

## EDITORIALS



## Cord-Blood Transplantation in Patients with Leukemia — A Real Alternative for Adults

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A steady stream of advances in allogeneic hematopoietic stem-cell transplantation has not only improved the clinical outcome in a variety of malignant and nonmalignant diseases but also widened the indications for such transplants. One important advance is the use of sources of hematopoietic stem cells other than bone marrow from HLA-identical siblings, which is a resource available to only about 30 percent of potential recipients.

By searching international databases, which contain more than 9 million potential volunteer stem-cell donors,<sup>1</sup> a matched unrelated donor can be found for an additional 50 to 80 percent of patients, depending on ethnic group. In the United States, however, only 30 percent of whites (and a slightly lower percentage of members of minority populations) for whom a search is initiated ultimately receive a marrow transplant from an unrelated donor. This low proportion is mainly due to deterioration of the patient's condition or death during the search.<sup>2</sup> For situations in which a matched unrelated donor cannot be found within a reasonable time, umbilical-cord blood has emerged as an attractive source of hematopoietic stem cells. Acceptable cord-blood units can be identified for most patients, because less stringent HLA compatibility with the recipient is required. Another important advantage of cord blood is the rapidity with which an acceptable cord-blood unit, once identified, can be acquired (median interval, 13.5 days).<sup>3</sup>

The establishment of many cord-blood banks in recent years has expanded the donor pool. There are now about 170,000 frozen units in 37 cord-blood registries in 21 countries.<sup>1</sup> The current inventory of the NetCord network<sup>4</sup> contains approximately 85,000 units stored in 15 of the largest cord-blood banks in New York City, Tokyo, and several sites in

Europe; adults have received one third of the approximately 2900 transplanted units.

The main obstacles to more widespread use of cord-blood transplantation in adults have been the risks of graft failure and delayed hematopoietic recovery, both due primarily to an imbalance between the body size of most adult recipients and the number of hematopoietic progenitor cells in a cord-blood unit, which is about 1/10 the number in a marrow harvest. For this reason, cord blood was originally used as a last resort for patients with high-risk hematologic cancers.

Studies of adults who received transplants of cord blood have had promising results<sup>5-7</sup> and have identified the main factors that should be taken into account in selecting a suitable cord-blood unit.<sup>8,9</sup> These data have increased the acceptance and early use of cord-blood transplantation in adults. But despite the evidence that cord-blood and bone marrow transplants result in similar long-term outcomes in children with leukemia,<sup>10,11</sup> until now, no such comparison has been made in a large series of adults.

In this issue of the *Journal*, two groups of investigators report the results of large registry-based studies that compared outcomes in adults with leukemia after transplantation of stem cells from unrelated bone marrow donors with outcomes after cord-blood transplantation.<sup>12,13</sup> Both studies have the inherent limitations of any observational study, and in both, the effect of the stem-cell source on various outcomes was analyzed by multivariate methods to allow a controlled comparison. The two investigations differ in their study populations and other methodologic issues that may have influenced their results.

In both studies, recipients of cord blood were

younger, weighed less, were more likely to have advanced leukemia at the time of transplantation, and received grafts with lower cell doses and greater HLA disparities than patients who received marrow transplants. The study by Rocha et al.<sup>12</sup> showed that adults with acute leukemia had slower engraftment and a lower risk of severe acute graft-versus-host disease (GVHD) with cord-blood transplantation (HLA-mismatched in 94 percent of transplants) than with HLA-matched bone marrow transplantation. There were, however, no clear differences between the cord-blood group and the bone marrow group in the risks of chronic GVHD or relapse or in survival outcomes. These results led Rocha et al. to conclude that cord blood can be used as an alternative to matched bone marrow from unrelated donors as a source of stem cells for transplantation in adults with acute leukemia who lack an HLA-identical sibling donor.

The study by Laughlin et al.<sup>13</sup> included patients with chronic myeloid leukemia, myelodysplastic syndrome, and acute leukemia, and it extended the comparison to recipients of bone marrow transplants that were mismatched for only one HLA antigen. The researchers found that hematopoietic recovery was slower among recipients of cord blood or mismatched bone marrow than among recipients of matched bone marrow but that the relapse rate was similar in all three groups. In contrast to the study by Rocha et al., there were no clear differences in the severity of acute GVHD, whereas chronic GVHD was more likely but less extensive after cord-blood transplantation. Furthermore, Laughlin et al. found that treatment-related mortality, treatment failure, and overall mortality were lower after HLA-matched marrow transplantation than after cord-blood transplantation. They cautiously concluded that cord blood is an acceptable source of stem-cell grafts only if an HLA-matched adult donor is not available within a reasonable time.

