blood advances

Cord blood power and the definition of success after BMT

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Comment on Martinez et al, page 1823

In this issue of *Blood Advances*, Martinez et al[1] show in a well-designed prospective trial that single unrelated cord blood transplantation (CBT) after myeloablative antithymocyte globulin (ATG)-free conditioning for nonmalignant indications (n = 55) resulted in high engraftment survival (>90%). Even patients with severe combined immunodeficiency (SCID) who had active infections before the transplantation (N = 26) had similarly high survival rates, associated with early infection-specific immunity and clearance of infection. Importantly, long-term IV immunoglobulin (IVIG)-dependency was very low, as were the graft-versus-host disease rates. Despite these excellent results, some consider myeloablation and the use of cord blood grafts controversial because one can engraft donor T cells in many forms of SCID without conditioning.

In transplantation for nonmalignant indications, it is important to agree on the definition of success. Is this engraftment survival, or should we also consider residual disease or the incomplete correction of the underlying disease in a composite endpoint? For example, for primary immunodeficiency (PID)/SCID, IVIG-dependency, and, later in life, the recurrence of mild or moderate T-cell deficiency due to the loss of the T-cell repertoire could be serious problems that affect the quality of life; it may even be the reason necessitating a second transplantation with all the associated risks. In the study, almost all patients were producing immunoglobulins at 6 months, were IVIG independent, and had immunizations started after a median time of 6 months. IVIG independence and a long-term, diverse T-cell repertoire both depend on stable long-term myeloid and lymphoid progenitor engraftment. Without myeloablation, this typically remains a problem resulting in an incomplete correction of the PID. The article confirmed that.

But what is optimal myeloablation (in this context), or what is the sweet spot for patients with PID/SCID to prevent these residual immune defects? Bartelink et al[2] described in a large pharmacokinetic/pharmacodynamic analysis that, like all other indications, a full myeloablative busulfan exposure (cumulative 90 mg*h/L) resulted in the best outcomes for patients with PID (n = 176). However, the patient numbers were small and underpowered for the analysis of all PID subgroups. Unfortunately, the highly variable practices over the past decades regarding conditioning, stem cell source, and T-cell depletion techniques make it difficult to study this in a retrospective way. Thus, sadly, even after >5 decades of transplantation for SCID/PID, we are still having a debate regarding the optimal transplantation platform for patients with SCID.

However, the European Society for Blood and Marrow Transplantation inborn errors working party, which has, for 2 decades, published guidelines on how to treat patients with PID, recently published a comparison of conditioning regimens among patients undergoing hematopoietic cell transplantations for Wiskott-Aldrich syndrome.[3] Patients who received the myeloablative busulfan-based regimen had superior engraftment survival compared with those who received treosulfan-based conditioning, because of higher rejection rates in the treosulfan-arm (>20%). Obviously, prospective trials are superior, preferably in a multicenter setting; only by working collaboratively in the field of rare diseases can we move the field forward.

CBT for patients with SCID does not have a great track record; in 2014, Pai et al demonstrated in a donor graft comparison that patients who received CBT had the least favorable outcome.[4] In this retrospective analysis, all CBT recipients were lumped into 1 group, without considering conditioning or serotherapy, such as ATG. Similarly, the Center for International Blood and Marrow Transplant Research conducted an analysis of 1199 patients who received CBT for the treatment of nonmalignant diseases, (35% had SCID/non–SCID PID) with most receiving ATG, the 5-year overall survival rate was at best 79% (95% confidence interval, 74-85) and the graft failure ranged from 16% to 28%, both correlated with HLA allele level matches.[5] Recently, it was shown that survival chances after CBT are significantly affected by ATG

exposure after transplantation,[6,7] and even very low exposures to ATG after CBT had a dramatic impact on immune reconstitution and chances of survival. On the contrary, in the same study as well as in other studies,[8-12] CBT without ATG exposure resulted in a spectacularly fast immune reconstitution with a highly diverse T-cell repertoire (even quicker than that in bone marrow transplantation without ATG exposure). Moreover, the reconstituting naïve immune system can transition to an infection-specific effector phenotype, resulting in early infection control.[8,11,12] Hiwarkar et al[9] showed the lowest incidence of viral reactivations after CBT without serotherapy compared with using other cell sources, and Admiraal et al[11] demonstrated that after omitting ATG, the incidence of clinically significant viral infection was negligible. These 2 groups also showed early induction of virus specific cytotoxic T lymphocytes after transplantation (for adenovirus and cytomegalovirus).[8,10] The immune recovery and control of infection results by Martinez et al are in line with those shown in these previously published papers.

