Hemophilia program and performed grant review for the latter program. ■

REFERENCES

1. Hu Z, Liu Y, Huarng MC, et al. Genome editing of factor X in zebrafish reveals unexpected tolerance of severe defects in the common pathway. *Blood*. 2017;130(5):666-676.
2. Dewerchin M, Liang Z, Moons L, et al. Blood coagulation factor X deficiency causes partial embryonic lethality and fatal neonatal bleeding in mice. *Thromb Haemost*. 2000;83(2):185-190.
3. Cui J, O'Shea KS, Purkayastha A, Saunders TL, Ginsburg D. Fatal haemorrhage and incomplete block to embryogenesis in mice lacking coagulation factor V. *Nature*. 1996;384(6604):66-68.
4. Sun WY, Witte DP, Degen JL, et al. Prothrombin deficiency results in embryonic and neonatal lethality in mice. *Proc Natl Acad Sci USA*. 1998;95(13):7597-7602.
5. Xue J, Wu Q, Westfield LA, et al. Incomplete embryonic lethality and fatal neonatal hemorrhage caused by prothrombin deficiency in mice. *Proc Natl Acad Sci USA*. 1998;95(13):7603-7607.
6. Connolly AJ, Ishihara H, Kahn ML, Farese RV Jr, Coughlin SR. Role of the thrombin receptor in development and evidence for a second receptor. *Nature*. 1996;381(6582):516-519.
7. Tai SJ, Herzog RW, Margaritis P, et al. A viable mouse model of factor X deficiency provides evidence for maternal transfer of factor X. *J Thromb Haemost*. 2008;6(2):339-345.
8. Glasauer SM, Neuhauss SC. Whole-genome duplication in teleost fishes and its evolutionary consequences. *Mol Genet Genomics*. 2014;289(6):1045-1060.

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● ● ● TRANSPLANTATION

Comment on Locatelli et al, page 677

Sometimes less might be more, or at least equal

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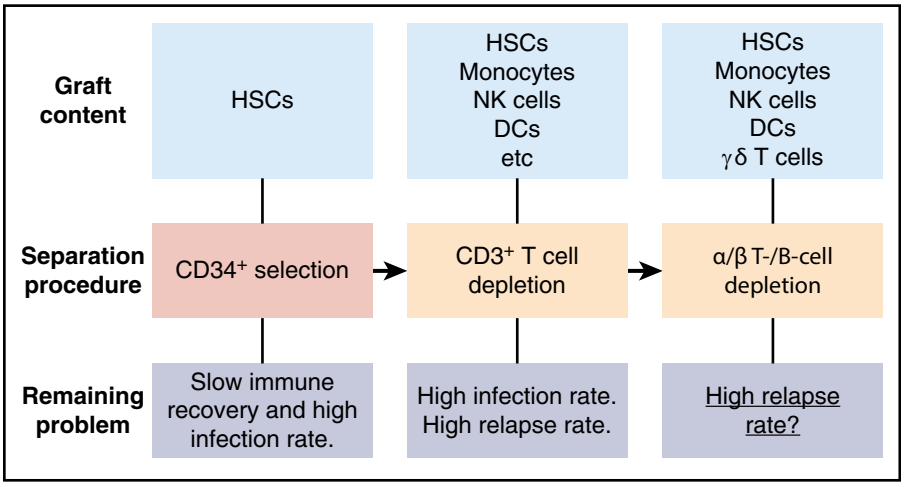
In this issue of *Blood*, Locatelli et al describe their trial of allogeneic hematopoietic stem cell transplantation (HSCT) using α/β T-cell–depleted grafts in a haploidentical setting. The procedure was performed with very promising results in 80 children with acute leukemia.[1]

The development of haploidentical HSCT has made great progress in the last 2 decades and is today a viable option when choosing a transplant strategy.[2] This is especially true for those patients with an uncommon HLA type or in need of a rapid treatment.

