Fetal Maternal Immunity and Antileukemia Activity in Cord Blood Transplant Recipients

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Umbilical cord blood has become a viable and widely used alternative stem cell source for patients with hematologic diseases in need of hematopoietic cell transplant (1-4). Several studies have reported comparable survival rates for adult cord blood transplant (CBT) recipients when compared to unrelated donor (URD) peripheral blood or bone marrow transplantation [5-6]. Moreover, Brunstein et al. recently reported a lower rate of relapse among double CBT recipients than patients who received either matched or mismatched URD transplants [7]. The vast majority of CBT recipients receive highly HLA-mismatched grafts which may contribute to the lower incidence of relapse. Interestingly, a recent study suggests maternal cells in CB grafts that are sensitized to fetal inherited paternal antigens (IPAs) [Figure 1] may also contribute to the lower incidence of relapse [8].

Fetal exposure to noninherited maternal HLA antigens (NIMA) [Figure 2] is thought to produce tolerance to NIMA, and improved outcome was previously reported when NIMA of the CB donor was shared by a recipient [9]. On the other hand, during pregnancy women develop B- and T-cell immunity against fetal histocompatibility antigens (HLA) and minor histocompatibility antigens that are paternally-inherited. Although CB grafts consist primarily of fetal cells, some maternal cells are present [10,11]. Indirect evidence reported by van Rood and colleagues strongly implicates maternal immune cells with anti-IPA activity in the graft versus leukemia (GVL) effect observed with CBT. Maternal cells are implicated because relapse was reduced specifically when the transplant recipient had one or more HLA antigens that were the same as an IPA of the CB donor [8]. The study included patients with hematological malignancies (n=1155) who were transplanted with a single CB unit from the New York Cord Blood Bank between 1993 and 2006. The majority of patients (n=1030) shared one or more HLA antigens with CB IPAs and had at least 1, 2 or 3 HLA-A, -B, -DRB1 mismatches. No differences, with respect to total nucleated cell dose and patient characteristics, were seen between no-shared IPA (n=64) and shared IPA transplants. Interestingly, the risk of relapse within the first 3 years was significantly lower among the patients with shared-IPA than those that with no shared-IPA. The risk reduction was stronger in patients who received CBT that had one HLA mismatch. In this group of patients lower relapse risk was associated with a lower risk of treatment failure, although without significant improvement in overall survival.

Of note, van Rood et al. also showed that the risk of relapse was lower when the CB unit came from a later birth order versus a first birth, further supporting a role of maternal exposure to fetal paternally-inherited HLA-antigens. In addition, when HLA mismatch of the mother and the CBT recipient was considered in a multivariate model, the association between shared-IPA and relapse risk reduction remained significant. The latter analysis confirmed that the GVL effect could not be attributed to maternal mismatch but was putatively due to maternal cells with anti-IPA activity. The price to pay for increased GVL activity was a slightly higher risk of acute grade III-IV graft-versus-host-disease (GVHD) among patients with shared IPAs. However, GVHD incidence was only significant in patients with 2 HLA mismatches, and not significant in patients with only 1 HLA mismatch.

This important work brings a new perspective to the way we think of the immunological potential of CBT. The anti-leukemia activity of CB grafts is likely due at least in part to

maternal immune cells contained within the graft conferring a potent GVL effect. However, this indirect evidence needs now to be followed by specific work that identifies and characterizes the type of maternal cells in CB and the mechanism of action for the observed GVL effect. From a practical standpoint, the evaluation of IPA match in CB selection can be considered at the time a CB donor search is initiated. Although the majority of patients will share one or more antigen with CB IPAs, the benefit of knowing IPAs along with NIMA is likely to improve CB unit selection and consequently to significantly enhance the efficacy of CBT for patients with hematological malignancies.

Potential conflicts of interest: All authors report no potential conflict of interests.

Reference

1. Laughlin MJ, Barker J, Bambach B, et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *N Engl J Med* 2001;344(24):1815-1822.
2. Laughlin MJ, Eapen M, Rubinstein P, et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. *N Engl J Med* 2004;351(22):2265-2275.
3. Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med* 2004;351(22):2276-2285.
4. Kurtzberg J, Laughlin M, Graham ML, et al. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. *N Engl J Med* 1996;335(3):157-166.
5. Eapen M, Rubinstein P, Zhang MJ, et al. Comparison of outcomes after transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukemia. *Lancet* 2007;369(9577):1947-1954.
6. Gutman JA, Leisenring W, Delaney C, et al. Low relapse without excessive transplant-related mortality following myeloablative cord blood transplantation for acute leukemia in complete remission: a matched cohort analysis. *Biol Blood Marrow Transplant* 2009;15(9):1122-1129.
7. Brunstein C, Gutman JA, Delaney C, et al. Allogeneic hematopoietic cell transplantation for hematological malignancy: relative risk and benefits of double umbilical cord. *Blood* 2010; 116(22):4693-4699.
8. van Rood J, Scaradavou A, Stevens C. Indirect evidence that maternal microchimerism in cord blood mediates a graft-versus-leukemia effect in cord blood transplantation. *Proc Natl Acad Sci* 2012;109(7):2509-2514.
9. van Rood J, Stevens C, Scaradavou A, et al. Reexposure of cord blood to noninherited maternal HLA antigens improves transplant outcome in hematological malignancies. *Proc Natl Acad Sci* 2009;106(47):19952-19957.
10. Lo YMD, Lo SF, Watson N, Noakes L, Sargent IL, Thilaganathan B, Wainscoat JS. Two-way cell traffic between mother and fetus: biologic and clinical implications. *Blood* 1996; 88:4390-5.

