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This Article

REVIEW IN TRANSLATIONAL HEMATOLOGY

New trends in umbilical cord blood transplantation

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Abstract

Since the first report of a successful umbilical cord blood transplantation in 1988, there has been great interest in the use of cord blood as an alternative stem cell source to treat cancer and genetic diseases. More than 4000 cord blood transplantations have been performed worldwide. In this review, the scientific rationale for this therapy, as well as related preclinical studies, cord blood banking issues, and ethical concerns, will be addressed. Results of studies in both pediatric and adult transplantation will be discussed. Finally, new indications for cord blood use and emerging technologies will be addressed.

Preclinical studies

Broxmeyer and colleagues in Indiana performed many of the initial studies on the potential of cord blood cells. Their observations came from Knudtzon and other investigators who showed that neonatal and cord blood contain a much higher number of granulocyte-macrophage progenitor cells. Murine experiments demonstrate that neonatal mice contain a high number of adequate progenitor cells for bone marrow reconstitutive ability. In addition, human cord blood was shown to have sufficient progenitor cells to support durable engraftment. These studies paved the way for the first clinical use of cord blood transplantation, and for the growth of cord blood banking.

Several unique properties of cord blood were learned from these experiments. Cord blood CD34+ cells increase in cell number every 7 to 10 days, several hundred-fold. The increase in cultures of similar cells from adult bone marrow. Compared with adult bone marrow, CD34+/CD38- cord blood cells proliferate more rapidly and generate larger...
progeny cells. Longer telomere length of cord blood cells has been proposed as explanation for the greater proliferative capacity of cord blood.

The immunologic properties of cord blood differ from mature bone marrow or peripheral blood stem cells. The initial clinical observations of decreased graft-versus-host disease following related cord blood transplantation prompted investigation into the unique features of cord blood cells. Cord blood contains a high proportion of T cells with CD45RA+/CD45RO−, CD62L+ “naive” phenotype. The chemokine receptor CCR5, expressed by T helper 1 T cells, is less abundant among cord blood compared with adult T cells. Studies show that cord blood cells produce increased amounts of the anti-inflammatory cytokine interleukin-10, which may downmodulate graft-versus-host disease.

Cord blood banking

With the increased recognition that cord blood constitutes a viable source of stem cells, cord blood banks were established worldwide to provide a large number of high-quality cord blood units to transplant centers. The first operational cord blood banks were established in New York, Milan, and Dusseldorf. The New York Blood Center, under the guidance of Rubinstein, established protocols for collection, processing, and freezing of cord blood. Currently, Bone Marrow Donors Worldwide lists approximately 150,000 available from 35 different cord blood banks in 21 countries. Almost all the units are typed for HLA A, B, and DR; 76% of the units have molecular typing for class II, and 49% have molecular class I.

Cord blood banking involves the following phases: (1) recruitment, consent and testing of maternal donors; (2) collection of the cord blood unit; (3) processing, freezing, and testing of the cord blood unit; and (4) release of cord blood unit to transplant center.

Recruitment and consent of donors

In most cord blood banks, pregnant women are recruited as potential cord blood donors prior to delivery through their obstetrician/midwife/family practice physician performing their obstetric care or by trained personnel from the cord blood bank. Most American cord blood banks bar an Investigational New Drug (IND) application from the Food and Drug Administration and require an institutional review board–approved research consent is required. Consent for the collection of the cord blood sample, for processing a cord blood unit, for maternal infectious disease testing, and for the storage of cord blood samples, for possible future genetic and infectious disease testing. A medical and genetic history is obtained, and there are similar exclusion criteria for cord blood donors. Sugarman et al have summarized the ethical issues involved in consent for cord blood banking. Different consent methods have been used by the different cord blood banks.

The American Red Cross Cord Blood Program, North Central region, investigate consent policy. The phased consent approach is a 3-step process involving (1) targeting information about cord blood banking to pregnant women; (2) allowing early labor ex utero collection and temporary storage of cord blood; and (3) permitting post-collection consent to the permanent storage, donation, and testing of the cord blood. Mothers who intralabor consent had to meet strict eligibility criteria including dilation less than 18 years, more than 36 weeks gestation, and no use of narcotics.

