



Annotated Bibliography

II. Transplantation of Adults Using Cord Blood Units



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Introduction

Perhaps the most critical issue in cord blood transplantation is the effectiveness of cord blood units for transplantation of adults because at least 75% of patients in need of a hematopoietic cell transplant are adults.

Can cord blood units, which require less stringent HLA matching of donor and recipient, satisfy the unmet need for donors for adult patients in need of hematopoietic cell transplants? Guidelines for an adequate cell dose in cord blood transplantation have steadily evolved and the critical importance of cell dose is now firmly established. Selection of a single cord blood unit with adequate cell dose, or the use of more than one cord blood unit are being utilized successfully in a number of transplant centers. In addition, reduced-intensity (nonmyeloablative) conditioning regimens have contributed to successful outcome.

Also, in *Annotated Bibliography*, see under headings: III. Multi-cord Transplants; IV. Reduced Intensity and Non-Myeloablative Transplants; V. Donor Selection for Unrelated Cord Blood Transplantation; VI. Availability and Time Required to Obtain Cord Blood versus Bone Marrow

(For a commentary regarding the unrealized potential of umbilical cord blood (UCB) units for unrelated donor hematopoietic cell transplantation, go to: [Interactive Forum for Medical Professionals](#) on the left hand column of the [Home Page](#) of this website.)

1. Cord blood transplantation for adults. Brunstein CG, Wagner JE. Vox Sang. 2006; 91:195-205. **Abstract**

Advantages and disadvantages of umbilical cord blood (UCB) over donations from unrelated adults: **Advantages** are (1) that UCB units are immediately available for transplantation, (2) there is no risk to the donor, (3) there is a low risk of viral transmission of CMV, hepatitis and HIV, and (4) a higher degree of HLA mismatch appears to be acceptable with a comparatively lower risk of acute and chronic GVHD. **Disadvantages** are (1) there are a limited number of hematopoietic progenitor cells in a single UCB unit and cell dose has been shown to be a major determinant of engraftment and survival. (2) there is no access to donor lymphocytes in the event of relapse after UCB transplantation, and (3) there is significantly less experience with UCB than with unrelated donors, especially in adults.

COMPARISONS OF UCB AND OTHER HSC SOURCES:

The results of **two reported studies that compared related donor HSC vs. unrelated UCB transplantation** are summarized in the text and in a detailed table. **The first study** compared unrelated UCB to HLA- and partially HLA-matched related donors after a myeloablative preparative regimen. Time to neutrophil and platelet recovery were longer in the UCB cohort, but overall donor-derived engraftment was comparable by day 42. The rate of aGVHD grades II-IV was the same but grade III-IV aGVHD was significantly more frequent among recipients of a related donor graft (8% vs. 19%, $p=0.04$). The incidences of cGVHD and TRM, and the 3-year relapse rate, as well as probability of 3-year survival were comparable between the two groups. **The second study** compared outcomes in patients transplanted with unrelated UCB and haploidentical T-cell depleted marrow grafts for the treatment of AML and ALL. Once again, median time to neutrophil recovery was longer in the UCB cohort. The incidence of grades II-IV aGVHD was higher for the UCB group. Other than GVHD, patients with AML had similar outcomes, regardless of graft source. However, patients with ALL had a higher probability of 2-year-leukemia-free survival if they received a UCB graft.

At least three retrospective studies have been reported that compared UCB with unrelated donor transplantation in adults after a myeloablative preparative regimen. Again the tie to neutrophil and platelet recovery was significantly delayed, and graft failure was higher after UCB transplantation. The incidence of grades II-IV aGVHD after UCB transplantation was similar or lower. Relapse rates were similar between UCB and unrelated donor grafts in all studies. The impact of graft source on TRM and survival has been more controversial. One study showed TRM after UCB transplantation to be significantly higher than after HLA-matched unrelated marrow (although similar to HLA-mismatched unrelated marrow), another study showed similar TRM rates for UCB and unrelated marrow grafts, while the third study observed lower TRM for the UCB group compared with unrelated marrow. **Overall, these studies suggest that UCB transplantation is an acceptable alternative for all patients who do not have a suitable related and unrelated donor. The question, at present, is the relative place of UCB – first-line or second-line therapy.**

MULTIPLE UCB UNITS

It is unequivocally clear that cell dose and HLA match are central factors in predicting the risk of TRM. Furthermore it is clear that low cell dose amplifies the deleterious effect of HLA mismatch. The use of "double" UCB transplantation is based on the rationale that if a single unit does not provide an adequate cell dose for an adult patient, perhaps the combined cell dose of two partially HLA-matched units could improve the outcome.

