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ORAL ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

HLA Class I Genotypes Predict the Survival after Hematopoietic Stem Cell Transplantation in Immune Aplastic Anemia

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Introduction
Immune aplastic anemia (AA) is a bone marrow failure syndrome mediated by cytotoxic T cells, leading to the loss of HLA class I allele expression in hematopoietic stem and progenitor cells. In unrelated hematopoietic stem cell transplantation (HSCT), we recently reported an association between HLA loss and a short time to transplantation (TTT), consistent with an abrupt onset of immune AA. In addition, patients who lost *HLA-A*02:06* or *HLA-B*40:02* showed better survival outcomes after HSCT than those with other HLA allele losses. To clarify the clinical significance of the loss of specific HLA class I alleles in AA, we correlated loss-prone HLA class I allele genotypes with HSCT outcomes in patients with a short TTT, assuming the frequent absence of these alleles in this subgroup.
Methods
We conducted a nationwide retrospective analysis of patients with acquired AA ≥16 years old who underwent their first allogeneic HSCT in Japan between 2006 and 2020. Patient data were obtained from the Transplant Registry Unified Management Program (TRUMP ®), a comprehensive Japanese HSCT registry.
Results
From 1025 patients with acquired AA, we excluded patients with drug-induced AA and those missing 2-field HLA allele information and TTT information, leaving 874 patients for the analysis. The median patient age at HSCT was 34 years old, and the median TTT was 14 months. When focusing on the most frequently absent HLA class I alleles in Japanese patients with AA, including *HLA-B*40:02*, *HLA-A*02:06*, *HLA-A*02:01*, *HLA-B*54:01*, and *HLA-A*31:01*, all 5 alleles were associated with higher survival rates than in 220 patients without these alleles (Figure 1A). As expected, this association was more pronounced with a

shorter TTT. For instance, among the 424 patients with a TTT <14 months, the 5-year survival rates were 79%, 78%, 85%, 78%, and 81% in patient groups with the respective HLA class I alleles above, while it was 55% in the other 101 patients (Figure 1B). Of note, having any of the 5 alleles (5-allele $^{+}$) proved to be the best predictor of a survival out of 242792 combinations of 2 to 5 *HLA-A*, *HLA-B*, and *HLA-DRB1* alleles. To adjust for potential confounders, such as age and graft sources, we performed propensity score matching and confirmed that the overall survival was significantly lower in patients without any of the 5 alleles (5-allele $^{-}$) than in 5-allele $^{+}$ patients ($P = .00018$). A multivariable Cox regression analysis including age, AA severity, prior IST, graft sources, HLA disparity, and *HLA-B* leader peptide dimorphism as covariates further demonstrated that the 5-allele genotype was an independent predictor of the survival. The consistent effect of the 5 alleles on the survival has been internally validated across various subgroups. In contrast, the 5 HLA class I alleles did not affect the survival in patients with hematological malignancies, including acute myeloid leukemia, acute lymphoblastic leukemia, and myelodysplastic syndrome. Regarding other post-HSCT complications, 5-allele $^{-}$ AA patients had a higher incidence of primary graft failure (GF) than 5-allele $^{+}$ AA patients, even when deaths before engraftment were censored and when compared to the propensity score-matched patients. Nevertheless, the 5 HLA alleles continued to stratify the survival among patients who achieved engraftment ($P < .0001$). There were no significant differences in the incidence of acute and chronic graft-versus-host disease, late GF, or cause of death between 5-allele $^{-}$and 5-allele $^{+}$ AA patients. To further stratify the survival rate in 5-allele $^{-}$ AA patients with a short TTT, we examined the impact of other HLA class I alleles and found that patients carrying *HLA-B*07:02* or *HLA-B*48:01*, in which HLA loss had been previously detected in some AA patients, showed a particularly poor survival (Figure 1C; $P = .0082$). This association remained significant even after propensity score matching ($P = .031$).

Conclusions

Significant associations between specific loss-prone HLA class I alleles and diverse survival outcomes after HSCT in AA patients with short TTT indicate the relevance of HLA information in patient selection for allogeneic HSCT. These findings also support the existence of a distinct immune pathogenesis affecting the clinical manifestations of AA differently, as observed in IST-treated patients. Further investigations in other ethnic groups are required to validate these observations.

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Figure 1

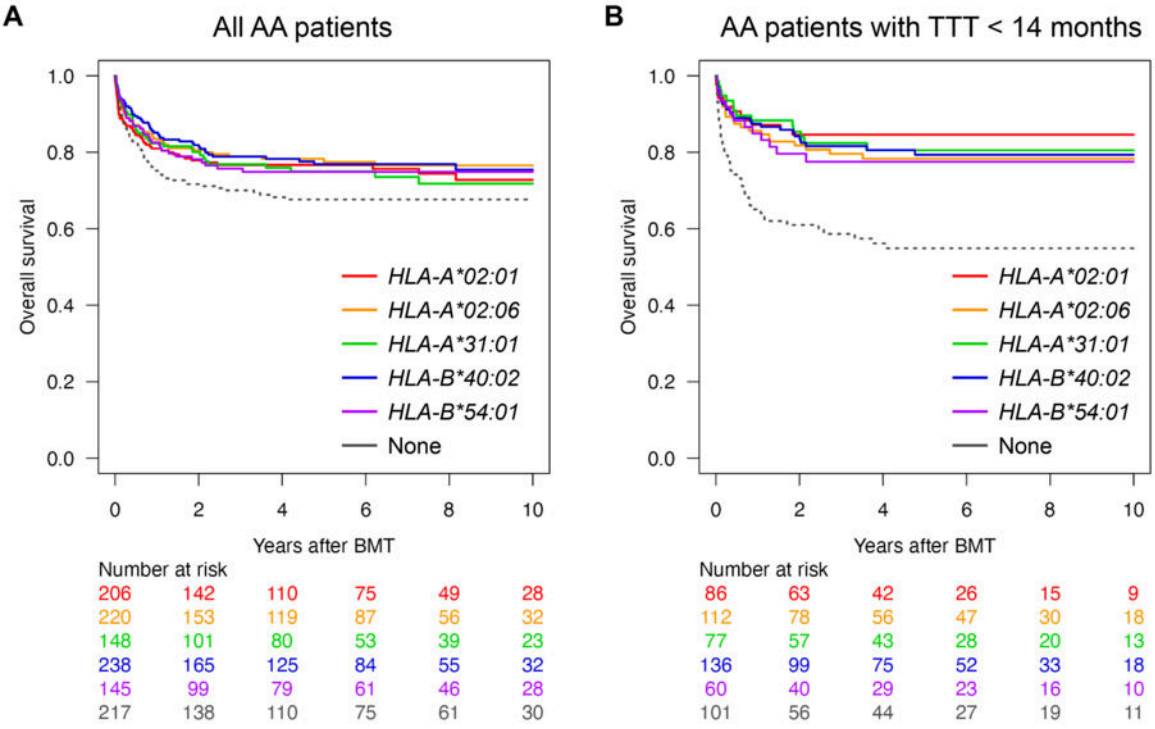

Figure 1

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