Double cord blood transplantation: co-operation or competition?

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Abstract

Over the last two decades umbilical cord blood (UCB) transplantation (UCBT) is increasingly used for a variety of malignant and benign hematological and other diseases. The main factor that limits the use of UCB to low weight recipients, mainly children and adolescents, is its low progenitor cell content. Various alternatives have been exploited to overcome this difficulty, including the transplantation of two UCB units (double umbilical cord blood transplantation, dUCBT). Following dUCBT, donor(s) hematopoietic stem cells (HSC) can be detected in the peripheral blood of the recipient as soon as 14 days post-transplantation. Sustained engraftment of HSC from one or both donors can be observed- dominance or mixed chimerism respectively, although single donor unit dominance has been observed in over 85% of patients. The underlying biology, which accounts for the interactions both between the two infused UCB units- cooperative or competitive, and with the recipient's immune system, has not been elucidated.

Brief Report

Since the first dUCBT in 2005, its safety and efficacy have been examined in over 993 patients.1 Compared to single UCB, dUCBT is associated with: i) Higher incidence of acute GvHD grade II, though not higher treatment-related mortality or chronic GvHD; ii) Lower leukemia relapse for patients with good disease status (complete remission 1-2).[1-3] In more than 85% of patients undergoing dUCBT, regardless of the conditioning scheme, long-term hematopoiesis is derived from one of the infused cord blood units.[1,4] The time-frame for the engraftment of the dominant unit has not yet been elucidated. However, in over 80% of patients, single unit dominance can be detected three weeks post-transplantation.[4] Mixed chimerism can be detected in the one fifth of the patients under reduced intensity conditioning (RIC) regimens4. Cases whereby dominance reversion or loss of single unit dominance in favor of mixed donor chimerism have, also, been reported.[5,6] There are mathematical models that can provide approximations of the chimerism pattern following dUCBT, but the prediction of the winning unit seems to be impossible (atmospheric noise theory).[7,8]

In attempting to explain single unit dominance in dUCBT, both intrinsic properties of the infused units and immune interactions between the recipient and the donors are taken into consideration. However, the former are difficult to rationalize, especially since variations regarding the *in vitro* proliferation potential of UCB CD34$^+$ cells have been reported.[9] Nevertheless, it has been demonstrated that there is no association between dominance and number of nucleated cells, CD34$^+$, CD3$^+$, degree of HLA/sex mismatch, ABO group, viability, order and route of infusion.[4] However, Avery et al reported an association between higher CD3$^+$ cell dose and unit dominance in patients undergoing dUCBT following myeloablative regime.[10] Cell viability is a controversial issue. Clinical experience shows that cord blood with viability less than 70% could be easily engrafted, although Scaradavou *et al.* recently analyzed 46 cord blood transplants and suggested that low CD34$^+$ cell viability (<75%) UCB units in dUCBT have low probability of engraftment.[11] In this study, infusion of one high (>75%) and one low (75%) CD34$^+$ viability unit resulted in engraftment of the high viability unit. Either unit engrafted in patients transplanted with two units of high (27 patients) or low viability (1 patient). It has, also, been proposed that the order of infusion may influence unit dominance. Intravenous infusion of the units in dUCBT with 3.5-4.5 hour interval promotes the engraftment of the first infused unit.[5] Bearing in mind that the HSC could home to the endosteal niche in under five hours post-infusion, it is likely that even a short interval may contribute to the dominance of the first infused unit.[12] Furthermore, the tight balance between proliferation and quiescence of the resident stem cells in the endosteal niche could influence the long-term engraftment of the dominant unit.[13] Clinical trials comparing the different routes of infusion have not demonstrated any selective advantage between intravenous and intrabone administration.[14]

On the other hand, there is increasing evidence that single unit dominance in dUCBT recipients is the result of the immune-mediated rejection of the non-engrafting unit.[5] It has been demonstrated in vivo that naive CD8$^+$ T cells in one UCB unit expanded and differentiated into IFN-γ secreting effector T cells that specifically recognized the non-engrafting unit and caused its rejection.[9] However, these cytotoxic cells were transiently detected in the peripheral blood of dUCBT recipients with single unit dominance and are, therefore, not likely to be the sole cause of rejection. The chronic GvHD in patients with mixed chimerism following RIC regimens suggests graft-versus-graft interactions between the two units and between the units and the recipient.[5] In cases with mixed chimerism, more studies are needed to clarify the interactions between the three different elements, the two infused units and the recipients. A recent study provides further evidence in favor of immune interactions between the infused units, since recipients of units closely (7-10 to 10-10) HLA-matched to each other, undergoing myeloablative regime, were more likely to demonstrate initial engraftment of both units.[10]

Bearing in mind the incompatibility between the two units, the allo-reactive response could be triggered by immune system components, such as minor H antigens that are shared between the UCB units. This hypothesis could account for the enhanced graft-versus-leukemia (GvL) effect associated with dUCBT, if the progenitor cells of the non-engrafted unit have similar major or minor antigens with the leukemic cells. It is not clear whether HLA disparity contributes, too. The identification of the antigens expressed on HSCs that activate the T-cells of the dominant unit is ongoing. Furthermore, the in utero development of CD4$^+$ T cells, which can be tolerant to non-inherited maternal allo-antigens present in the other UCB unit, could account for the mixed chimerism.[9,15] Studies on murine models revealed that the addition of

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the corresponding mononuclear cells or CD34$^-$ to CD34$^+$ cells restored single-unit dominance following dUCBT, suggesting that unit dominance is probably associated with T-cell mediated graft-versus-graft immune interactions. Other immune-related mechanisms can, also, be involved, such as killer-immunoglobulin-like receptor-ligand incompatibility and NK-cell activation.[16,17]

Several clinical trials have shown that co-transplantation of third-party mesenchymal stromal cells (MSCs) derived from various sources (bone marrow, placenta) could improve the engraftment, although marginally.[18] In murine models, dUCBT accompanied by co-infusion of MSCs improved engraftment and reduced the extent of single unit dominance in favor of mixed chimerism.[19] MSCs have immunosuppressive/immunomodulatory properties and exert trophic activity- via the secretion of immune-related molecules, with which they can modulate T-cell responses.[19] Furthermore, culture-expanded MSCs do not express MHC class II surface markers and co-stimulatory molecules, so that they can neither function as antigen-presenting cells nor can they be directly involved in T-cell triggering.[20] Whether the improved engraftment in the presence of MSCs is associated with improved homing or increased bone marrow tropism or promotion of immunotolerance remains to be determined.

In conclusion, intrinsic factors of the stem cells not yet fully understood, such as homing to the niche, as well as, prior therapy, intensity of conditioning regime, trophic effects, host factors and interactions between the grafts and the host are all likely contribute to the pattern of chimerism in dUCBT. The implication of immune-mediated mechanisms could be of significance in the context of leukemia; if the dominant unit can be predicted prior to transplantation; a non-engrafting unit sharing host antigens not present on the engrafting unit can be selected to promote the GvL effect. Ongoing clinical trials and prolonged patient follow-up will contribute in clarifying the underlying biology of dUCBT and demonstrate its safety and efficacy.

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