HLA-Mismatched, Noninherited Maternal Antigen–Matched Unrelated Cord Blood Transplantations Have Superior Survival: How HLA Typing the Cord Blood Donor’s Mother can Move the Field Forward

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The fetus inherits one HLA haplotype from the father (ie, inherited paternal antigens [IPA]) and one HLA haplotype from the mother (ie, inherited maternal antigens [IMA]) (Figure 1). During pregnancy, bidirectional transplacental trafficking of cells exposes the fetus to maternal cells expressing both IMA and noninherited maternal antigens (NIMA), resulting in the development of NIMA-specific responses. Furthermore, fetal cells enter the maternal circulation, sensitizing the mother to the IPA of the fetus [1,2].

FETAL TOLERANCE TO NIMA

The “NIMA effect” has been studied extensively. A possible mechanism for this effect, proposed by Mold et al. [3], involves the development of CD4+CD25+Fox+ regulatory T cells that suppress fetal responses specifically to NIMA. The presence of regulatory T cells has been implicated in the role of NIMA in related kidney [4] and related hematopoietic stem cell transplantations [5]. Recent studies also indicate that these regulatory T cells are responsible for suppressing the expansion of donor alloreactive cells that cause graft-versus-host disease (GVHD). Importantly, however, they do not abrogate the cytotoxic effect of the graft-versus-tumor function [6]. An alternative mechanism, proposed by Mommaas et al. [7], is that cord blood (CB) carries NIMA-specific cytotoxic CD8 T cells capable of lysing targets in vitro. Additional evidence for the presence of cytotoxic and regulatory CD8 cells in CB comes from the study of van Halteren et al. [8], which identified CD8 cells against maternal minor H antigens in offspring.

MATERNAL MICROCHIMERISM IN FETUS AND CB

Small numbers of maternal cells can be detected in fetal tissues [9], as well as in CB samples [10]. Some of these maternal cells are memory lymphocytes, which can persist for long times. These maternal T cells have been exposed and sensitized to the IPA expressed on the fetal cells that enter in the maternal circulation. The presence of anti-IPA cells may be responsible for the superior outcomes of haploidentical T cell–depleted transplantations from maternal donors compared with those from paternal donors [11].

MATERNAL–FETAL INTERACTIONS AFFECT UNRELATED CB TRANSPLANTATION OUTCOMES

The first study to evaluate the impact of fetal exposure to NIMA on the outcome of unrelated CB transplantations was published in 2009 [12]. The hypothesis that exposure to NIMA during fetal life would have an effect on transplantation outcomes in cases with an NIMA match between CB donor and recipient was evaluated in 1,121 patients with hematologic malignancies who received single-unit CB grafts from the New York Blood Center. Patients were assigned in 3 groups: those with 0 mismatched (MM) grafts (n = 62; 6% of total), those with HLA-MM, NIMA-matched (M) grafts (n = 79; 7% of total), and those with HLA-MM, no NIMA-M grafts (n = 980). Of note, NIMA matching was assigned retrospectively, so matches occurred only by chance; the CB grafts were not selected based on NIMA.

The analysis showed statistically significant improvements in transplantation-related mortality, overall mortality, and treatment failure for HLA-MM, NIMA-M grafts, as well as improved engraftment, particularly in recipients of lower cell doses. Overall, outcomes of 1 HLA-MM, NIMA-M grafts were
similar to those of 0 MM grafts. Importantly, post-transplantation relapse tended to be lower in patients with myeloid malignancies who received 1 HLA-MM, NIMA-M CB units. Recipients of HLA-MM, NIMA-M grafts had no increased incidence of GVHD [12].

The study by Rocha et al. [13] published in this issue of *Biology of Blood and Marrow Transplantation* aimed to confirm the superior outcomes of HLA-MM, NIMA-M CB grafts. Using a smaller patient cohort and a different analytic approach, the authors compared results in 48 recipients of HLA-MM, NIMA-M CB grafts and 118 recipients of HLA-MM, NIMA-MM CB grafts. This study also assigned NIMA matches retrospectively, using similar assignments as in the New York Blood Center analysis (although not described in detail). Among the 508 eligible patients, the frequency of NIMA-M CB grafts was 8.5%. Importantly, in this study, transplantation-related mortality was lower in recipients of NIMA-M grafts (RR, 0.48; \( P = .05 \)). Consequently, overall survival was higher after NIMA-M CB transplantations; the 5-year probability of overall survival was 55% with NIMA-M grafts versus 38% with NIMA-MM grafts (\( P = .04 \)). Outcomes of 1 HLA-MM, NIMA-M transplantations are not shown separately in this analysis, to allow direct comparison with the previous study [12]. No effects on engraftment, incidence of GVHD, or relapse were detectable.

**WHAT ARE THE NEXT STEPS?**

Transplantation with HLA-MM, NIMA-M CB grafts was not associated with adverse effects in either study. Furthermore, using different analytical approaches, both studies showed significantly improved posttransplantation survival. Although the precise mechanism remains unclear, the previous work on the effects of NIMA on transplantation supports further study. Moreover, the recent finding of a lower relapse rate in patients with hematologic malignancies who shared IPA targets with their CB donors [14] further highlights the beneficial role of fetal-maternal interactions and warrants additional studies in this area.

To overcome the low frequency of NIMA-M grafts occurring just by chance and involving the more common HLA antigens [13], preferential selection of NIMA-M CB units will substantially increase the number of patients that can be evaluated in a relatively short time. This strategy will require HLA typing of the CB donor mothers, to allow assignment of NIMAs before final CB unit selection. The approach may be somewhat complex, but the first steps have already been implemented by Bone Marrow Donors Worldwide, with the inclusion of NIMA in CB search algorithms [15]. Another important consideration is evaluation of the NIMA effect in the outcomes of the large proportion of patients receiving double-unit CB grafts.

**WHAT ARE THE IMPLICATIONS?**

Unrelated CB is an increasingly used alternative stem cell source for patients requiring hematopoietic reconstitution, particularly those of ethnic minorities. Despite the expanding worldwide inventory (approximately 600,000 CB units according to the World Marrow Donors Association), the majority of patients do not receive HLA-A, -B, -DRB1 M HLA grafts [16]. Including NIMA in the search algorithm allows for the selection of “permissible” mismatches that lead to superior clinical outcomes. The numerical improvement in the probability of finding donor grafts by including NIMA in CB searches is currently under evaluation (van der Zanden et al., manuscript in preparation). The cost-effectiveness of such an approach must be assessed, considering the costs of adding a large number of new, HLA-diverse CB units to the inventory (for the banks) or the costs related to posttransplantation complications (for the transplantation centers).

**CONCLUSION**

Paraphrasing Rocha et al. the statistically significant survival advantage associated with NIMA-matched transplantations cannot be ignored. CB banks need to implement maternal HLA typing on CB units, and transplantation centers should use NIMA in CB selection algorithms and select CB units that lead to improved transplantation outcomes, enhancing the overall efficacy of unrelated CB transplantation.
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REFERENCES