11. Mold J, Michaelsson J, Burt T, Muench M, Beckerman K, Busch M, Lee TH, Nixon D, McCune J. Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. *Science* 2008; 322:1562-5.

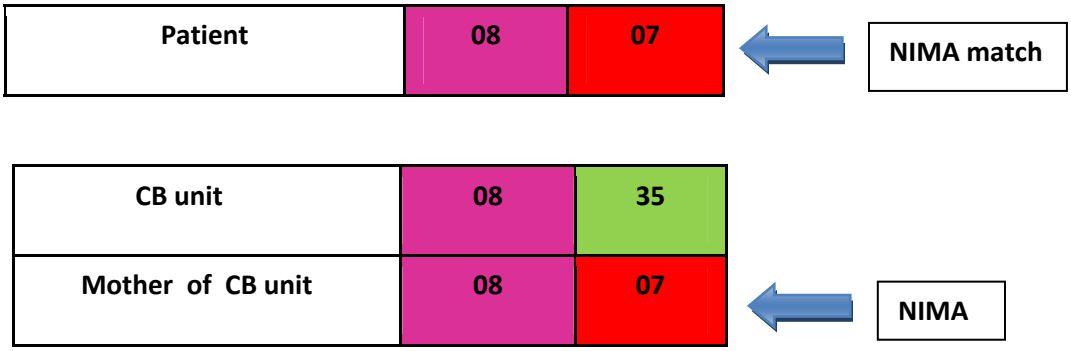
Figure 1A. HLA-B typing is used as an example to illustrate the inherited paternal antigen (IPA) in Cord Blood Transplantation. Anti-relapse benefit is predicted in the example illustrated because the mother's T cells would be sensitized to the HLA-B antigen encoded by B*15 (IPA) and the CB recipient has B*15 (shared IPA target)

Example: IPA Effect

Patient and Donor CB unit match for B antigens encoded by B*08 and B*15.
Based on the HLA typing of the CB and its mother, B*15 is the IPA in the CB. In this case, the patient also has a B*15, so IPA sensitized maternal cells have a target.

Figure 1B. Decreased transplant related mortality was reported in an earlier paper (9) for patients receiving one or two antigen mismatched cord blood transplants when the patient had the same HLA antigen as the CB's NIMA.

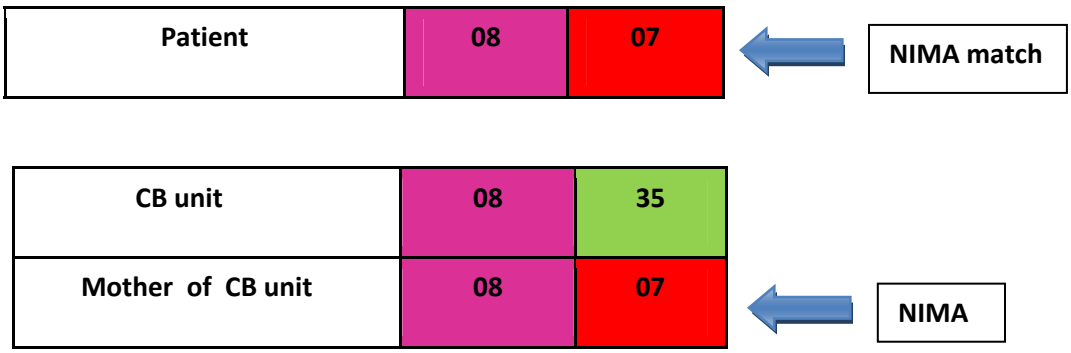
Example: NIMA Effect



Patient and Donor CB unit are mismatched at the B locus: patient has B*07 while CB has B*35. However, the patient's mismatched B*07 matches the CB's NIMA at the same locus.

Figure 2. Decreased transplant related mortality was reported in an earlier paper (9) for patients receiving one or two antigen mismatched cord blood transplants when the patient had the same HLA antigen as the CB's NIMA.

Example: NIMA Effect



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