The 2 strategies used today in association with haploidentical HSCT are high-dose, posttransplantation cyclophosphamide or graft manipulation by magnetic enrichment or depletion. Both methods aim to reduce graft-versus-host disease (GVHD) while keeping cells that can facilitate beneficial effects, such as a graft-versus-leukemia (GVL) effect or antimicrobial control.[3,4]



Development of hematopoietic stem cell (HSC) graft manipulation by enrichment or depletion strategies. DCs, dendritic cells; NK, natural killer.

Graft manipulation has evolved from positive selection of $CD34^+$ progenitor cells to depletion of $CD3^+$ cells to what is described in this paper. Here, α/β T-cell depletion was performed prior to HSCT in combination with rituximab depletion of B cells (see figure). All techniques are associated with different potential problems and benefits.

A retrospective report of α/β T-cell depletion prior to HSCT in children with nonmalignant and malignant disease reported a high rate of engraftment and rapid immune recovery, but clinical long-term effects were unavailable at the time.[5] Smaller series of patients treated with α/β T-cell–depleted grafts both before and after HSCT as stem cell boosters to treat graft failure have also been reported, with promising results.[6-8] So far, larger studies with greater number of patients have been lacking.

The study by Locatelli et al is in many ways very important for the future development of graft manipulation in combination with not only haploidentical transplantation, but also HSCT as a whole. One important concern with α/β depletion is whether the depleted T cells will reduce not only the risk of GVHD but also the beneficial effect of GVL. Even if both NK and γ/δ T cells have been shown to have antileukemic properties, the question remains whether this is sufficient.

This well-performed study in children with acute leukemia strongly argues that the intrinsic antileukemic effect of NK and γ/δ cells, which remain together with other facilitating cells after depletion, is adequate to create a robust GVL effect. Even if the study is not a randomized trial, the data are greatly strengthened by the fact that 2 control groups of patients were treated at the same hospital during the same time period. In the study, the authors show that haploidentical HSCT after α/β T-cell and B-cell depletion is comparable with regards to both leukemia-free survival and GVHD incidence in children transplanted with HLA-identical sibling donors or matched unrelated donors. In addition, the study has a long-term follow-up for a substantial number of patients included.

This study suggests that all patients, including individuals with acute leukemia, could benefit from haplo-HSCT with α/β T-cell depletion, with an outcome comparable to that obtained with HLA-matched siblings or HLA-matched volunteers. The question mark (see figure) regarding a potentially higher relapse rate might not be erased yet, but the results from this study are encouraging.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Locatelli F, Merli P, Pagliara D, et al. Outcome of children with acute leukemia given HLA-haploidentical HSCT after αβ T-cell and B-cell depletion. *Blood*. 2017; 130(5):677-685.

2. Piemontese S, Ciceri F, Labopin M, et al; Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). A comparison between allogeneic stem cell transplantation from unmanipulated haploidentical and unrelated donors in acute leukemia. *J Hematol Oncol*. 2017;10(1):24.

3. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008; 14(6):641-650.

4. Maschan M, Shelikhova L, Ilushina M, et al. TCR-alpha/beta and CD19 depletion and treosulfan-based conditioning regimen in unrelated and haploidentical transplantation in children with acute myeloid leukemia. *Bone Marrow Transplant*. 2016;51(5):668-674.

5. Lang P, Feuchtinger T, Teltschik HM, et al. Improved immune recovery after transplantation of TCRαβ/CD19-depleted allografts from haploidentical donors in pediatric patients. *Bone Marrow Transplant*. 2015; 50(suppl 2):S6-S10.

6. Bertaina A, Merli P, Rutella S, et al. HLA-haploidentical stem cell transplantation after removal of αβ+ T and B cells in children with nonmalignant disorders. *Blood*. 2014;124(5):822-826.

7. Radestad E, Wikell H, Engstrom M, et al. Alpha/beta T-cell depleted grafts as an immunological booster to treat graft failure after hematopoietic stem cell transplantation with HLA-matched related and unrelated donors. *J Immunol Res*. 2014;2014:578741.

8. Mainardi C, Tumino M, Gazzola MV, Rampazzo A, Scarpa M, Messina C. TCRαβ CD19 depletion in allogeneic haematopoietic stem cell transplantation performed for Hurler syndrome. *Bone Marrow Transplant*. 2016;51(3):438-439.

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