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ORAL ABSTRACTS

503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Clonal Hematopoiesis Is Common in Unrelated Stem Cell Donors but Has No Impact on Patient Outcome after Hematopoietic Stem Cell Transplantation

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Introduction. Clonal hematopoiesis (CH) has been associated with increased mortality mainly due to associations with cardiovascular diseases and hematologic cancer. Previous studies with predominantly related stem cell donors suggest that donor CH modulates graft-versus-host reactions and may augment graft-versus-leukemia effects after allogeneic hematopoietic cell transplantation (alloHCT). The impact of donor CH in the setting of unrelated alloHCT remains to be determined. To address this question, we initiated a joint study of the Transplant Complications Working Party of EBMT and DKMS.
Patients and Methods. Donor samples from the time of stem cell donation were taken from the Collaborative Biobank. Patient baseline and outcome data were retrieved from the EBMT registry. Unrelated donor-recipient pairs were selected for a minimum donor age of 35 years. CH analysis was performed with an error-corrected ultra-deep NGS assay for 45 genes with a median sensitivity of 0.2% variant allele frequency (VAF). Accuracy of low frequency CH findings was checked by cross validation with an orthogonal assay. The primary objective was to assess the impact of donor CH on overall survival (OS). Major secondary endpoints were the risk of relapse/progression and non-relapse mortality (NRM), cumulative incidences of acute and chronic GVHD and event-free survival (EFS). All endpoints were evaluated with (cause-specific) multivariable Cox regression models. Adjustment factors were patient and donor age, diagnosis, disease risk index, Karnofsky performance status, conditioning intensity, GVHD-prophylaxis, graft source, HLA-match, sex match and CMV match. We did not adjust for multiple testing.
Results. Data from 2584 unrelated donor-recipient pairs were analyzed. Median patient follow-up after alloHCT was 60 months. The median donor age was 46 years (range, 39-61 years). The median patient age was 54 years (range, 0-79 years). Indications for alloHCT were AML (44%), ALL (10%), MDS (10%), MPN (6%), B-cell lymphoma (6%), Multiple Myeloma (5%), CML 3%, inherited disorders (3%), CLL 2% and other (13%). Transplantations were performed between 2005 and 2018. In vivo or ex vivo T-cell depletion (TCD) was used in 81% of transplants, PTCY in 5% and no TCD in 14%. Mutations in *DNMT3A*, *TET2*, and *ASXL1* defined CH most frequently. The distribution of donor CH across leukemia driver genes was comparable to previous reports (Panel A). With 0.2% (2%) VAF cutoffs, rates of *DNMT3A*-mutations were 19% (2%) among donors younger than 41 years compared to 37% (6%) among donors aged 55 years and higher. Corresponding rates for 0.2% (2%) VAF cutoffs for total CH were 38% (4%) among donors younger than 41 years compared to 67% (14%) among donors aged 55 years and higher. We tested systematically increasing VAF cutoffs ($\geq$0.2% versus <0.2%, $\geq$1% versus <1%, $\geq$2% versus <2%, $\geq$5% versus <5%, and $\geq$5% versus <0.2%) for *DNMT3A*-CH and total CH for associations with clinical endpoints. Panel B shows results for multivariable regression analyses for total donor CH. Although we observed trends towards increased mortality and inferior EFS for some cutoffs, no incremental impact of donor CH with higher VAF was found and no systematic changes of the risk for GVHD and relapse/progression were observed.
Conclusions. We conclude that donor CH has no significant impact on the risk for GVHD, relapse and survival in the context of HLA-compatible unrelated donor alloHCT with GVHD-prophylaxis based predominantly on T-cell depletion with ATG.

Disclosures Schetelig: *Eurocept:* Honoraria; *Novartis:* Honoraria; *BeiGene:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria. **Menghrajani:** *Gilead:* Consultancy. **Bolton:** *GoodCell:* Membership on an entity's Board of Directors or advisory committees; *Servier:* Research Funding. **Bug:** *BMS:* Honoraria, Research Funding; *Jazz:* Honoraria, Research Funding; *Gilead:* Honoraria, Research Funding; *Pfizer:* Honoraria; *Novartis:* Honoraria. **Schoemans:** *Janssen:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *BHS:* Honoraria; *Sanofi:* Consultancy, Honoraria. **Koenecke:** *Miltenyi Biotec:* Consultancy; *Kite/Gilead:* Consultancy; *Novartis:* Consultancy, Speakers Bureau; *Pierre Fabre:* Consultancy; *Roche:* Consultancy, Speakers Bureau; *Sanofi-Aventis:* Consultancy, Speakers Bureau; *Medigene:* Consultancy; *Pfizer:* Consultancy; *Amgen:* Consultancy; *Glaxo Smith Kline:* Consultancy; *Janssen:* Consultancy, Speakers Bureau; *BMS:* Consultancy. **Teipel:** *Abbvie, Inc., Amgen, Astra Zeneca, BMS/ Celgene, BeiGene, Janssen, GSK, Oncopeptides, Pfizer, Sanofi, Stemline, Takeda:* Honoraria; *Janssen:* Research Funding. **von Bonin:** *Janssen:* Research Funding; *BMS:* Other: Advisory Board; *Novartis:* Other: Advisory Board; *Kite:* Other: Advisory Board. **Bullinger:** *Celgene/BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Astellas:* Honoraria; *Gilead:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Jazz Pharmaceuticals:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Bayer Oncology:* Research Funding; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria; *Bristol-Myers Squibb:* Honoraria; *Daiichi Sankyo:* Honoraria; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Honoraria. **van den Brink:** *Seres Therapeutics:* Consultancy, Current holder of *stock options* in a privately-held company, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: IP licensing , Research Funding; *Nektar Therapeutics:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Lygenesis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Ceramedix:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Rheos Medicines:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Notch Therapeutics:* Consultancy, Current holder of *stock options* in a privately-held company, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Pluto Immunotherapeutics:* Consultancy, Current holder of *stock options* in a privately-held company, Honoraria, Membership on an entity's Board of Directors or

