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POSTER ABSTRACTS

732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

Donor NK Cell Education By *KIR3DL1* and *HLA-B* Associates with Reduced Relapse in Unrelated Bone Marrow Transplantation for Adult T-Cell Leukemia

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Background: Adult T-cell leukemia/lymphoma (ATL) derives from human T-cell leukemia virus-1 (HTLV-1)-infected T cells, and its prognosis is still dismal. Whereas allogeneic stem cell transplant (allo-HSCT) may lead to long-term remission, 1-year relapse rate is still high at 35-47% (Muranushi *et al*, *Bone Marrow Transplant*. 2021). As for NK cell modulation against ATL, polymorphisms of killer-cell immunoglobulin-like receptors (KIRs) are of interest. NK cell inhibition by donor KIR/patient HLA interaction and NK cell education status have been reported to affect the prognosis of allo-HSCT, but no consensus has been reached. Furthermore, the effects of entire KIR haplotypes have not been extensively studied.
Aim: Using high-resolution genotyping of all 15 functional KIR genes based on long-range PCR and long-read sequencer, correlations between KIR/HLA polymorphisms and relapses in unrelated bone marrow transplantation (UR-BMT) for ATL were evaluated.
Methods: DNAs and clinical data of 264 transplants performed between 2007 and 2016 were obtained. Alleles of 15 *KIRs*, *HLA-A*, *B*, *C*, *DRB1*, *DPB1* and *DQB1* were genotyped for patients and donors. Prognostic factors for relapse were evaluated using the Fine-Gray proportional-hazards models.
Results: Donor *KIR3DL1* and patient *HLA-B* combination predictive of strong interaction (n=74) showed a trend for a lower relapse rate than weak or non-interactive combinations (n=145) (HR, 0.64; p=0.100), raising the beneficial impact of donor NK cell education at KIR3DL1/HLA-B interaction. Comprehensive analysis focusing on amino acids of donors' KIRs/HLAs specified combinations of *HLA-B* isoleucine 80 (80I)/ *KIR3DL2* aspartic acid 42 and *HLA-B* threonine 80 (80T)/ *KIR3DL2* glutamic acid 42 (n=76) associated with decreased relapse (HR, 0.35; 95%CI, 0.19-0.65; p=0.00087). On the other hand, combinations of *HLA-B* glutamic acid 152 (152E)/ *KIR2DL4* cysteine 30 and *HLA-B* valine 152 (152V)/ *KIR2DL4* tyrosine 30 (n=27) were associated

with increased relapse (HR, 11.79; 95%CI, 1.6-86.58; p=0.015). Given that *KIR3DL2/ KIR2DL4* do not bind *HLA-B* and are closely linked to *KIR3DL1/S1* in KIR haplotypes, specific *KIR3DL1/S1* alleles were further explored by subgroup analyses. As a result, combinations of *HLA-B* 80I/ *KIR3DL1*015*& *KIR3DL2*002* and *HLA-B* 80T/ *KIR3DL1∗001*, *∗005*, *∗007*, *∗020*, *∗038*, *∗097* (n=60) were defined as the group at low risk for relapse (adjusted HR, 0.21; 95%CI, 0.09-0.48; p=0.00026) (Figure 1A), and combinations of *HLA-B* 152E/ *KIR3DS1* and *HLA-B* 152V/ *KIR3DL1∗001*, *∗007*, *∗015*, *∗020*, *∗029*, *∗038* (n=176) were defined as the group at high-risk for relapse (adjusted HR, 5.31; 95%CI, 1.72-16.39; p=0.0037) (Figure 1B). The cases in the low-risk group and/or not in the high-risk group (n=84) had a lower relapse rate (adjusted HR, 0.20; 95%CI, 0.10-0.40; p=0.0000059) (Figure 1C) and a higher overall survival (adjusted HR, 0.66; 95%CI, 0.46-0.95; p=0.0265389) (Figure 1D) than the remaining cases (n=130). In spite of reduced relapse rate, the former showed a lower rate of grades II-IV acute GVHD (HR 0.65; p=0.049). Finally, CD107a degranulation of NK cells was measured following coincubation of HLA-null K562 cells and PBMCs from healthy donors with or without genotypes of the low-risk group. KIR3DL1(+) NK cells showed increased CD107a degranulation compared with KIR3DL1(−) NK cells in healthy donors with the low-risk group genotype (p=0.031), but this difference was not apparent in healthy donors without the low-risk group genotype (p=0.28) (Figure 2).
Conclusions: Allelic genotyping of KIRs enabled to specify donors associated with reduced relapses. Donor NK cell education status at HLA-B/KIR3DL1 interaction might confer enhanced GVT effects and better prognosis in UR-BMT against ATL.

