Does Donor KIR-Genotype Impact Outcome After Unrelated Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndromes or Secondary Acute Myeloid Leukemia?

Schetelig J[1,2], Baldauf H[1], Koster L[3], Kuxhausen M[4], Heidenreich F[1,2], de Wreede L[1,7], Spellman S[4], Massalski C[8], Lange V[8], van Gelder M[9], Bruno B[11], Onida F[12], Potter V[13], Ljungman P[14], Schaap N[15], Hayden P[16], Kröger N[17], Lee S[18], Hsu K[19], Yakoub-Agha I[20], Robin M[21]

[1]DKMS, Dresden & Tuebingen, Germany, [2]University Hospital Carl Gustav Carus, Dresden, Germany, [3]EBMT Data Office Leiden, The Netherlands, [4]CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Minneapolis, United States, [7]Leiden University Medical Center, The Netherlands, [8]DKMS Life Science Lab, Dresden, Germany, [9]Maastricht University Medical Center, Maastricht, The Netherlands, [10]A.O.U. Città della Salute e della Scienza di Torino, Torino, Italy, [12]University of Milano, Milano, Italy, [13]Kings College Hospital NHS Trust, London, United Kingdom, [14]Karolinska University Hospital, Stockholm, Sweden, [15]Radboud University – Nijmegen Medical Centre, Nijmegen, The Netherlands, [16]St. James's Hospital, Dublin, Ireland, [17]UKE (University Hospital Eppendorf) University Medical Center, Hamburg, Germany, [18]Fred Hutchinson Cancer Research Center, Seattle, United States, [19]Memorial Sloan Kettering Cancer Center, New York, United States, [20]Lille University Hospital, Lille, France, [21]Hospital St. Antoine, Paris, France

Background

Relapse and subsequent death are the major reasons for failure of allogeneic hematopoietic cell transplantation. Natural Killer (NK) cells might contribute to Graft versus Leukemia (GvL) effects. Their degranulation depends on the net effect of activating versus inhibiting signals. Killer cell immunoglobulin-like receptor (KIR) genes are encoded on Chromosome 19 and are inherited independently from the major histocompatibility (MHC) complex. KIR genotype information has been associated with transplant outcomes in the framework of a Receptor-Ligand model aiming at maximization of activation and minimization of inhibition (KIR2DS1 and KIR3DL1; Venstrom, NEJM, 2012 & Boudreau, JCO, 2017) and by grouping donors according to presence or absence of haplotype B motifs which contain more activating KIRs (Cooley, Blood, 2010). Here we report results of a large confirmatory study.

Medical Data

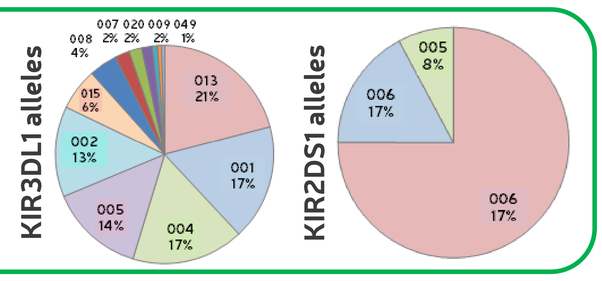
1704 patients with sAML, tAML or MDS transplanted from HLA-compatible unrelated donors between 2008 and 2017

1208 patients from EBMT and 496 patients from CIBMTR

Bw4/Bw6 and C1/C2 class mismatches in only 1.1% and 1.4% donor-recipient pairs

Geno-type

KIR-typing with high-resolution amplicon-based Next Generation Sequencing (NGS) method