A purported goal of the cord blood banks is to increase minority donation, to help patients who have a more difficult time finding donors through the National Marrow
Program (NMDP) and other international registries. However, an early study of 5 blood banks found no improvement in cord blood donation from minorities compared to marrow registries in the same geographic area. In fact, in California, Florida, and Massachusetts, the cord blood banks recruited a lower percentage of minorities corresponding marrow donor centers. A more recent survey of the American Red Cross blood banks revealed a diverse donor population: 64% white, 16% African American, 4% Asian, 1% Native American, and 3% other. Nucleated cell counts among the different racial/ethnic groups, but CD34+ counts were lower for blacks in the Midwest, Northwest, and North Carolina collection sites. These data suggest that even greater recruitment efforts are needed to increase the number of suitable cord blood units from certain racial/ethnic groups. The current racial/ethnic composition of the NMDP cord blood registry is 52% white, 5% African American, 5% Asian, 13% Hispanic, 12% multiple race, 1% Native American, and 12% other or unknown (personal written communication, NMDP, 2004). Thus, increased recent attention to minority recruitment has resulted in more diverse cord blood units.

Collection of the cord blood unit

The cord blood can be collected either in utero, before the delivery of the placenta, or ex utero, after placental delivery. In utero collections are usually performed by the obstetrician/midwife attending the delivery, while trained personnel from the cord blood bank, collection outside the delivery room, more often perform ex utero collections. The Blood Bank uses an obstetrician-based cord blood collection network, using more delivering physicians and 40 obstetric units. In contrast, the 3 cord blood banks National Heart, Lung, and Blood Institute Cord Blood Transplantation Study (COBLT) used trained technicians who collected the cord blood following the delivery of the placenta. Utero collections are less invasive, and there is better control over technique, but they may be more expensive because of the additional personnel involved. One study showed counts and CD34+ counts with either method. The New York Blood Center harvests the cord blood from the delivered placenta and has reported an association between length of the cord and volume of collection. There have been no reports of a serious adverse event with either in utero or ex utero collections.

Processing and freezing of the cord blood unit

Most of the cord blood banks operate under strict guidelines, analogous to blood instituted by either NETCORD, FACT (Foundation for Accreditation of Cellular Therapy), or AABB (American Association of Blood Banks). For example, the group in Milan operates under a strict quality control system, which controls staff organization and training, collection and storage, and periodic audits. In the early years (1993-1996) of cord banking, the cord blood was frozen as whole blood in 10% dimethylsulphoxide (DMSO). Space considerations became paramount, and the cord blood volume was reduced by removal of the red blood cells and plasma. Freezing is usually done at a controlled rate, such as down to -4°C, then transferred to -80°C freezer, and finally to either the liquid or vapor phase of liquid nitrogen freezers, achieving a temperature of less than -180°C, for long-term storage. Recovery of hematopoietic progenitor cells (colony-forming unit–granulocyte macrophages [CFU-GMs]) has been studied in cord blood cells frozen for up to 12 years. Recovery was more than 90% at 10 years. Blood from the maternal donor is tested for infectious disease markers, including...
syphilis, human T-cell lymphotropic virus 1 (HTLV-1), HIV, hepatitis B, and hepatitis C. Recently, nucleic acid testing has been used as a more sensitive test for hepatitis B and H addition, blood is tested for cytomegalovirus (CMV) antibodies. The cord blood u cultured, and HLA testing, usually by molecular methods, is used. A nucleated cell and after processing, CD34+ testing, and in some cases, CFU-GMs are tested o product. The lack of standardization among banks for CD34 and CFU-GM testing makes comparison of cord blood units difficult. About half of the cord blood units collect for banking are not frozen for potential transplant use; the most common reason product. In Italy, the mother and baby are re-evaluated at 6 months after delivery, medical history and repeat infectious disease tests are obtained. This program h success rate of having the mothers return at 6 months; based on this 6-month cl (0.3%) were discarded. The procedure in American banks varies from no mate distribution of contact materials to the mother in case of the baby's illness, postp calls, to a formal 6-month visit.

Release of cord blood unit to transplant center

Possible HLA-matched cord blood units for patients are found via computerized searches. NMDP has approximately 34 000 units listed from several cord blood banks; transplant coordinators can locate cord blood units for patients via the NMDP computerized while also performing an unrelated bone marrow donor search. The New York Blood Center, for example, has its own search engine, and transplant centers can contact the bank for potential units. In Europe, the NETCORD system has 59 000 listed units. Rubinstein et al pioneered a popular thawing technique, using a dextran/albumin wash. The technique is different from a standard bedside thaw and requires an experienced laboratory.

