case the old studies, even those more than 50 years old, had it right.

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## REFERENCES


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### The power of cord blood cells

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In this issue of *Blood*, Michel et al. showed in a well-designed randomized controlled study that single unrelated cord blood transplantation (UCBT), with adequate cell dose, remains the standard of care. The single-unit UCBT arm had good survival (≈70%), low transplantation-related mortality (TRM: 5–6%), and a lower rate of extensive chronic graft-versus-host disease (GVHD) compared with the double-unit transplantation arm. This study provides important information on optimal cord blood donor selection. In addition, this study, as well as data from other recent reports, shows that immune reconstitution after UCBT is excellent (provided no antithymocyte globulin [ATG] is given). Furthermore, by refining and individualizing the conditioning regimens used for UCBT, the survival chances may improve further.

Historically, the limited number of hematopoietic cells in a single cord blood unit was believed to result in delayed hematopoietic recovery and higher mortality in larger recipients. It was hypothesized that the greater numbers of hematopoietic cells in 2 units of cord blood would improve outcomes. Some registry and single center data suggested that relapse rate was lower after double-unit transplantation compared with single-unit transplantation, resulting in inferior disease-free survival after single-unit transplantation. Obviously, randomized controlled trials, as in this article, are of great interest and importance to either prove or reject this hypothesis.

The primary end point in this study was transplantation failure, which was hypothesized to be higher in the single-unit arm compared with the double-unit arm (40% vs 20%, respectively). The study, however, failed to prove this; survival was similar (≈70%) in both arms. Although the acute GVHD rates were similar between the 2 arms, extensive chronic GVHD was more frequent in the double-unit arm (P = .02). These results confirm a recent similar report by Wagner et al.; double-unit UCBT fails to provide benefit above adequately dosed single-unit transplants, and toxicity was higher after double-unit UCBT: higher acute GVHD2-4 and extensive chronic GVHD.

Michel et al. suggest that double-unit UCBT after fludarabine + cyclophosphamide + total body irradiation (without ATG) may result in a lower relapse probability (P = .05). This, however, needs further analyses, as the greater HLA mismatch in the double-unit arm may be an alternative explanation for this as well. Others, including the recent report by Wagner et al., have reported on the potential beneficial effect of greater HLA mismatch on relapse. In Wagner et al., there was even a survival advantage for patients receiving a 4/6-matched cord blood unit compared with patients receiving a 5-6/6 matched unit (P = .03). This is an intriguing feature specifically associated with cord blood cells, as multiple mismatches using T-repleted unrelated volunteer donor cells would be associated with very poor survival chances. Future studies should focus on identifying the optimal mismatch mediating the strongest antileukemic activity. This may result in better disease control; eg, recently high predicted indirectly recognizable HLA epitopes in class I was found to promote antileukemia responses after UCBT. That cord blood T cells mediate enhanced antitumor effects, compared with adult peripheral blood T cells, was also recently shown in a xenograft Epstein-Barr virus lymphoma model. For the optimal effect, prompt immune reconstitution is essential. The use of ATG in the conditioning is considered to be the major limitation for prompt immune reconstitution after UCBT. Although ATG is given prior to UCBT, it will give exposure after UCBT, as the half-life of ATG is long (days to weeks).

Recent studies of ATG have shown that ATG and cord blood T cells are a very bad combination: very low exposure of ATG after UCBT had a dramatic effect on the probability of CD4+ reconstitution. Bone marrow– and peripheral blood–derived T cells are less susceptible to in vivo lysis after comparable exposure to ATG. This enhanced in vivo depletion may be due to the fact that ATG is produced in rabbits using infant human thymus, which may result in more antibodies against naive receptors. Generally, T-cell reconstitution has been considered poor and therefore a major drawback for using cord blood as an alternative cell source. It is important to realize, however, that in many studies quoted to support this conclusion, ATG was part of the conditioning closely prior to UCBT. This may also be the reason that, in another study comparing single- vs double-unit UCBT, in the double-unit group,
which received no ATG, less relapse and higher disease-free survival was reported than in the single-unit group, where 60% received ATG.²

All recent reports,³⁹ including the current study, prove that the immune reconstitution after UCBT is excellent in the absence of ATG. Achieving a CD4⁺ count of only 50/μL within 100 days after transplantation was recently found to be the strongest predictor for survival, TRM, and relapse.³ Patients not receiving ATG easily achieved these counts within 100 days after UCBT.³⁹ This also stresses the importance of selecting the best conditioning regimen for use in UCBT: either omitting ATG or individualizing ATG seems to be of crucial importance to achieve predictable timely CD4⁺ immune reconstitution after transplantation. Omitting ATG can be done safely in patients transplanted for a malignant indication, even with 4/6-matched units. However, for immune-competent patients undergoing UCBT, ATG is required to prevent rejection. For them, individualizing ATG may be the preferred strategy. This may be achieved by giving “earlier ATG” (more distal prior to UCBT) and using a pharmacologic model to calculate the optimal individual dose.⁷⁹ This should result in predictable high exposure before UCBT to prevent rejection and low or no exposure after UCBT to promote immune reconstitution. Adding the time to CD4⁺ reconstitution as a standard end point after transplantation may in this context be important for future transplantation studies.⁷

Taken together, we learn the following from this article, when combined with recent literature:

- Single-unit cord blood with adequate cell dose (>3NC*Kg before cryopreservation) in pediatric and (young) adult acute leukemia and myelodysplasia patients after myeloablative conditioning is preferred over double-unit transplantation;
- Single-unit UCBT is a safe (TRM <6%) and effective treatment (relapse ~20%, survival ~70%);
- Double-unit transplantation should be reserved as an alternative option when single units lack the minimal criteria;
- ATG can safely be omitted in (mismatched) UCBT for a malignant indication. For “non-immune-deficient benign disorders,” ATG should be given earlier and in an individualized way;
- T-cell reconstitution after UCBT is excellent in the absence of ATG (exposure after transplantation); and
- (Mismatched) cord blood T cells mediate enhanced antitumor activity.

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REFERENCES


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