers. Median patient age (range) was 59 (1-81), 354 (20%) were from racial/ethnic minority groups, 878 (50%) had AML, and 802 (46%) had an initial performance score of ≥90. As of data analysis, 1140 (65%) reached HCT, 331 (19%) died without HCT, and 284 (16%) remained alive without HCT. Search prognosis categories were 958 (55%) very likely, 518 (30%) less likely and 279 (16%) very unlikely. Compliance with the intended algorithm was excellent, as 94% of the very likely group transplanted from 8/8 MUD donors and 84% of the very unlikely group transplanted from alternative donors (69% haploidentical, 22% mismatched unrelated donor, and 9% cord blood). The adjusted cumulative incidence (95% CI) of HCT at 2-years was 70.5% (67.2-73.7) in very likely vs 65.3% (58.6-71.9) very unlikely. In multivariate analysis, there were no significant differences in the cumulative incidence of HCT per search prognosis with HR = 0.85 for very unlikely vs very likely, 95% CI: 0.70–1.04, $p = 0.109$. Factors significantly associated with not reaching HCT were older patient age, lower performance status, disease, and not in remission. Table 1 shows the barriers to HCT. Patient health and uncontrolled primary disease comprised the most prevalent delays (67%) and cancellations (69%).

Table 1: Primary Barriers to Transplant

Primary Reason	Transplant Delay	Transplant Cancellation
	***N* = 504** ***N* (%)**	***N* = 564** ***N* (%)**
Patient Health Related	**339 (67)**	**389 (69)**
Patient death	-	197 (35)
Lack of disease response	72 (14)	28 (5)

Primary Reason	Transplant Delay	Transplant Cancellation
Disease progression	87 (17)	50 (9)
Excellent disease response (transplant not recommended)	44 (9)	51 (9)
Due to general health	41 (8)	20 (4)
Worsening pre-existing co-morbidities (organ function, psych illness)	23 (5)	17 (3)
Newly diagnosed or developed co-morbidity	62 (12)	15 (3)
Worsening performance status, not related to specific comorbidity	9 (2)	5 (1)
Pursuing Auto Transplant or other cell therapy	1 (0)	6 (1)
Donor Reason	**67 (13)**	**15 (3)**
Change in donor suitability or eligibility criteria	26 (5)	9 (2)
Donor not available for requested product type	18 (4)	6 (1)
Identified donor not available for desired timeline	23 (5)	-
Transplant Support	**15 (3)**	**45 (8)**
Patient Preference Reason	**34 (7)**	**101 (18)**
COVID19 Pandemic	**45 (9)**	**2 (1)**
Other	**4 (1)**	**12 (2)**

Conclusions: We demonstrate for the first time that a search prognosis-based algorithm can be implemented in a national multicenter prospective clinical trial. This approach enabled rapid alternative donor identification and comparable rates of achieving HCT in patients very unlikely to find an 8/8 MUD. These results suggest a new era in donor search strategy to enhance equitable access to HCT as a curative therapy.

Clinical Trial Registry: NCT#: 03904134
clinicaltrials.gov
Disclosure: Bronwen E Shaw: OrcaBio, Mallinkrodt

9 - Stem Cell Source

O172

BONE MARROW (BM) VERSUS PERIPHERAL-BLOOD-STEM-CELL (PBSC) GRAFT IN HAPLOIDENTICAL TRANSPLANTS (HAPLO) USING POST CYCLOPHOSPHAMIDE (PTCY) IN ADULTS WITH MALIGNANT DISORDERS, ON BEHALF OF CTIWP-EBMT

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Background: Haplo-PTCY has been increasingly used in adults with hematological-diseases, lacking HLA-identical-donor; however very few studies have analyzed the impact of cell source(BM or PBSC) on outcomes after Haplo-PTCY. In a recent meta-analysis, PBSC was associated with increased risk of acute/chronic-GVHD, decreased relapse, however no impact on other outcomes.

Methods: To evaluate this impact on a large cohort of patients, we have analyzed 8854 adults with malignant disorders (acute leukemias $n = 5308$, 60%; MDS/MPD, $n = 1674$; 19%; lymphomas $n = 1872$, 21%), given a first Haplo-PTCY and reported to EBMT. BM as a graft source was used in 2914 patients and PBSC in 5940 patients. There were some statistical differences among the groups given BM compared to PBSC. BM recipients were younger (50.7years versus 54.1y in the PBSC group, $p < 0.0001$), 18.2% had HTCI score >=3 (versus 22.9% in PBSC group, $p < 0.001$), were transplanted earlier (2016 versus 2018 in the PBSC group, $p < 0.001$) more frequently with MAC regimen (47.6% versus 39.6% in PBSC group, $p < 0.001$) and less frequently received in vivo T-cell depletion (4.6% versus 11% in the PBSC group, $p < 0.001$). There were no statistical differences between groups for type of disease, patients and donor gender, CMV serology status and disease risk index (DRI).

Results: Median-follow-up was 48 and 30 months, in BM and PBSC groups, respectively. Neutrophil engraftment was observed in 92.4% of BM recipients and 93.7% in the PBSC group ($p = 0.01$). At day 180, cumulative Incidence (CI) of acute GVHD (grade II-IV) and grade III-IV were 22.3% and 7.3% in the BM group compared to 32.7% ($p = 0.001$) and 12.6% ($p = 0.001$) in the PBSC group, respectively. At 3y, CI of chronic GVHD and extensive cGVHD for BM were 25.8% and 9.5% versus 30.3% ($p = 0.01$) and 11.9% ($p = 0.01$), respectively. Compared to BM, use of PBSC was associated with higher incidence of acute and chronic-GVHD, increased non-relapse-mortality (NRM), similar risk of relapse, but decreased overall-survival (OS), PFS and GVHD-Relapse free survival (GRFS).Since PBSC cell dose is a modifiable factor, that may play an important role on Haplo-PTCY outcomes, we conducted a subgroup analysis for patients given PBSC with available data on total nucleated cell (TNC) and CD34+cell dose ($n = 3945$ PBSC) versus BM recipients. The median number of TNC and CD34+cell were $8.73x10^8$/kg(range:3-14) and $6x10^6$/kg(range: 2–12) respectively. The best TNC and CD34+cell dose cut-off associated with GFRS were $8.9x10^8$/kg ($p = 0.001$) and $5.1x10^6$/kg ($p = 0.09$), respectively. There was no statistical association of CD34+cell on outcomes. By multivariate analysis including BM and PBSC divided in 2 groups according to the TNC dose, higher TNC(>$8.9x10^8$/kg) in PBSC was associated with increased incidence of GVHD (II-IV)(HR = 1.60; $p = <0.0001$), chronic-GVHD(HR = 2.06; $p = <0.0001$), NRM(HR = 1.27; $p = 0.037$) and decreased GRFS(HR = 1.33, $p < 0.0001$) when compared to BM grafts.

Conclusions: In conclusion, use of PBSC as a graft source in the setting of haplo-PTCY is associated with worse outcomes compared to the use of BM cells and therefore BM cells should be prioritized. However, when PBSC are used, high TNC should be avoided.

Disclosure: The authors declare no COI