Congress has recently allocated federal funds in support of cord blood banking and transplantation. The Institute of Medicine has been asked for advice on the appropriate use of the funds.

One advantage of cord blood as opposed to unrelated bone marrow is the speed of the search process, since there is no living donor to contact and retest.

Clinical studies in cord blood transplantation

Pediatric studies

Related donor transplantations. Although the primary interest in cord blood is as an unrelated donor source, umbilical cord blood has been used successfully in relation both malignant and nonmalignant diseases. The Eurocord group reported on 10 children with acute leukemia receiving cord blood transplants; 42 received a related donor transplant in these patients, 12 received a mismatched graft; neutrophil engraftment was 84% and event-free survival was 41%. A nucleated cell dose more than 3.7 x 10^7/kg correlated with engraftment. The same group recently analyzed their results for related cord blood transplant for children with sickle cell anemia and thalassemia. There were 44 patients who received cord blood transplant. The 100-day transplant-related mortality was 0; 4 patients experienced grade 2 acute GVHD. Of the patients, 1 with sickle cell disease and 7 with thalassemia have sustained donor engraftment. The 2-year probability of event-free survival was 79% for thalassemia and 90% for sickle cell anemia. Cord blood, a naturally T-cell–depleted product, has a low risk of graft-versus-host disease, and may be well suited to the treatment c
diseases, where there is no need for a graft-versus-leukemia effect.

**Unrelated cord blood transplantations.** The first unrelated cord blood transplantations were performed in children. The first 25 unrelated cord blood transplantations were reported in 1996. Of these patients, 24 were children, and 30% were nonwhite and had searched for a marrow donor for at least 6 months. The cord blood was mismatched to the patient at 1 to 3 HLA loci. Of 55 patients, 23 engrafted. There were 2 patients with graft-versus-host disease, and the event-free survival was 48% with a median follow-up of 12 months. These data suggested that engraftment could occur even with cord blood units that were mismatched at 2 loci, that severe graft-versus-host disease was low, and that a higher cell dose may be an important prognostic feature.

This work has been followed by several studies, showing similar results in children. Blood Center reported on 562 cases, 82% children, who underwent transplantations in centers with differing conditioning regimens and graft-versus-host disease prophylaxis. Engraftment was 81%, and the risk of grades III to IV GVHD was 23%. Younger nucleated cell dose/kg infused correlated with improved engraftment and survival improved with selection of cord blood units with higher cell doses. The Eurocord group analyzed 95 children receiving unrelated cord blood transplants for acute myeloid leukemia. Nucleated cell dose per kilogram was $5.2 \times 10^7$. Transplant-related mortality was 20%; 2-year disease-free survival was 42% for patients in complete remission 1 (CR1), 50% for CR2, and 21% for refractory patients.

Wagner et al from the University of Minnesota performed transplantations in unrelated umbilical cord blood. Of the children, 65 had malignant diseases (68% had nonmalignant diseases. The incidence of neutrophil engraftment was 88%; engraftment 65%. The incidence of graft-versus-host disease was low; severe acute GVHD was seen in 11% of patients and chronic GVHD, in 10% of patients. The low incidence of graft-versus-host disease following cord blood transplantations has raised the question of whether a detrimental decrease in the graft-versus-leukemia effect occurs. In this study, the rate of leukemia relapse was low, 17% for standard-risk patients and 45% for high-risk patients. Transplant-related mortality was 30% and survival at 2 years was 47%.

There have been no randomized studies comparing outcomes after unrelated bone marrow or unrelated cord blood transplantation. However, there have been retrospective analyses. Rocha et al compared 113 related cord blood recipients with 2052 related bone marrow recipients. GVHD was lower among cord blood patients, and mortality was similar in the 2 groups, which included patients with both malignant and nonmalignant diseases. The group also compared children receiving unrelated 1- to 2-antigen–mismatched cord transplants, unrelated matched and 1-antigen–mismatched bone marrow transplants, and unrelated T-cell–depleted bone marrow transplants. Engraftment was delayed in the T-cell–depleted group, and acute GVHD was decreased in the cord blood and T-cell–depleted group. Disease-free survival was comparable, 31% for cord blood, 37% for the T-cell–depleted group, and 43% for the unrelated marrow group.

