ATG has been used as a form of in vivo T-cell depletion to reduce the risk of GVHD after allogeneic HSCT from related sibling and unrelated donors. Finke et al[6] reported a randomized study of ATG-Fresenius preparation added to standard cyclosporine and methotrexate GVHD prophylaxis for patients receiving a myeloablative transplant; survival was similar in both arms, but the incidence of GVHD was lower in the ATG arm. Soiffer et al[7] analyzed 1676 adults with hematologic malignancies undergoing a reduced-intensity conditioning (RIC) related or unrelated donor HSCT using fludarabine-based conditioning regimens. The relapse rate was higher and the disease-free survival lower when either ATG or alemtuzumab was added to the preparative regimen. The risk of acute GVHD was similar among patients who received either ATG or a T-cell replete HSCT. This study, however, did not include children or patients undergoing UCBT. With UCBT, several small studies have indicated a higher risk of infection with the use of ATG for UCBT, but there have been no large comparative studies to date. Delayed immune recovery after UCBT is characterized by prolonged T lymphopenia, compensatory expansion of B and natural killer cells, and late memory T-cell skewing.[8] In essence, a UCBT is a naturally T-cell depleted HSCT. In a study of immune recovery after RIC HSCT, Jacobson et al[9] compared 102 adult unrelated donor recipients with 42 adult double UCBT recipients, all of whom had received rabbit ATG. Reconstitution of $CD3^+$ T cells, including naïve ($CD45RO^-$) and memory ($CD45RO^+$) $CD4^+$ T cells, regulatory ($CD4^+CD25^+$) T cells, and $CD8^+$ T cells was delayed for 6 months post-HSCT in the UCBT patients. Clinically, these findings were correlated with an increased risk of infection, including Epstein Barr virus–associated lymphoproliferative disease, in the first 6 months after UCBT.[10] Lower doses of ATG may reduce this risk. Multiple successful UCBT conditioning regimens have been developed without ATG, but they have not been directly compared with ATG-containing regimens.

The article by Lindemans et al[1] seeks to address this important question in a large study of 127 children receiving unrelated UCBT in London or Utrecht. Patients were divided into 3 groups: an early ATG group receiving ATG between days −9 and −5, a late ATG group receiving ATG between days −5 and 0, and a no-ATG group. The ATG administered was rabbit ATG at a total dose of 10 mg/kg. Survival was excellent overall (71% in the no-ATG group, 68% in the early ATG group, and 61% in the late ATG group), with no differences among the groups (see figure). Neutrophil recovery was also similar among the 3 groups. $CD4^+$ T-cell counts were higher in the first year after UCBT in the patients who did not receive ATG, and this finding correlated with a lower incidence of viral reactivation and death from viral infections ($P = .002$) in the patients who did not receive ATG. As expected, the incidence of acute GVHD was higher in the no-ATG group, but the incidence of chronic GVHD was similar across all the groups. The authors concluded that the omission of ATG may be important to prevent viral reactivation after pediatric unrelated UCBT. They also suggest an individualized approach for each patient, based on disease status, infection history, and pharmacokinetic modeling to determine the optimal dose of ATG.

For UCBT, should the answer to ATG be yes or no? A randomized study will be required to determine whether ATG confers a survival advantage for patients undergoing UCBT. Different dosages and preparations of ATG may need to be considered, with a uniform conditioning regimen and GVHD prophylaxis. The article by Lindemans et al helps to address this ATG question, but the answer (for now) is maybe.

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● ● ● TRANSPLANTATION

Comment on Eapen et al, page 133

Allele-level HLA cord blood matching matters

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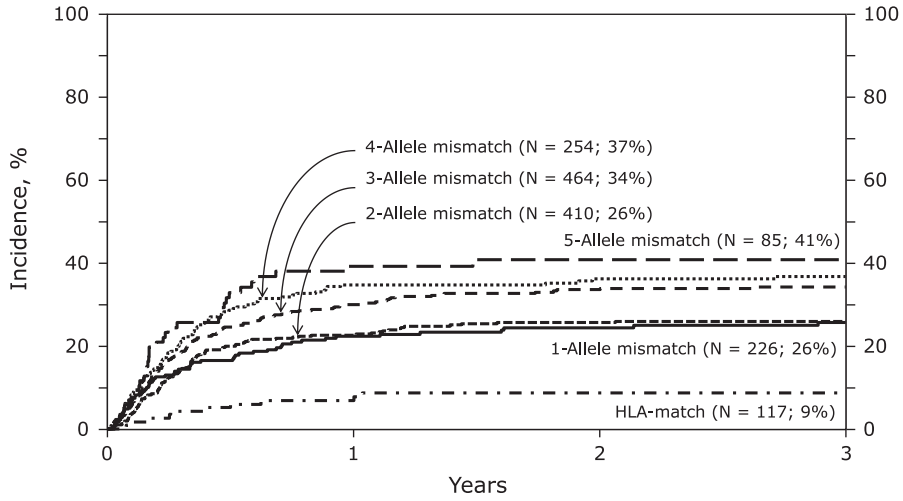
In this issue of *Blood*, Eapen et al report that improved allele-level matching for 4 HLA loci (-A, -B, -C, and -DRB1) produces better outcomes in single cord blood transplants (CBTs). We applaud the investigators for advancing cord blood selection criteria that will improve patient survival.[1]