Outline of Classification Approaches

Table A

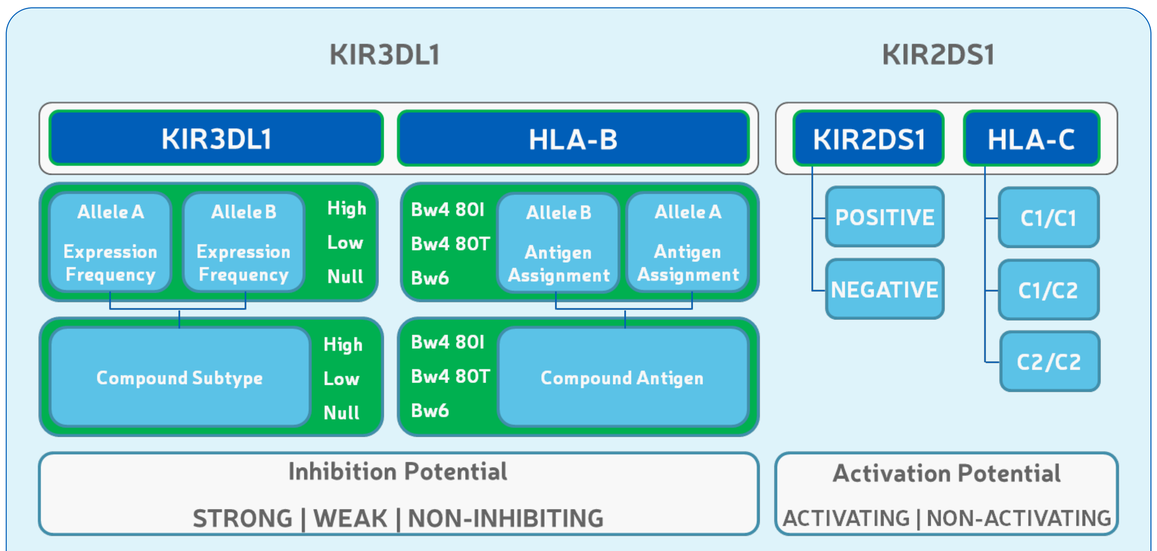
		Centromeric part									Telomeric part								
Haplotype	Cen motif	3DL3	2DS2	2DL2	2DL3	2DL5B	2DS3/5	2DP1	2DL1	3DP1	2DL4	3DL1	3DS1	2DL5A	2DS3/5	2DS1	2DS4	3DL2	Tel motif
A	Cen-A1	■			■			■	■	■	■	■					■	■	Tel-A1
B	Cen-A1	■			■			■	■	■	■		■	■	■	■		■	Tel-B1
	Cen-B1	■	■	■						■	■	■					■	■	Tel-A1
	Cen-B2	■	■	■		■	■	■	■	■	■	■					■	■	Tel-A1
	Cen-B1	■	■	■						■	■		■	■	■	■		■	Tel-B1
	Cen-B2	■	■	■		■	■	■	■	■	■		■	■	■	■		■	Tel-B1

(A) The gene content of the common motifs is shown. The conserved framework genes are shaded grey, B haplotype genes are blue, and A haplotype genes are green.

Table B

B content score	0	1		2			3		4
Centromeric part	A/A	A/A	A/B	A/A	A/B	B/B	A/B	B/B	B/B
Telomeric part	A/A	A/B	A/A	B/B	A/B	A/A	B/B	A/B	B/B

(B) The KIR B-content score is calculated by adding the number of Cen-B and/or Tel-B motifs.

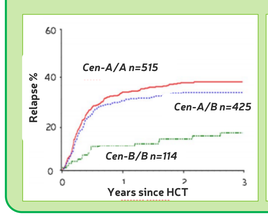


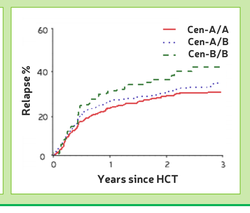
Almost identical distributions of 3DL1 strong / weak /non-inhibiting and 2DS1 activating / non activating donor-recipient constellations were found in our data as compared to the study from Boudreau, JCO, 2017.