Cord blood transplantation has also been shown effective in metabolic storage diseases. There were 20 children with Hurler syndrome who received conditioning with busulfan, cyclophosphamide, and antithymocyte globulin followed by infusion of unrelated 3-antigen–mismatched cord blood. With a median follow-up of 905 days, 17 of
alive with complete donor chimerism and normal peripheral blood alpha-1-iduronidase.

The results from some of the major pediatric, nonregistry studies are outlined in Table 1. In general, the pediatric data indicate that cord blood transplantation can be successful, even if the patient and cord blood donor are mismatched at 2 antigens. Therefore, the potential donor pool is considerably increased from unrelated bone marrow or peripheral blood stem cells. The incidence of severe graft-versus-host disease is low, but engraftment, particularly platelet engraftment, is delayed. There does not appear to be a diminution of the graft-versus-leukemia effect. The cell dose infused is consistently an important marker for improved engraftment and survival.

### View this table: Table 1. Pediatric unrelated cord blood transplant results

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#### Adult unrelated cord blood transplantation

Some of the initial studies of cord blood transplantation included adult patients, but the majority of patients were children. In the last 5 years, several investigators have published cord blood transplantations in adult patients. These studies have included patients with leukemia, lymphoma, and myelodysplasia, treated with a variety of conditioning regimens and GVHD prophylaxis regimens. Laughlin et al. analyzed the outcome of 68 adults, media who received cord blood transplants. Of the patients, 71% received units that were 2 or more HLA antigens. The incidence of neutrophil engraftment was 90%, but engraftment was delayed compared with unrelated bone marrow, at 27 days to a platelet count more than 20 x 10⁹/L unsupported was 58 days. Grade III or IV acute GVHD was seen in 20% of patients, and chronic GVHD in 30% of the evaluable patients. Transplant-related mortality was high in this series; 47% of patients died prior to day +100; there were 21 deaths related to infection. Actuarial projected 3-year survival was 19%.

Slightly better results have been reported from the Spanish and Japanese groups. There were 22 patients, median age 29 years, who received cord blood transplants. Median days to neutrophil and platelet engraftment were 22 and 69, respectively. Disease-free survival was 53% at one year. Younger age was correlated with improved survival. The Japanese group reported results for 18 patients with acute myelogenous leukemia receiving cord blood transplants. The regimen was cyclophosphamide, cytosine arabinoside, and total body irradiation. The median cryopreserved cell dose was 2.5 x 10⁷ nucleated cells/kg. The median time to neutrophil engraftment was 23 days. Acute GVHD grades II to IV were seen in 11 patients. The probability of disease-free survival was 76%. An additional study from this group
outcomes among 8 acute leukemia patients receiving umbilical cord blood to outpatients receiving unrelated bone marrow. Patients received the same condictiGVHD prophylaxis, and supportive care regimen. Hematopoietic recovery was differential for the cord blood group, chronic GVHD was higher in the cord blood group, and acute GVHD was comparable. The probability of 2-year disease-free survival was similar between this small study, 85% for cord blood versus 75% for bone marrow.

Recently, the International Bone Marrow Transplant Registry reported results ofa study comparing survival after unrelated umbilical cord blood transplantations to survivunrelated bone marrow transplantations. A total of 116 adults with leukemia receiving an 2-antigen–mismatched cord blood transplants were compared with 367 adults receiving unrelated donor bone marrow transplants and 83 patients receiving 1-antigen–mismatched bone marrow transplants. The median cell dose was 2.2 x 10^7 nucleated cells/kg, similar to the Japanese study. Deaths related to infection were highest in the cord blood group, compared with the mismatched bone marrow cohort. The 3-year leukemia-free survival was 33% for HLA-matched bone marrow and 19% for 1-antigen–mismatched bone marrow. These results suggest that outcomes are improved for patients receiving a matched unrelated bone marrow transplant cord blood and 1-antigen–mismatched unrelated bone marrow had similar survival.

