Umbilical cord-blood transplantation in adults: will it be coming back?

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The standard optimal donor source for allogeneic stem cell transplantation (SCT) is an HLA-matched related or unrelated donor. Umbilical cord blood (UCB) and haploidentical donors are established alternatives for patients who lack a matched donor. Both are more rapidly available than an unrelated donor. UCB transplant (UCBT) provides tolerance across HLA barriers expanding the donor pool, especially for minorities. The naïve immune system is associated with low risk of chronic GvHD. The graft-*versus*-leukemia (GvL) effect is increased with a lower risk of relapse.[1] Naïve CD8$^+$ T lymphocytes show enhanced recruitment, prompt differentiation to memory effector cells with gain of cytotoxic function and no increased alloreactivity.[2] However, UCBT is associated with delayed engraftment and immune reconstitution, a high risk of graft failure, increased rate of infections and early non-relapse mortality (NRM).[3] UCBT in adults is limited by the cell dose and algorithms for selection of the best UCB are based on HLA-matching and total nucleated cell (TNC) / CD34$^+$ cell dose.[4]

Almost all patients have a haploidentical donor. Historically, haploidentical transplant was limited by a high rate of graft rejection and GvHD. Extensive *ex vivo* T-cell depletion was associated with slow immune recovery and high NRM. The introduction of post-transplant cyclophosphamide (PTCy) revolutionized the field with a marked improvement in outcome.[3] The treatment protocol is simple and can be given in all centers with no need for special expertise. The costs are also lower than for other donor sources. Several retrospective studies and meta-analyses showed similar survival following UCBT and haploidentical transplants.[3] The BMT CTN 1101 randomized study compared haploidentical transplant with double-unit UCBT using reduced-intensity conditioning. There were similar rates of 2-year progression-free survival and relapse, but NRM was lower and 2-year survival was higher after haploidentical transplant.[5] While this issue remains controversial, the alternative donor field has moved in recent years towards haplo-transplants. The haploidentical transplant rates in the US increased from 6% of all transplants in 2013 to 21% in 2023, while the rate of UCBT decreased from 10% to 3% over the same time.[6]

Several approaches have been used to increase TNC/stem cell dose of UCBT to improve engraftment. Double-unit UCBT achieves comparable survival as adequately dosed single-unit UCBT. There is less delayed engraftment but more severe acute and chronic GvHD. Double UCBT may offer improved GvL, especially in patients with high-risk or active / measurable residual disease positivity at the time of transplant.[1] Usually only one unit engrafts and the second one is rejected. Relapses are reduced when the losing unit shares the HLA-mismatch (mostly locus A) with the recipient. The winning unit will reject the losing unit while promoting a GvL effect through antigen-specific CD8$^+$ T lymphocytes.[3] However, there are no reliable methods to predict which will be the winning unit and to select HLA mismatches accordingly. There is also a documented alloreactivity of CD4$^+$ T lymphocytes towards mismatched HLA class II alleles.

There are several approaches for *ex vivo* CB expansion. Omidubicel is an FDA-approved patient-specific product produced by *ex vivo* expansion of the CD133$^+$ fraction of a single unit with nicotinamide. A randomized study showed a marked reduction in time to engraftment and a lower infection rate but no difference in GvHD or survival compared with a single non-expanded UCBT.[7] A second product uses UM171 for expansion. Preliminary results show that even small CBU can be expanded and engrafted with promising outcomes, less NRM and GvHD, and improved survival compared with non-expanded UCBT.[8] Another approach to facilitate engraftment is combining a T-cell depleted haploidentical graft with the CBU.[9] However, all these patient-specific approaches are relatively complicated and costly, and require unique expertise, and they cannot compete with the much simpler to perform and less expensive haploidentical transplant with PTCy.

In this issue of *Haematologica*, Liu *et al*. report their

research at the Karolinska Institute to explore the use of neonatal exchange blood (NEB) as a novel alternative stem cell source for transplantation that is similar to UCB but with larger numbers of HSC.[10] NEB is collected from newborns during exchange transfusion for hemolytic disease of the newborn and is otherwise discarded. In the study by Liu *et al.*, the mean number of TNC and $CD34^+$ cells in the 12 tested NEB units was about 4 times higher than that of standard banked UCB units: $5.4x10^9$ and $16.6x10^6$ compared to $1.3x10^9$ and $4.4x10^6$, respectively.[10] These can accommodate transplantation of most adults according to standard selection criteria of a single UCB unit. NEB supported engraftment with multilineage reconstitution in murine xenotransplantation models, similar to UCB. The number of T and B lymphocytes was higher and the absolute number of natural killer cells was similar to those in UCB. There was a similar phenotype of CD4:CD8 ratio and activation markers, as well as similar proliferation and cytokine release in mixed lymphocyte reaction, as UCB controls. While promising, these data are based on a limited number of experiments and there are so far no clinical studies in humans supporting the potential for engraftment and relative rates of GvHD and GvL compared with standard UCB.

Neonatal exchange blood could potentially be collected with no need for additional staff or significant regulations and cryopreserved in regular CB banks. Therefore, theoretically, it should cause no significant increase in costs. As an off-the-shelf product, it may also have an advantage of quicker availability than the production of patient-specific products. However, there are currently about 800,000 UCBU stored in cord-blood banks around the world, sufficient to meet current UCBT needs. There are at best several thousand neonatal exchange transfusions yearly, such that this approach may ultimately enrich the cord blood banks with usable UCB units; however, it is likely to contribute only a small fraction of the units currently available for transplantation.

While the number of UCBT has been decreasing in recent years, they may still have a role to play, particularly in children and in patients with high-risk or active malignancies. Advances in supportive care and improved UCB grafts, achieved with no significant increase in cost (such as those that possibly would be met using NEB), may help relaunch this transplant approach.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors wrote the manuscript and approved the final version for publication.

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