Is it possible to reconcile the apparently different conclusions of these two reports? I think it is. Several differences between the two studies could explain some of the discrepant results, especially with cord blood. The study period in the report by Laughlin et al. encompasses the pioneering period of cord-blood transplantation in adults, when the general practice was to use these grafts in patients in whom there were no other curative options and when the relevance of cell dose and HLA matching had not yet been recognized.<sup>8,9</sup> By contrast, Rocha et al. restricted their analysis to patients who re-

ceived transplants after 1998, because they had previously identified substantially better outcomes after that date<sup>14</sup> that probably were due to better selection of patients and cord-blood units. A recent single-center study from Japan found better outcomes in terms of acute GVHD, transplant-related mortality, and disease-free survival after cord-blood transplantation (performed after 1998) than after bone marrow transplantation from unrelated donors.<sup>15</sup> The remarkable differences in HLA disparity in the cord-blood recipients reported by Laughlin et al. and by Rocha et al. (77 percent vs. 43 percent in more than one HLA antigen, respectively) may, at least in part, also explain the poorer results in several outcome measures among patients who received transplants of cord blood than among those who received HLA-matched bone marrow in the study by Rocha et al. Finally, it should be emphasized that all available comparative studies of cord blood and bone marrow, in both children and adults with leukemia, show no significant difference in relapse rates, despite the lower incidence of acute GVHD reported with cord blood in most studies.<sup>10-12,15</sup>

Both reports reinforce the role of cord-blood transplantation in the treatment of adults with leukemia. However, neither group recommends cord-blood transplants over HLA-matched marrow from unrelated donors in adults, even though in children, cord-blood transplantation is now often used as an alternative to HLA-matched bone marrow from unrelated donors. Both groups of authors agree on the use of cord blood if an HLA-matched adult donor is not available within a reasonable time, and I strongly recommend a simultaneous search for an unrelated donor in both bone marrow and cord-blood registries.

Can we imagine a scenario for adults with leukemia that is similar to the current situation with cord-blood transplantation in children? I think we can. Once cord-blood transplantation is a real alternative for many adults, it is reasonable to assume that there will still be room for improvement. Outcomes could improve simply by performing transplantation with the currently recommended cell dose and HLA disparity<sup>14</sup> (more than  $2 \times 10^7$  nucleated cells per kilogram of the recipient's body weight and fewer than three of six HLA mismatches, respectively). Expansion of the pool of cord-blood units will substantially increase the chance of finding units that are better matched for individual patients. Clinical trials aimed at hastening engraftment with the use of multiple cord-blood trans-

plants, ex vivo expansion of cord-blood stem cells, and cotransplantation of CD34+ cells from a haploidentical donor are ongoing. It is realistic to anticipate that the current results for cord-blood transplantation in adults with hematologic cancers will contribute to more extended use in the coming years for many patients in need.

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## Intradermal Influenza Vaccination — Can Less Be More?

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The current shortfall in anticipated doses of vaccine for the upcoming influenza season<sup>1</sup> makes the reports by Belshe et al.<sup>2</sup> and Kenney et al.<sup>3</sup> in this issue of the *Journal* particularly timely. These studies raise the possibility of using alternative routes of immunization (e.g., intradermal, as opposed to intramuscular, administration) with smaller doses of vaccine as a means of “stretching” available doses of influenza vaccine in times of shortages. In addition, the studies indirectly raise provocative issues regarding the potential effect of these alternative routes of immunization in targeting specialized cells of the immune system to enhance the immunogenicity of certain vaccine antigens, particularly in populations such as the elderly and those with chronic diseases, who may not have a robust response to antigenic challenge.

Influenza remains a major health problem in the United States, resulting each year in an estimated 36,000 deaths and 200,000 hospitalizations.<sup>4</sup> Those who have been shown to be at high risk for the complications of influenza infection are chil-

dren 6 to 23 months of age; healthy persons 65 years of age or older; adults and children with chronic diseases, including asthma, heart and lung disease, and diabetes; residents of nursing homes and other long-term care facilities; and pregnant women.<sup>4</sup> It is for this reason that the Centers for Disease Control and Prevention (CDC) has recommended that these groups, together with health care workers and others with direct patient-care responsibilities, should be given priority for influenza vaccination this season in the face of the current shortage.<sup>1</sup> Other high-priority groups include children and teenagers 6 months to 18 years of age whose underlying medical condition requires the daily use of aspirin and household members and out-of-home caregivers of infants less than 6 months old.<sup>1</sup> Hence, in the case of vaccine shortages resulting either from the unanticipated loss of expected supplies or from the emergence of greater-than-expected global influenza activity — such as pandemic influenza, which would prompt a greater demand for vaccination<sup>5</sup> — the capability of extending ex-