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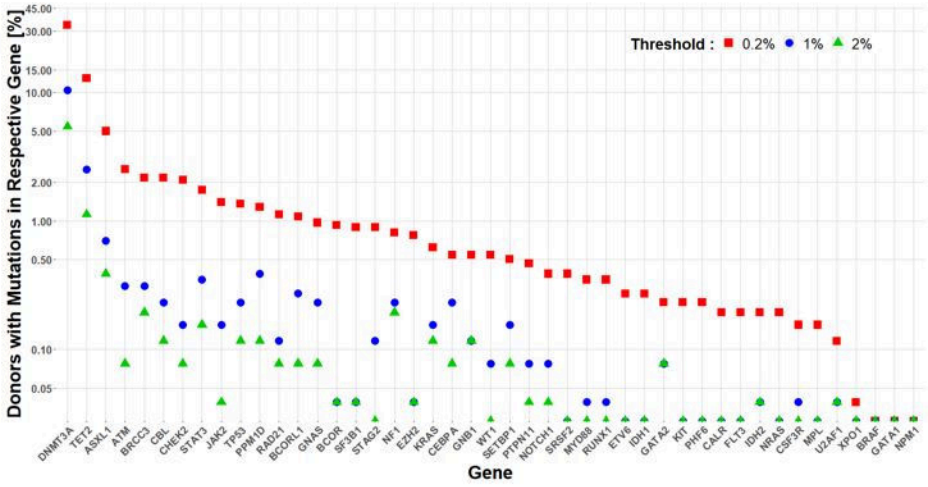
Panel A. Rate of CH in Stem Cell Donors by Gene and Variant Allele Frequency



Panel B. Impact of Total Donor CH on Clinical Endpoints by Different Cutoffs

VAF	N_{neg}	N_{pos}	OS		EFS		Relapse		NRM		aGvHD		cGvHD	
			HR [95%-CI]	p	HR [95%-CI]	p	HR [95%-CI]	p	HR [95%-CI]	p	HR [95%-CI]	p	HR [95%-CI]	p
≥0.2% vs <0.2%	1140 (44.1%)	1444 (55.9%)	1.01 [0.90-1.12]	.92	1.02 [0.92-1.14]	.69	1.14 [0.97-1.33]	.11	0.93 [0.79-1.08]	.33	1.02 [0.88-1.18]	.79	0.99 [0.85-1.16]	.94
≥1% vs <1%	2170 (84%)	414 (16%)	1.16 [1.00-1.34]	.05	1.15 [0.99-1.33]	.07	1.12 [0.91-1.38]	.29	1.18 [0.96-1.44]	.12	1.11 [0.92-1.33]	.29	0.92 [0.75-1.14]	.47
≥2% vs <2%	2366 (84%)	218 (16%)	1.22 [1.01-1.48]	.04	1.27 [1.05-1.52]	.01	1.24 [0.95-1.62]	.12	1.30 [1.00-1.69]	.05	1.19 [0.94-1.52]	.14	0.84 [0.62–1.12]	.22
≥5% vs <5%	2514 (91.6%)	70 (8.4%)	1.04 [0.73–1.48]	.82	1.08 [0.77-1.51]	.67	0.96 [0.57-1.6]	.87	1.20 [0.76-1.88]	.44	1.24 [0.84-1.84]	.28	0.89 [0.56-1.43]	.64
≥5% vs <0.2%	1140 (94.2%)	70 (5.8%)	1.04 [0.73–1.49]	.81	1.09 [0.77–1.54]	.63	1.03 [0.61–1.74]	.91	1.14 [0.72–1.81]	.57	1.25 [0.83–1.87]	.28	0.89 [0.55–1.44]	.65

Figure 1

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