How can we further improve the outcomes and disseminate effective transplantation platforms for patients with PID? Firstly, a better understanding of the optimal myeloablation would help tremendously. For example, for the SCID group as described by Martinez et al, one can argue whether both cyclophosphamide and fludarabine were needed for immune suppression. In addition, given the data from the analysis conducted by the Center for International Blood and Marrow Transplant Research, using high-resolution HLA typing would be preferable.[5] Hopefully, soon, myeloablation with a nongenotoxic agent (antibody) will be preferred. This will prevent infertility problems that can result from alkylator-based myeloablation. Till then, (optimal) exposure-targeted busulfan is probably the most reliable agent to treat patients with PID/SCID by ensuring engraftment of donor cells that completely correct the underlying immune defect, without the need to see an immunologist in a long-term follow-up clinic visit (besides maybe just having a social conversation).

In summary, all we can learn from the study by Martinez et al and the recent literature have been listed below:

1. Myeloablative CBT is not controversial for patients with PID when engraftment survival rates are >90% (associated with complete correction of the underlying disease). Therefore, CB grafts with appropriate cell doses and HLA allele level matches should be seriously considered as a treatment option and/or studied in multicenter trials.
2. For patients with PID who had active infections before transplantation, myeloablative CBT is not contraindicated. Moreover, it may be the preferred strategy given the early infection control by cord blood cells and high survival rates.
3. We do, however, need to develop better composite endpoints to measure transplantation success for patients with PID. Engraftment (T-cell) survival does not tell us the whole story.
4. We also need a better understanding of the level of myeloablation required to achieve optimal PID control (ie, complete correction of the underlying PID).
5. In addition to the harmonization and standardization of transplantation approaches, prospective clinical trials are desperately needed to further improve patient outcomes and are the only way to get the answers we need.

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References

1. Martinez C, Aguayo-Hiraldo P, Chaimowitz N, et al. Cord blood transplantation for non-malignant disorders; early functional immunity and high survival. *Blood Adv*. 2023;7(9):1823-1830.
2. Bartelink IH, Lalmohamed A, van Reij EML, et al. Association of busulfan exposure with survival and toxicity after haemopoietic cell transplantation in children and young adults: a multicentre, retrospective cohort analysis. *Lancet Haematol*. 2016;3(11):e526-e536.
3. Albert MH, Slatter MA, Gennery AR, et al. Hematopoietic stem cell transplantation for Wiskott-Aldrich syndrome: an EBMT inborn errors working party analysis. *Blood*. 2022;139(13):2066-2079.
4. Pai S-Y, Logan BR, Griffith LM, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. *N Engl J Med*. 2014;371(5):434-446.
5. Eapen M, Wang T, Veys PA, et al. Allele-level HLA matching for umbilical cord blood transplantation for non-malignant diseases in children. *Lancet Haematol*. 2017;4(7):e325-e333.
6. Gabelich J-A, Langenhorst J, Admiraal R, et al. Filgrastim enhances T-cell clearance by antithymocyte globulin exposure after unrelated cord blood transplantation. *Blood Adv*. 2018;2(5):565-574.
7. Admiraal R, Nierkens S, Bierings MB, et al. Individualised dosing of antithymocyte globulin in paediatric unrelated allogeneic haematopoietic stem-cell transplantation (PARACHUTE): a single-arm, phase 2 clinical trial. *Lancet Haematol*. 2022;9(2):e111-e120.
8. Chiesa R, Gilmour K, Qasim W, et al. Omission of in vivo T-cell depletion promotes rapid expansion of naïve CD4$^+$ cord blood lymphocytes and restores adaptive immunity within 2 months after unrelated cord blood transplant. *Br J Haematol*. 2012;156(5):656-666.
9. Hiwarkar P, Gaspar HB, Gilmour K, et al. Impact of viral reactivations in the era of pre-emptive antiviral drug therapy following allogeneic haematopoietic SCT in paediatric recipients. *Bone Marrow Transplant*. 2013;48(6):803-808.
10. Flinsenberg TWH, Spel L, Jansen M, et al. Cognate CD4 T-cell licensing of dendritic cells heralds anti-cytomegalovirus CD8 T-cell immunity after human allogeneic umbilical cord blood transplantation. *J Virol*. 2015;89(2):1058-1069.
11. Admiraal R, Lindemans CA, van Kesteren C, et al. Excellent T-cell reconstitution and survival depend on low ATG exposure after pediatric cord blood transplantation. *Blood*. 2016;128(23):2734-2741.
12. Politikos I, Lavery JA, Hilden P, et al. Robust CD4$^+$ T-cell recovery in adults transplanted with cord blood and no antithymocyte globulin. *Blood Adv*. 2020;4(1):191-202.

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