The authors report the outcomes of 1568 CBTs using myeloablative conditioning for acute leukemia and myelodysplastic syndrome in patients with a median age of 9 years. Center for International Blood and Marrow Transplant Research and



The 3-year cumulative incidence of nonrelapse mortality was increased by more allele-level mismatches after single CBT. See Figure 1A in the article by Eapen et al that begins on page 133.

Eurocord-European Group for Blood and Marrow Transplantation data were used. Of note, donor-recipient HLA typing at allele level was not available in 784 cases (50%), and in those cases, donor-recipient HLA matching was estimated using the HaplogicSM III developed by the National Marrow Donor Program based on the available low/intermediate level testing that might have confounded the outcomes. The investigators showed that the frequency of neutrophil recovery was lower for recipients of mismatches at 3, 4, or 5 but not at 1 or 2 alleles compared with those of HLA-matched units. Nonrelapse mortality (NRM) was higher with units mismatched at 1 to 5 alleles compared with matched units (see figure). Overall mortality was not significantly different among the majority of cohorts except being higher for those that received units mismatched at 5 alleles. This retrospective study confirms the clinical importance of selecting better HLA allele-matched units for single CBT, an observation already well described for bone marrow and peripheral blood progenitor cell transplantation.[2]

The authors conclude that CB transplantation with ≥3 allele level mismatches should be avoided due to unacceptable NRM with inferior survival. Using this principle, approximately half of the patients in their study would not have received a CBT. This policy would have its impact primarily on the 4/6 matched patients using the current standard with intermediate level testing for HLA-A and -B and high-resolution testing for DRB1; 90% of the 4/6 matched patients were reported to have ≥3 allele-level mismatches in their series. This information underscores the fact that additional high-quality CB units need to be added to the global inventory for optimal CBT outcomes.

Eapen et al also report that CB unit cell dose has an impact on NRM independent of HLA matching. In fact, among patients transplanted with CB units mismatched at 3 alleles, units with total nucleated cell (TNC) dose $\geq 3 \times 10^7$ cells/kg had an NRM of 29% to 35% compared with an NRM of 52% observed with lower TNC doses, comparable with an NRM incidence of 26% observed with 1 or 2 allele mismatches. Thus, unit cell dose may overcome the negative impact of allele mismatches. A matrix of cell dose and allele matching will need to be considered to optimize CBT outcome.

Many patients deemed eligible for hematopoietic stem cell transplantation (HSCT) do not proceed due to unavailability of adequately matched related and unrelated donors. Patients of racial and ethnic minorities are more disadvantaged because of their relatively lower representation in donor registries. CB has been a great resource for extending the access to HSCT, especially to minorities, because mismatched CB is better tolerated than similar mismatches when bone marrow or peripheral blood progenitor cells are used. The increased use of CBT over the last decade reflects this fact.

It is obvious that with stricter criteria for allele-level matching applied, fewer patients will be eligible to proceed with CBT. Two strategies might help us to overcome this barrier until we have better units in the global inventory. First would be to identify possible permissive mismatches if units mismatched at ≤2 allele levels are not available. CBT with units matched with noninherited maternal HLA antigens[3] or mismatched at graft-versus-host-only direction are reported to have lower NRM and improved survival.[4] Second, graft manipulation might allow us to use smaller CB units with better HLA allele level matches. Currently, there are a number of promising graft manipulation strategies in the clinic for the ex vivo expansion[5,6] and enhanced homing of CB units.[7,8]

In conclusion, Eapen et al suggest that allele-level matching improves transplant outcomes but at the price of reducing the number of available units for a given patient. The continued procurement of high-quality units with higher TNC doses in the global inventory will offset this restriction in the years to come. Additional analysis of allele matching in the double CBT setting is needed, particularly for older patients.

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