At the same time, the Eurocord group reported results of a retrospective study outcomes of 98 adults with acute leukemia receiving unrelated 1- or 2-antigen–mismatched cord blood with 584 adults with acute leukemia receiving unrelated matched bone marrow transplants. Neutrophil recovery was delayed after cord blood transplantation (26 days vs 19 days). Graft failure occurred in 20% of the cord blood recipients and 7% of the bone marrow recipients. The incidence of grades II to IV acute GVHD was 26% after cord blood transplantation and 39% after unrelated bone marrow transplantation. Relapse was similar in both groups. The 2-year leukemia-free survival was similar in both groups, 33% for cord blood and 38% for unrelated bone marrow. This study suggests that outcomes after cord blood transplantation may be similar to outcomes after matched unrelated bone marrow transplantation.

The Japanese group has just published impressive data comparing 68 adult umbilical cord blood recipients with 45 adult unrelated bone marrow recipients. Ninety-four percent received a cell dose of more than 2.0 x 10^7 nucleated cells/kg. Neutrophil and platelet engraftment were delayed in the cord blood recipients. The transplant-related mortality was 9% for cord blood, 29% for unrelated bone marrow recipients. The 2-year probability of disease-free survival was 74% for cord blood and 44% for unrelated bone marrow. These results are superior to those reported in the American and European series, perhaps due to the smaller size and genetic homogeneity of this population.

The results of the single cord blood studies in adults are presented in Table 2. These studies show that engraftment can be achieved in adult patients but is delayed compared with unrelated bone marrow. Early transplant-related mortality is high, mostly due to infection. The cell dose (either nucleated cell/kg or CD34^+ cells/kg) correlated with outcome in most studies and strategies have been developed to improve these outcomes: (1) pooled or sequential cord blood transplantation; (2) cord blood expansion; (3) combination cord blood and haploidentical transplants; and (4) nonmyeloablative or reduced intensity conditioning regimens.
Pooled or sequential cord blood transplantation is the addition of a second, partially matched cord blood unit to increase the cell count and improve engraftment and immune reconstitution. A report of patients infused with multiple, mismatched units suggested that cross-rejection would not occur. The University of Minnesota program has done extensive double or sequential cord blood transplantation, using a nonmyeloablative regimen. Barker et al transplanted 1 or 2 cord blood units to achieve a minimum cell dose of $3.5 \times 10^7$ nucleated cells/kg. Of the patients, 21 received busulfan/fludarabine/low-dose TBI, and 22 received cyclophosphamide/fludarabine. Cyclosporine and mycophenolate mofetil were used for GVHD prophylaxis. Of the 43 patients, 24 received 2 cord blood units. The incidence of neutrophil engraftment was 76% for the first regimen and 94% for the second regimen; the median days to an absolute neutrophil count of 1,000 mm$^3$ were 26 for the first regimen and 10 for the second regimen. The risk of grades III or IV acute GVHD was 9%. The 100-day transplant-related mortality was 48% for the busulfan-based regimen and 28% for the cyclophosphamide-based regimen. Overall survival at 1 year was 39%. These studies have shown that in ablative transplantations the incidence of engraftment increased, but the time to engraftment was not changed; also, for patients receiving a nonmyeloablative regimen, the day +10 myeloid recovery was autologous, and engraftment of cord units occurred later after transplantation.

We have pursued the sequential cord blood transplant approach in a current phase 1 study at the Massachusetts General Hospital and Dana Farber Cancer Institute. Patients received 2 cord blood units, which need to be an HLA 4/6 match with each other and with the patient, and achieve a combined cell dose of more than $3.7 \times 10^7$ nucleated cells (NC)/kg. There are 15 patients who have undergone transplantation; 7 have more than 100 days of follow-up. By day +100, one cord unit had predominated, as documented by chimerism analysis. Of 15 patients, 12 are alive without evidence of disease. There were 2 deaths prior to day +100, 1 related to a central nervous system (CNS) bleed, and 1 related to sepsis; and 1 patient died after day +100 from chronic GVHD and sepsis.

Cord blood expansion

There have been many preclinical trials studying expansion of cord blood cells using cytokine mixtures. One approach is to use a continuous perfusion device. In a study using the Aastrom/Replicell system, 28 patients received a conventional single cord blood transplant, followed by the infusion of the expanded cells on day +12 after transplantation. Ex vivo–expanded cells were well tolerated, but engraftment was unchanged. The 3-year probability of event-free survival was 39%. Shpall et al expanded a portion (40%-60%) of the cord blood unit using a combination of stem cell factor, granulocyte colony-stimulating factor (G-CSF), and megakaryocyte growth and development factor in a study of 37 patients. The remainder of the cord blood unit was unmanipulated. All patients engrafted with a median time to neutrophil engraftment of 28 days. Survival was 35% at 30 months. The M. D. Anderson Cancer Center is currently...
blood expansion in a phase 2 study, comparing 2 unmanipulated cord blood units versus 1 expanded cord blood unit (personal oral communication, D Anderson Cancer Center, 2004). Cord blood cells are selected with a CD133 selection device and cultured with stem cell factor, G-CSF, and megakaryocyte growth and developm infusion.