Double UCB transplantation after a myeloablative preparative regimen: In a study comparing outcomes after single or double UCB transplantation for acute leukemia patients, sustained neutrophil engraftment and TRM were virtually the same indicating that patients can receive single UCB unit grafts if the cell dose is high enough. There was a threefold higher incidence of grade II-IV aGVHD among recipients of double cords, but no difference in the incidence of grades III-IV aGVHD or cGVHD. **An unexpected finding was a lower leukemia relapse rate among recipients of double UCB graft when transplanted in first and second complete remission. The results of the multivariate analysis indicated that transplantation with two units is associated with a 10-fold lower risk of relapse.** This may be explained by the fact that recipients of a double UCB graft most often receive a 4/6 HLA-matched graft, which may lead to more GVL effect.

Double UCB transplantation after non-myeloablative transplantation: Non-myeloablative (NMA) preparative regimens have allowed patients who are older, and heavily pretreated, and with significant comorbidities to undergo allogeneic transplantation. Most groups have used fludarabine combined with an alkylating agent preparative regimen with or without low-dose TBI. In two studies, patients who received double UCB unit grafts, with a higher median infused NCD and CD34 cell dose, were more likely to have sustained donor engraftment, at a median of approximately 2 weeks. The incidence of acute and chronic GVHD varied widely but TRM was consistently lower than 30%. In the largest single-center experience, progression-free survival was 38% and overall survival was 44%. However, patients who receive an NMA preparative regimen because of poor organ function, recent fungal infection, or low performance status still have a significantly higher risk of TRM and poor survival. Patients who were not exposed to multiagent chemotherapy in the 3 months before NMA UCB were at high risk of graft failure, and patients who receive ATG have an increased risk of EBV viremia and post-transplant lymphoproliferative disorder. **In summary, the data clearly support the utilization of UCB as an HSC source for NMA transplantation.**

NOVEL STRATEGIES TO IMPROVE ENGRAFTMENT, REDUCE GVHD, REDUCE TRM AND ENHANCE GFL:

1. Use of drugs or cell populations to reduce host resistance.
2. Ex- vivo expansion to augment the HSC and progenitor cell numbers.
3. Use of novel therapies that limit the use of myelotoxic drugs in the peritransplant period.
4. Ways to minimize the non-specific loss of circulating HSCs and potentially homing to the marrow microenvironment.

2. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplant outcomes in 110 adults with hematological disease. Brunstein CG, Barker JN, Weisdorf DJ, Defor TE, Miller JS, Blazar BR, McGlave PB, Wagner JE. Blood 2007;110:3064-70. [Abstract](#)

This report establishes the safety profile of a nonmyeloablative treatment regimen consisting of fludarabine (FLU), cyclophosphamide (CY) and single fraction total body irradiation (TBI) in recipients of UCB in 110 consecutive adult patients with hematological disease. Ninety-three of the 110 patients received a double cord transplant.

Inclusion Criteria. Patients with advanced or high-risk hematologic disease were eligible for UCB transplantation if they had no related donor matched at 5-6/6 HLA loci (A, B, and DRB1). Patients were eligible for nonmyeloablative therapy if they met any of the following criteria: age >45 years, pre-existing high risk clinical features for TRM (serious organ dysfunction; invasive mold infection within 4 months prior to transplantation; Karnofsky Performance score 50-60 or history of extensive prior therapy [defined as: >12 months alkylator-based chemotherapy; >6 months alkylator-based chemotherapy plus extensive radiation; or history of autologous transplantation]).