Study Results

Donor KIR centromeric genotypes

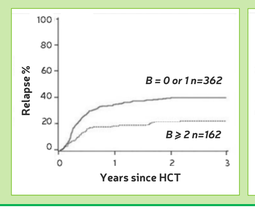
Donor KIR	Cooley et al Study				EBMT/CIBMTR Study			
	n	RR	95% CI	p value	n	HR	95% CI	p value
Cen-A/A	515	1.00			798	1.00		
Cen-A/B	425	0.87	0.70-1.09	.20	735	1.17	0.96-1.43	.13
Cen-B/B	114	0.34	0.20-0.57	<.001	171	1.20	0.89-1.63	.23

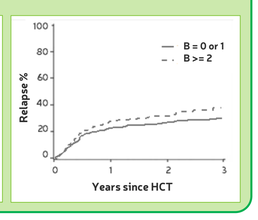




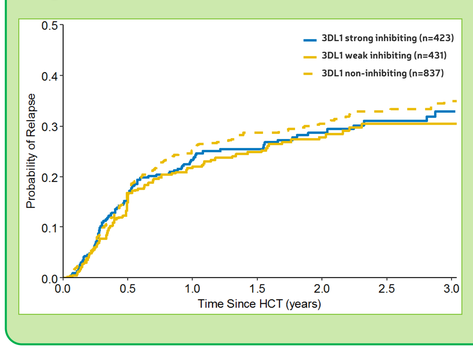
HLA-matched donor KIR B-content group

Donor KIR	Cooley et al Study				EBMT/CIBMTR Study			
	n	RR	95% CI	p value	n	HR	95% CI	p value
B = 0 or 1	374	1.00			955	1.00		
B ≥ 2	165	0.52	0.36-0.75	<.001	450	1.16	0.93-1.44	.19

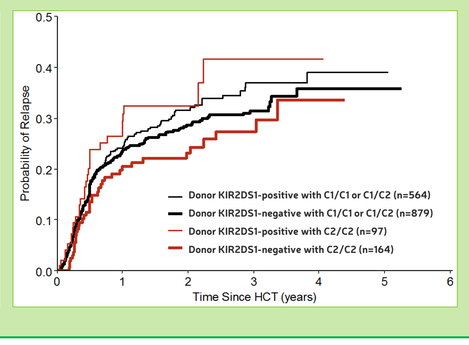




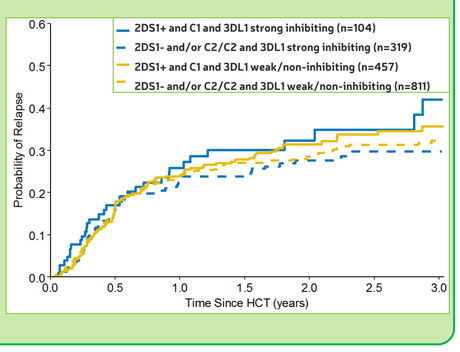
Donor KIR3DL1 – Ligand Interaction



Donor KIR2DS1 – Ligand Interaction



Donor 3DL1 and 2DS1 – Ligand Interaction



*Hazard Ratios from multivariable Cox-Models are adjusted for: registry, patient & donor age, CMV & sex constellation, HLA-match, performance status, diagnosis, disease risk index, conditioning intensity, T-cell depletion and stem cell source.

Conclusions & Outlook

Donor-KIR-gene based classification using information on 2DS1/3DL1 KIRs to predict risk of relapse could not be replicated in a large cohort of MDS/sAML patients. Impact of donor KIR haplotype using different classification approaches on the risk of relapse could not be replicated. Differences in transplant procedures between the original and contemporary cohorts may impact on NK-cell alloreactivity. The clue to predict NK alloreactivity has not yet been found.

Next steps:

- ⇨ Explore more genotype information
- ⇨ Create 'Data Warehouse' to speed up research
- ⇨ Engage in collaborations

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CoBi COLLABORATIVE BIOBANK Collaborative Biobank, E-Mail: biobank@dkms.de, Website: www.cobi-biobank.org