**Combination cord blood and haploidentical bone marrow transplant**

The Spanish group has pioneered this unique approach. There were 11 adults who received single cord blood units and haploidentical CD34+ selected cells from a family member. Neutrophil engraftment occurred at 12 days (range, 9-36 days). There were 4 patients who experienced grade II or higher acute GVHD. Of the 11 patients, 5 survive disease-free with complete cord blood chimerism at 6 to 43 months after transplantation.

There are now alternatives to single cord blood transplantation for adult patients. Cord blood results appear promising in terms of neutrophil recovery, and a low risk of more work is needed in larger studies with diverse patient populations. A suggested algorithm for choosing an optimal donor source for adults is presented in Figure 1. Patients with matched sibling donor should search simultaneously for unrelated bone marrow and unrelated cord blood. Patients without time to find an unrelated bone marrow donor, or who have a 10/10 or 9/10 unrelated adult volunteer donor should be considered for cord blood transplantation. The goal should be to procure a safe donor source, either bone marrow or cord blood, in a timely fashion so no appropriate patients are denied transplantation.

**Unique problems in cord blood transplantation**

Early infections continue to be a major problem in allogeneic transplantation. Because of the delayed immune reconstitution, infections are a serious problem in cord blood transplantation. The Spanish group analyzed the infections in 27 adult patients undergoing cord blood transplantation. In this group of patients, 55% experienced bacteremia, 58% developed CMV infection, and 11% had documented fungal disease. In this study, there were 3 deaths related to Acinetobacter infection. Recommendations for management include prophylaxis against viral, bacterial, and pneumocystis infections; frequent monitoring of CMV antigenemia; and replacement of gamma globulin for immunoglobulin G levels below 500 mg/dL. Another problem unique to cord blood transplantation is that the original donor cannot be recontacted for donor lymphocyte infusion or more cells. Back-up donor sources should be reviewed prior to cord blood transplantation. Some of the unique issues related to cord blood transplantation are listed in Table 3.
Future trends in cord blood transplantation

As we look ahead to the next 5 to 10 years in cord blood transplantation, there will be continued studies on adult cord blood transplantation, with more centers examining double transplantation. Future trials are needed to define the best application of cord blood transplantation. There might be a future indication for cord blood transplantation in cases of a matched unrelated donor, for example, in elderly patients with a high risk of graft-versus-host disease. The unique immunologic properties of cord blood likely contribute to a lower risk of graft-versus-host disease. Additional experience in nonmalignant diseases is also needed. One application could be autoimmune diseases, where there has been some success with autologous transplantation and the low risk of graft-versus-host disease makes cord blood transplantation attractive.

Another intriguing application is in HIV disease, a major public health problem, in which the possibility of gene transfer to a hematopoietic reservoir may eventually be possible. In theory, an allogeneic stem cell vaccine may replace hematopoietic stem cells infected with HIV with uninfected umbilical cord blood cells.

Potential exciting uses of cord blood may be nonhematopoietic applications, such as the repair of damaged myocardium or neural tissue. Cord blood cells are a more primitive population than adult bone marrow, and have increased capacity for multilineage differentiation. Blood cells have been shown to improve functional recovery in rats who have been subjected to strokes, by middle cerebral artery occlusion. Infarct volume was reduced and behavioral performance increased when a higher dose of cord blood cells was infused.

Summary

Over the last 10 years, we have seen the growth in use of a common, often discarded stem cell source, umbilical cord blood. Transplantation outcome results in children mirror those with unrelated donor transplantations, and cord blood transplantation is widely accepted for use in the pediatric transplant community. The results in adults have been hampered by low cell dose. However, new techniques, such as sequential cord blood transplantation, may help to increase progenitor cell numbers and improve immune reconstitution. Over the next several years, growth in interest in transplantation for nonmalignant diseases and nonhematopoietic applications will make this one of the most exciting areas of hematology.

Footnotes

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Footnotes


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