haematologica
Journal of the Ferrata Storti Foundation

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

by Avichai Shimoni and Arnon Nagler

Received: May 11, 2026.
Accepted: May 21, 2026.

Citation: Avichai Shimoni and Arnon Nagler. Umbilical cord-blood transplantation in adults: will it be coming back?
Haematologica. 2026 May 28. doi: 10.3324/haematol.2026.301174 [Epub ahead of print]

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

Avichai Shimoni[1,2], Arnon Nagler [1,2]

[1]Division of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer, Israel

[2]Gray Faculty of Medical & Health Sciences, Tel-Aviv University, Tel-Aviv, Israel

Corresponding author:

Avichai Shimoni, MD

Department of Bone Marrow Transplantation

Chaim Sheba Medical Center, Tel-Hashomer, Israel

Tel: 972-3-530-5830

FAX: 972-3-530-5377

E-mail: ashimoni@sheba.health.gov.il

Author contributions: Both authors wrote the manuscript and approved the final version.

Disclosures: Both authors have no relevant disclosures

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 lower risk of relapse.[2] Naïve CD8+ T- lymphocytes show enhance recruitment, prompt differentiation to memory effector cells with gain of cytotoxic function and no increased alloreactivity.[3] 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)[1]. 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 marked improvement of outcome.[1] Treatment protocol is simple and can be given in all centers with no need for special expertise. The costs are also lower than in other donor sources. Several retrospective studies and meta-analyses showed similar survival following UCBT and haploidentical transplants.[1] 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 was reduced from 10% to 3% during 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 positive at the time of transplant.[2] 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 together with enhancing GVL 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 marked reduction of time to engraftment and reduced 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-deplete haploidentical graft with the CBU.[9] However, all these patient-specific approaches are relatively complicated and costly and require unique center expertise and could not compete with the much simpler to perform and less expensive haploidentical transplant with PTCy.

In this issue of *Haematologica* researches from Karolinska Institute explored the use of neonatal exchange blood (NEB) as a novel alterative stem-cell source for transplantation that is similar to UCB but with larger numbers of HSCs.[10] NEB is collected from newborns during exchange transfusion for hemolytic disease of the newborn and is otherwise discarded. The mean number of TNC and CD34+ cells in the 12 tested NEB units was about 4 times higher than standard banked UCB units, been 5.4×10^9 and 16.6×10^6 compared to 1.3×10^9 and 4.4×10^6, respectively, that 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 NK cells was similar to 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 limited number of experiments and there are so far no clinical studies in human supporting the potential for engraftment and relative rates of GVHD and GVL compared with standard UCB.

NEB could be potentially collected with no need for additional staff or significant regulations and cryopreserved in regular CB banks. Therefore, it should theoretically cause no significant excess costs. As an off the shelf product it may also have an advantage in rapid availability over the production of patient-specific products. However, there are currently about 800,000 UCBUs 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 good UCB units, however it is likely to contribute only a small fraction of the units currently available for transplantation.

While the number of UCBTs is decreasing in recent years, they may still have a role, particularly in children and in patients with high-risk or active malignancies. Advances in supportive care and in collection of better UCB grafts with no significant excess of costs (such as possibly of NEB) may help re- promote this transplant approach.

References

1. Nagler A, Mohty M. In 2022, which is preferred: haploidentical or cord transplant? Hematology Am Soc Hematol Educ Program. 2022;2022(1):64-73.
2. Milano F, Gooley T, Wood B, et al. Cord-Blood Transplantation in Patients with Minimal Residual Disease. N Engl J Med. 2016;375(10):944-953.
3. Wynn R, Volt F, Guardiola P, et al. Impact of shared HLA determinants between patient and losing cord blood unit on relapse after double cord blood transplantation. Blood Adv. 202;9(17):4425-4435.
4. Politikos I, Davis E, Nhaissi M, et al. Guidelines for Cord Blood Unit Selection. Biol Blood Marrow Transplant. 2020;26(12):2190-2196.
5. Fuchs EJ, O'Donnell PV, Eapen M, et al. Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation: the BMT CTN 1101 trial. Blood. 2021;137(3):420-428.
6. Spellman SR, Xu K, Oloyede T, et al. Current activity trends and outcomes in hematopoietic cell transplantation and cellular therapy - A report from the CIBMTR. Transplant Cell Ther. 2025;31(8):505-532.
7. Horwitz ME, Stiff PJ, Cutler C, et al. Omidubicel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study. Blood. 2021;138(16):1429-1440.
8. Cohen S, Bambace N, Ahmad I, et al. Improved outcomes of UM171-expanded cord blood transplantation compared with other graft sources: real-world evidence. Blood Adv. 2023;7(19):5717-5726.
9. Liu H, Rich ES, Godley L, et al. Reduced-intensity conditioning with combined haploidentical and cord blood transplantation results in rapid engraftment, low GVHD, and durable remissions. Blood. 2011;118(24):6438-6445.
10. Liu Y, Giusti P, Qian H, et al. Neonatal exchange blood is a rich source of hematopoietic stem and progenitor cells for transplantation. Haematologica. xxx