

CORRESPONDENCE



One-Unit versus Two-Unit Cord-Blood Transplantation

TO THE EDITOR: Wagner et al. (Oct. 30 issue)¹ report the results of transplantation of one versus two units of umbilical-cord blood, and they indicate that a better HLA-match score was associated with a lower rate of disease-free survival. One would expect a partial degree of correlation between the closeness of matching between units and the closeness of the donor–recipient matching, but it would be of interest to separate out these two types of matching and see how each type of mismatch may correlate with types of treatment failure.

In particular, HLA mismatch between the two units might not interfere much with the initial proliferation of each unit, so that the patient can benefit early from receiving a higher dose of transplanted cells. Later, as each unit has had a chance to proliferate into a more effective immunologic mass, HLA mismatch may cause each unit to interfere with the further proliferation of the other unit. The mismatch between the two units may also potentially modulate the ability of each of the units to produce chronic graft-versus-host disease (GVHD).

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No potential conflict of interest relevant to this letter was reported.

1. Wagner JE Jr, Eapen M, Carter S, et al. One-unit versus two-unit cord-blood transplantation for hematologic cancers. *N Engl J Med* 2014;371:1685-94.

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TO THE EDITOR: Wagner and colleagues describe the lack of a survival advantage among children and adolescents after double-unit cord-blood

transplantation. Regarding the poorer platelet recovery after double-unit transplantation than after single-unit transplantation, a potential relationship with the higher rate of GVHD was the only hypothesis proposed. Additional information would be valuable in considering other explanations. In particular, can the authors provide data on the graft characteristics of the double-unit group with respect to which units finally grafted (dominant units)? The comparison of the characteristics of these dominant units with those of the single-unit group might offer additional insights into the outcomes of both groups.

After this landmark study, it is timely to undertake a similar trial in adults. The statement that “many adults would not have had an adequate single unit” should be reevaluated in light of reports of successful strategies with lower cell doses.¹ In addition, the potential beneficial effect of greater HLA mismatch, as previously suggested,^{1,2} should be highlighted. If confirmed, it could challenge current recommendations for the selection of single-unit or double-unit cord-blood transplantation.

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1. Sanz J, Wagner JE, Sanz MA, et al. Myeloablative cord blood transplantation in adults with acute leukemia: comparison of two different transplant platforms. *Biol Blood Marrow Transplant* 2013;19:1725-30.
2. Atsuta Y, Kanda J, Takanashi M, et al. Different effects of HLA disparity on transplant outcomes after single-unit cord blood transplantation between pediatric and adult patients with leukemia. *Haematologica* 2013;98:814-22.

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THE AUTHORS REPLY: The observation that greater HLA mismatch is associated with better disease-free survival after cord-blood transplantation is clearly provocative and merits additional evaluation. The question posed by Nusbaum regarding further delineation of the mechanism or mechanisms involved in this association — specifically, separating out the effect of matching between two units versus donor–recipient matching — is important but unfortunately was beyond the scope of our study. The complexity of double-unit cord-blood transplantation, in which we need to consider the effect of HLA matching in six directions rather than two in addition to understanding the effect of the HLA match of the predominating unit responsible for hematopoiesis in the long term, demands substantially larger sample sizes within each subgroup for a meaningful analysis.

In response to the comments by Sanz and colleagues: we too are particularly interested in segregating out the effect of the engrafting from the nonengrafting unit in recipients of a double-unit cord-blood transplant. However, this is also a complex analysis that was beyond the scope of our study. It is possible that the immunologic graft-versus-graft response that is known to occur between the first and second cord-blood units might be responsible for some of the outcomes

that we reported. For example, the higher incidence of acute GVHD after double-unit cord-blood transplantation might be related to an “in vivo mixed lymphocyte response” between the two units, which in turn could have deleterious effects such as delayed platelet recovery¹ but also beneficial effects such as a lower relapse rate.² Alternatively, it is possible that the “tolerability” of greater HLA mismatch in patients receiving a cord-blood transplant unveils a greater graft-versus-leukemia effect without the expected concomitant increase in transplantation-related mortality. In fact, the beneficial effect of HLA mismatch on relapse and survival after cord-blood transplantation has already been reported.³ Although these possibilities are intriguing, they are only hypotheses at this time. If these observations hold in future studies, perhaps researchers who analyze databases with larger sample sizes can begin to explore the driving factors responsible for this apparent beneficial effect of HLA mismatch after double-unit cord-blood transplantation.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Ramírez P, Brunstein CG, Miller B, Defor T, Weisdorf D. Delayed platelet recovery after allogeneic transplantation: a predictor of increased treatment-related mortality and poorer survival. *Bone Marrow Transplant* 2011;46:981-6.
2. Verneris MR, Brunstein CG, Barker J, et al. Relapse risk after umbilical cord blood transplantation: enhanced graft-versus-leukemia effect in recipients of 2 units. *Blood* 2009;114:4293-9.
3. Sanz J, Jaramillo FJ, Planelles D, et al. Impact on outcomes of human leukocyte antigen matching by allele-level typing in adults with acute myeloid leukemia undergoing umbilical cord blood transplantation. *Biol Blood Marrow Transplant* 2014;20:106-10.

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Cardiovascular Risk and Events and Country Income Stratum

TO THE EDITOR: Yusuf et al. (Aug. 28 issue)¹ found that although the INTERHEART Risk Score classifies residents of high-income coun-

tries as being at greater cardiovascular risk than residents of low- and middle-income countries, the rates of major cardiovascular events and