UCB unit selection algorithm. UCB units were required to be matched at >4 of 6 HLA antigens based on antigen-level HLA-A and B typing and allele-level HLA-DRB1 typing. UCB units were required to have a minimum cryopreserved total nucleated cell (TNC) dose of 2.0×10^7 /kg. However, the target cell dose was 3.0×10^7 TNC/kg resulting in the selection of a second partially HLA matched UCB unit if available. In those for whom a second UCB unit could be identified, the second unit also had to be 4 of 6 antigen matched with the first unit.

Treatment. 110 patients received a single dose of CY 50 mg/kg on day -6, FLU 40 mg/m² daily on days -6 to -2, and a single fraction of TBI 200 cGy without shielding on day -1. ATG was given at 15 mg/kg every 12 hours on days -3 to -1 in a subpopulation of patients who had received less than two cycles of multiagent chemotherapy within the 3 months prior to enrollment (and no history of autologous transplantation.). All patients received CsA twice daily from day -3 for at least 3 months with target trough levels of 200-400 ng/ml and MMF at 1 g intravenously or orally twice daily from day -3 to +30.

Results. Most patients received two UCB units (n=93) to achieve the required cryopreserved cell dose. Neutrophil recovery was achieved in 92% at median of 12 days. Incidences of grades III-IV acute and chronic GVHD were 22% and 23%, respectively. Transplant-related mortality was 26% at 3 years. Survival and event-free survival at 3 years were 45% and 38%, respectively.

Favorable risk factors were absence of high risk clinical features and absence of severe GVHD (p=0.04) for survival, and absence of high risk clinical features (p<0.01) and use of two UCB units (p=0.07) for event-free survival.

Discussion. The study supports the use of UCB transplantation after a non-myeloablative therapy in adults with hematologic disease. **It is clear that the use of the double UCB platform in the setting of a nonmyeloablative therapy extends the availability of transplantation to those who cannot find a suitably HLA matched adult volunteer marrow or peripheral blood donor and who are at increased risk of regimen-related toxicity and transplant related mortality, such as older or heavily treated patients.**

3. Adult umbilical cord blood transplantation: a comprehensive review. Schoemans H, Theunissen K, Maertens J, Boogaerts M, Verfaillie C, Wagner J. Bone Marrow Transplant. 2006; 38: 83-93. [Abstract](#)

This article summarizes the evidence available to date supporting the efficacy of **umbilical cord blood transplantation (UCBT) in adults** based on published clinical trials, and puts into perspective the various approaches currently under investigation to improve these results.

In addition to a comprehensive text, the **article contains detailed tables including** (1) a comparison of the main features of UCBT and BMT, (2) summaries of studies comparing single unit unrelated UCBT and matched unrelated BMT, (3) studies of UCBT in adults, (4) studies using reduced intensity conditioning in adult UCBT, (5) studies of multiple unit UCBT, and (6) studies of newer approaches in adult UCBT.

Comparing UCBT to BMT. The **three most distinctive features** distinguishing unrelated donor UCB transplantation from PBSC or BMT are: (1) the number of stem cells available for transplantation, (2) the speed of their availability and (3) the HLA matching requirements.

Cell Dose: It is clear that transplantation outcome after UCBT is correlated with the cell dose infused: a threshold must be reached to get consistent engraftment and lower incidence of transplant-related events. Cell dose also directly correlates with rate of neutrophil and platelet recovery such that recipients of higher cell doses have significantly more rapid recovery as compared to those with lower cell doses. **The current empirically accepted threshold limits are 1.7×10^5 infused CD34⁺ cells/kg or 2.5×10^7 cryopreserved nucleated cells/kg.**

Graft availability: UCB units are almost immediately available for transplant as they are fully HLA-typed before storage without risk of donor morbidity or attrition. With the expansion of the UCB banks, **the search of a unit now takes about 1 day for University of Minnesota searches, whereas an unrelated PBSC/BMT donor search will take an average of 3-4 months.** Such

rapid availability can be particularly useful for patients with high-risk malignancy or rapidly progressive non-malignant diseases, although the clinical significance of this potential advantage has not yet been defined.

HLA matching: UCB is less restricted with regards to HLA matching requirements relative to bone marrow stem cells from adult donors. It is customary to accept HLA matching at the serological level for HLA-A and HLA-B, and high resolution allelic typing for HLA-DRB1. Attempts to better define compatibility through high resolution typing failed to correlate with survival, in sharp contrast to unrelated BMT where any single serological mismatch or multiple high resolution mismatches are considered as risk factors.

