Synergistic Impact of Donor KIR-BX Haplotypes and Recipient HLA-C1 Homozygosity on Survival Outcomes in Pediatric Haploidentical Hematopoietic Cell Transplantation: A Retrospective Cohort Study of 153 Cases

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Introduction

Donor KIR-B/X haplotypes have demonstrated survival benefits in adult acute myeloid leukemia (AML) patients undergoing unrelated hematopoietic cell transplantation (HCT) through natural killer (NK) cell-mediated alloreactivity, particularly in patients carrying HLA-C1 allele[1]. This KIR-HLA interaction was further validated in cord blood transplantation cohorts showing reduced relapse-related mortality[2]. Recent evidence suggests that in anti-thymocyte globulin (ATG)-based haploidentical HCT (haplo-HCT), the enhanced activating KIR (aKIR) profile of B/X haplotypes may potentiate NK cell cytotoxicity, improving outcomes in adult AML[3]. However, the pediatric-specific interplay between donor KIR haplotypes (AA vs B/X) and recipient HLA-C polymorphisms remains uncharacterized.

Methods

We analyzed 153 consecutive pediatric patients (median age of 8 years old; 82 AML, 60 ALL, 7 MPAL, 4 other malignancies) undergoing ATG-based haplo-HCT (Beijing protocol) between 2017 and 2023 at Beijing Children's Hospital. The median follow-up was 567 days (IQR: 279-1335). Recipients were stratified by HLA-C status (C1/C1 vs C2+ [C1/C2 or C2/C2]), with comprehensive KIR genotyping performed for all donors. Primary endpoints included overall survival (OS), disease-free survival (DFS), relapse incidence, relapse related mortality (RRM), and non-relapse mortality (NRM). Survival analyses employed Kaplan-Meier methodology with log-rank testing, while competing risks were assessed using cumulative incidence function method with Gray's test. Multivariable Cox regression models were used to adjust for disease type and age.

Figures

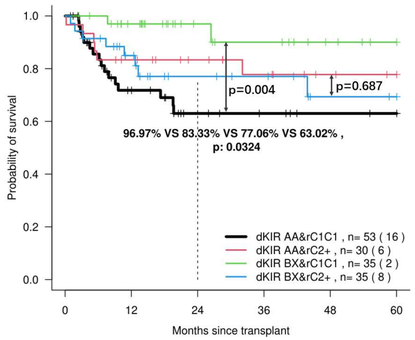

Figure 1. Synergistic analysis of donor KIR haplotype and recipient HLA-C for overall survival

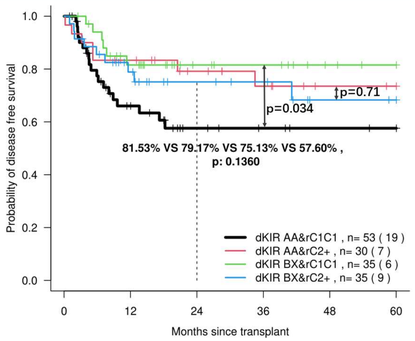

Figure 2. Synergistic analysis of donor KIR haplotype and recipient HLA-C for disease free survival

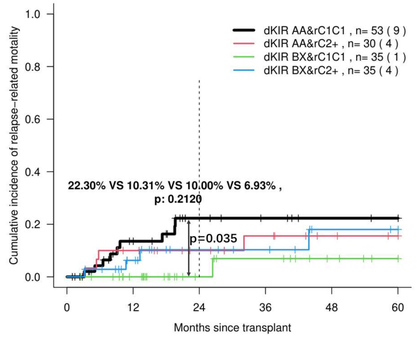

Figure 3. Synergistic analysis of donor KIR haplotype and recipient HLA-C for relapse related mortality

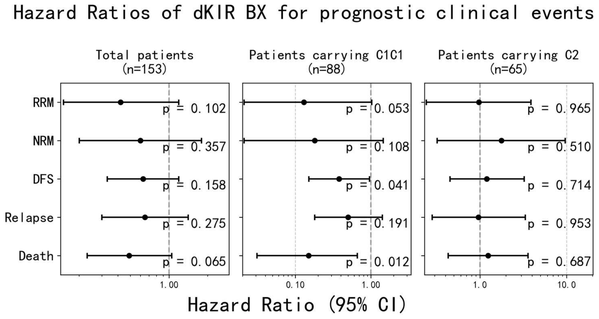

Figure 4. Forrest plot for hazard ratios of dKIR BX for prognostic clinical events with different patient groups

Interpretation of figure legends: **dKIR AA**, donor with KIR AA haplotype; **dKIR BX**, donor with KIR B/X haplotype; **rC1C1**, recipient carrying C1C1 of HLA-C**; rC2+**, recipient carrying C2 of HLA-C.

Results

Significant outcome disparities emerged in HLA-C1/C1 recipients (n=88). Those receiving KIR-B/X grafts (n=35) exhibited:

- superior 2-year OS (97.0% vs 63.0%, p=0.004)
- superior 2-year DFS (81.5% vs 57.6%, p=0.034)
- lower 2-year RRM (6.9% vs 22.3%, p=0.035)

when compared to KIR-AA donors (n=53), with non-significant trends toward lower relapse incidence (15.4% vs 25.5%, p=0.371) and NRM (3.0% vs 14.5%, p=0.078).

Conversely, C2+ recipients (n=65) showed comparable outcomes between KIR-B/X (n=35) and KIR-AA (n=30) donors (2-year OS: 77.1% vs 83.3%, p=0.687).

Multivariable analysis confirmed donor KIR-B/X haplotype as an independent prognostic factor for C1/C1 patients (OS: p=0.009).

Conclusions

This study establishes HLA-C1 homozygosity as a critical biological determinant of donor KIR-B/X efficacy in pediatric haplo-HCT. The dichotomous outcomes based on HLA-C polymorphism underscore the necessity for integrated KIR/HLA profiling in donor selection algorithms for C1/C1 pediatric recipients. These findings warrant prospective validation through multicenter trials to establish evidence-based guidelines for immunogenetic donor optimization.

References

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[2] Sun, Zimin, et al. "Refining eligibility criteria of unit selection for myeloablative cord blood transplantation in acute leukemia: Real-world experience of a referral center." *EJHaem* 4.2 (2023): 470-475.
[3] Zhang, Yu, et al. "Association of iKIR-mismatch model and donor aKIRs with better outcome in haploidentical hematopoietic stem cell transplantation for acute myeloid leukemia." Frontiers in Immunology 13 (2023): 1091188.

Acknowledgements

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