Donor KIR-Haplotype B Content does not Impact on Outcome after Unrelated Hematopoietic Stem Cell Transplantation in a Large Cohort of Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome

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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 complex (MHC). 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 & 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 the results of the largest confirmatory study, published so far, are reported.

Medical Data

HCT outcome data from 2,222 patients from German Registry for Stem Cell Transplantation & German Cooperative Transplant Study

Geno-type

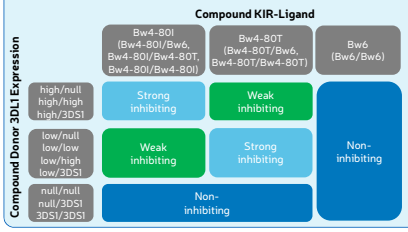
Allele-level KIR-typing of donor samples with high-resolution amplicon-based Next Generation Sequencing (NGS) method

Patient and Transplant Characteristics

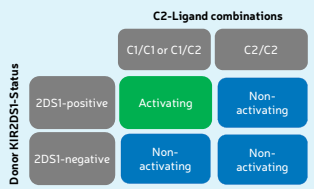
Characteristics		This Study	Boudreau, JCO, 2017 (Venstrom, NEJM, 2012)	Cooley , Blood, 2010
Number of patients		2,222	1,328 (1,277)	1,086
Patient's age in years, median (range)		59 (18 – 79)	41 (0 – 75)	39 (1 – 70)
Diagnosis	AML / MDS	80% / 20%	100% / 0%	100% / 0%
Year of HCT	< 2009 / ≥2009	6% / 94%	100% / 0%	100% / 0%
Conditioning	MAC / Other	20% / 80%	86% / 14%	(100%? / 0%?)
Stem cell source	PBSC / BM	4% / 96%	46% / 54%	41% / 59%
HLA match	10/10 / ≤9/10	81% / 19%	54% / 46%	50% / 50%
T-cell depletion	Yes / No	81% / 19%	8% / 92%	(0%? / 100%?)

Outline of Current Classification Approaches

KIR3DL1/Bw4-Ligand combinations



KIR2DS1/C2 combinations



Boudreau, JCO, 2017

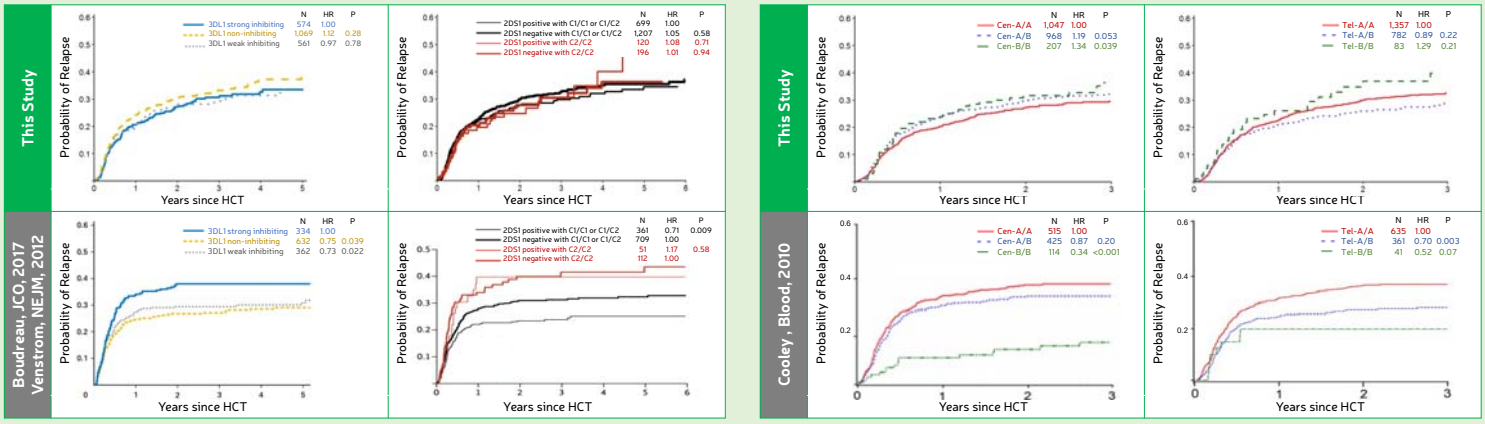
Donor KIR Haplotypes

		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
	Cen-A1	■			■			■	■	■	■		■	■	■	■		■	Tel-B1
B	Cen-B1	■	■	■						■	■	■					■	■	Tel-A1
	Cen-B2	■	■	■		■	■	■	■	■	■								Tel-A1
	Cen-B1	■	■	■						■	■		■	■	■	■		■	Tel-B1
	Cen-B2	■	■	■		■	■	■	■	■	■								Tel-B1

Conserved framework genes are shaded grey. B haplotype genes are displayed in blue, A haplotype genes in green.

Cooley, Blood, 2010

Comparison of Study Results



Multivariate analysis of relapse incidence by means of Cox regression models adjusted for patient age, donor age, disease risk, performance status, HLA-/CMV- and sex-match, conditioning regimen, T-cell depletion and graft type. Almost identical distributions of 3DL1 strong/weak/non-inhibiting and 2DS1 activating/non activating donor-recipient constellations and donor KIR B-haplotypes were found in this study compared to the studies from Boudreau et al., Venstrom et al. and Cooley et al.. However, the characteristic pattern of relapse incidence published was not observed. This was also true for the subgroup analyses in patients with or without myeloablative conditioning, with HLA-compatible donors, with AML or MDS, with or without ATG, or with or without total body irradiation.

Conclusions

The 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 patients with AML/MDS. Also, the impact of donor KIR haplotype on the risk of relapse could not be replicated. Striking differences between the transplant procedures of the original and the contemporary cohort may explain the conflicting results. NK alloreactivity cannot be predicted universally.

Next Steps

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

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