Disclosures Kanda: *Sanofi K.K.:* Honoraria; *AbbVie Pharma:* Honoraria; *Novartis Pharma K.K.:* Honoraria; *Janssen Pharmaceutical K.K.:* Honoraria; *Amgen:* Ended employment in the past 24 months, Honoraria; *Megakaryon Co.:* Honoraria; *Eisai Co.:* Research Funding. **Kato:** *AbbVie:* Consultancy, Research Funding; *AstraZeneca:* Consultancy; *Chugai:* Consultancy, Honoraria, Research Funding; *Daiichi Sankyo:* Consultancy, Research Funding; *Eisai:* Consultancy, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; *MSD:* Honoraria, Research Funding; *Bristol-Myers Squibb:* Honoraria, Research Funding; *Kyowa Kirin:* Honoraria, Research Funding; *Ono:* Honoraria, Research Funding. **Imada:** *Sanofi K.K.:* Honoraria; *AbbVie GK.:* Honoraria; *Alexion Pharmaceuticals, Inc.:* Honoraria; *Nippon Kayaku Co., Ltd.:* Honoraria; *AstraZeneca K.K.:* Honoraria; *Towa Pharmaceutical Co., Ltd.:* Honoraria; *Janssen Pharmaceutical K.K.:* Honoraria; *Ono Pharmaceutical Co., Ltd.:* Honoraria; *Meiji Seika Pharma Co. Ltd.:* Honoraria; *Astellas Pharma Inc.:* Honoraria; *Otuka Pharmaceutical Co. Ltd.:* Honoraria; *Chugai Pharmaceutical Co., Ltd.:* Honoraria; *Nippon Shinyaku Co., Ltd.:* Honoraria; *Novartis Pharma K.K.:* Honoraria; *Takeda Pharmaceutical Co. Ltd.:* Honoraria; *Bristol-Myers Squibb K.K.:* Honoraria; *Kyowa Hakko Kirin Co., Ltd.:* Honoraria; *Amgen K.K.:* Honoraria. **Suehiro:** *Meiji Pharma:* Honoraria; *Pfizer:* Honoraria; *Janssen:* Honoraria; *Sanofi:* Honoraria; *Nippon Shinyaku:* Honoraria; *Kyowa Kirin:* Research Funding; *Incyte:* Research Funding; *Otsuka:* Research Funding; *Amgen:* Research Funding; *BMS:* Honoraria; *Abbvie:* Honoraria, Research Funding; *Teijin:* Research Funding; *Nippon Kayaku:* Honoraria, Research Funding; *Genmab:* Honoraria, Research Funding; *Chugai:* Honoraria, Research Funding. **Ichinohe:** *Repertoire Genesis Inc.:* Research Funding; *Chugai Pharmaceutical Co.:* Research Funding; *Kyowa Kirin Co.:* Research Funding; *Takeda Pharmaceutical Co.:* Research Funding; *Ono Pharmaceutical Co.:* Research Funding; *Nippon Shinyaku Co.:* Research Funding. **Atsuta:** *Otsuka Pharmaceutical Co., Ltd:* Speakers Bureau; *CHUGAI PHARMACEUTICAL CO., LTD.:* Speakers Bureau; *Meiji Seika Pharma Co, Ltd.:* Honoraria; *JCR Pharmaceuticals Co., Ltd.:* Consultancy; *Novartis Pharma KK:* Speakers Bureau. **Takaori-Kondo:** *Shionogi Pharma:* Other; *AbbVie:* Other; *Kinshikourainininjin:* Other; *Ohara Pharmaceutical:* Other; *Eisai:* Other; *Chugai Pharmaceutical:* Other; *Kyowa Kirin:* Other: Subsidies ; *Takeda Pharmaceutical:* Other: Subsidies; *Pharma Essentia Japan:* Research Funding; *DKS Co. Ltd.:* Research Funding; *COGNANO:* Research Funding; *Ono Pharmaceutical:* Research Funding; *Megakaryon:* Honoraria; *Otsuka Pharmaceutical:* Honoraria, Other: Subsidies ; *Janssen Pharmaceutical K.K:* Honoraria; *Bristol Myers Squibb:* Honoraria; *Nippon Shinyaku Co., Ltd.:* Honoraria, Other: Subsidies; *ASAHI KASEI PHARMA:* Other.

Figure 1

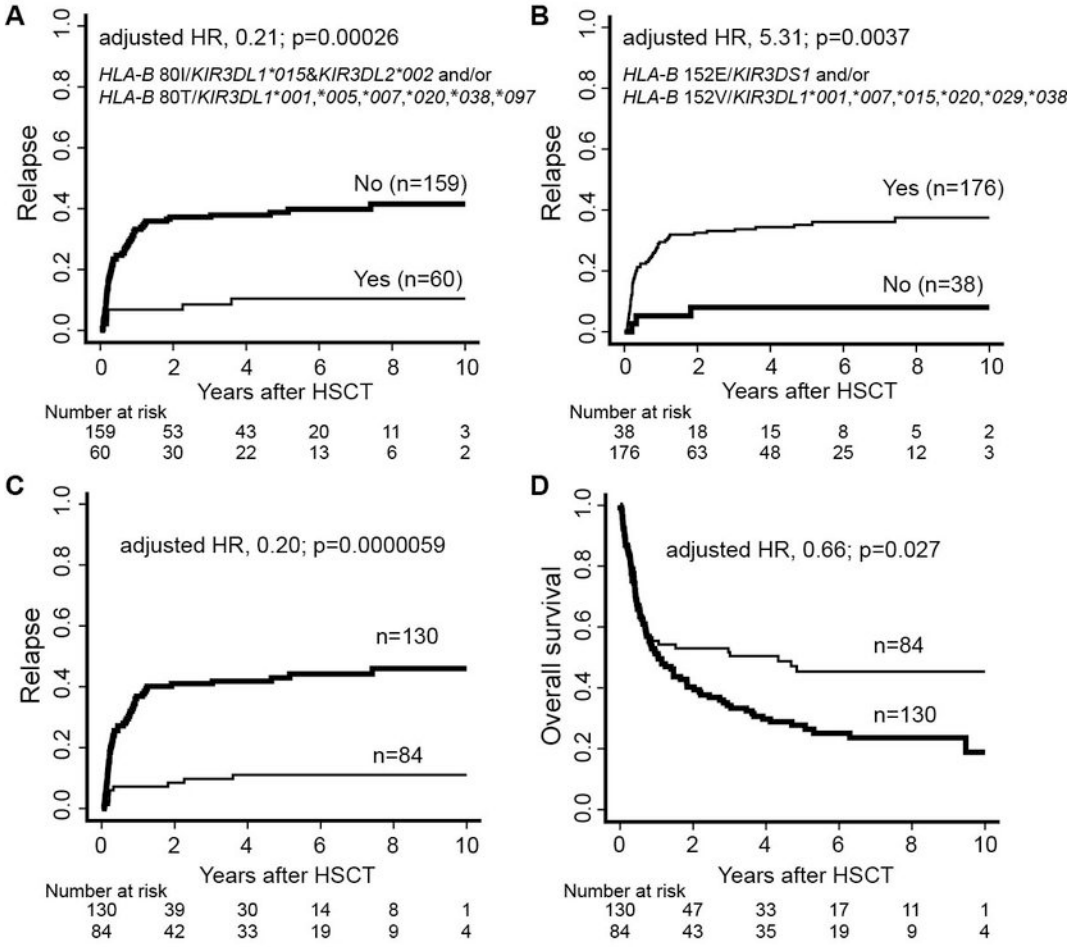

Figure 2

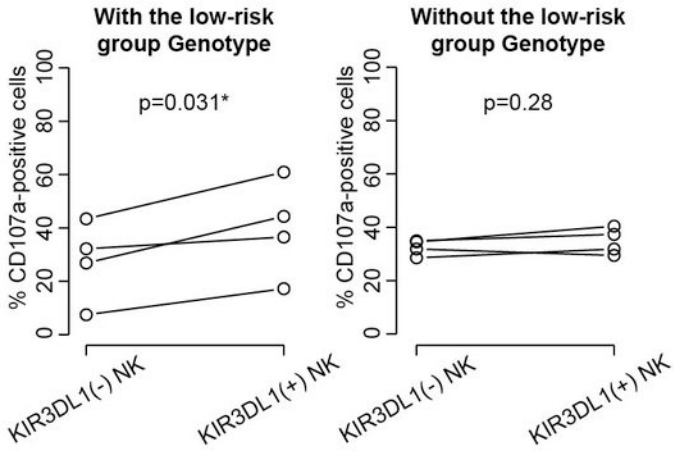

Figure 1

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