This permissive HLA mismatching increases the number of potential units available per patient. One cord blood bank recently reported that patients had a 99% chance of finding a 4/6 HLA matched unit, and a 70% chance of finding a 5/6 or 6/6 HLA match, without mismatch in the GVHD direction. Further limitations are linked to the cell content of the unit.

Choosing the “best” unit. While higher cell dose may partially overcome the negative impact of HLA disparity, **the best matched unit with a cell dose of >2. 5 x 10⁷ cryo-preserved nucleated cells per kilogram should be used.**

Comparing unrelated UCBT and unrelated BMT. Several reports reached somewhat discrepant conclusions. A report from the IBMTR/NYBC concluded that results of UCBT were comparable to those observed in recipients of one-HLA-mismatched unrelated BMT, but inferior to a fully HLA-matched unrelated BMT. A report from the EBMT considered both transplantation modalities (HLA-mismatched UCBT vs. HLA-matched unrelated BMT) to be equivalent. A study from Japan concluded that UCBT was superior to unrelated BMT in the light of their survival results.

Possible reasons for the differing results included the fact that the IBMTR/NYBC study included data from the pioneering period of UCBT and greater disparity in HLA matches between donor and recipient. The excellent data from Japan may be due their extensive experience with UCBT in more than 555 adults, lower median weight of Japanese patients, more homologous HLA genotype on the island, prolonged hospitalization of patients after transplant, the high proportion of limited cGVHD and possibly differences in conditioning therapy.

Reduced intensity conditioning in the setting of UCBT. From 2001 to 2005, results of about 330 reduced intensity conditioning (RIC) UCBT have been published. Interpretation of the data is difficult as some of these studies were carried out with multiple UCB units and conditioning regimens varied between centers.

Multiple unit UCB transplantation. Results of double unit UCBT in 142 patients have been reported and are summarized in a table. There is a wide range of neutrophil engraftment (12-26 days), partially explained by the different conditioning used, but impressively low frequencies of graft failure (0-22%). Only one of the two units infused predominated over time, generally by day 100. Incidence of grade II-IV aGVHD appeared to be slightly higher and cGVHD in the same range as previously described (44-65% for aGVHD and 21-25% for cGVHD). TRM rates remained low (14-48%) and 1-year survival ranged from 31 to 79%. **UCB transplantation with 2 units appears therefore safe and feasible both in the myeloablative and non-myeloablative setting. Double transplants make UCBT feasible for almost all adults for whom a single cord blood unit would have been insufficient.**

Some recent studies compare single unit to double unit UCBT. A retrospective comparative analysis of the University of Minnesota data demonstrated high engraftment and less relapse, but increased grade II-IV aGVHD, with possibly improved survival with double unit UCBT. However, as double unit transplants were initiated, the standard conditioning regimen also shifted from ATG to fludarabine, and GVHD prophylaxis was change from methylprednisone/cyclosporine to mycophenolate mofetyl/cyclosporine; this may explain the shorter time to engraftment and better over all survival. Creer *et al* also showed better time to engraftment and better survival in double unit UCBT essentially because of the absence of deaths due to opportunistic infections in the double UCBT cohort.

Ex vivo expansion. Clinical studies have confirmed the feasibility and safety of *ex vivo* expansion procedures in terms of infusional toxicity, but have failed to show better recovery kinetics than historical controls. Of note, however, pre-clinical data suggest superior engraftment capacity of UCB progenitor cells compared to BM and peripheral blood stem cells, thus perhaps signifying that these cells represent optimal targets for *ex vivo* expansion.

Co-infusion of PBSC in UCBT. Fernandez *et al* studied the effect of co-infusion of highly purified, T-cell depleted PBSC from a haploidentical donor, in an attempt to make use of the typically rapid neutrophil recovery observed with PBSC as a “cover” while waiting for UCB recovery. The impressive overall survival statistics (67% at 4 years, or 20/28 patients) of this small patient cohort warrant further study of this novel approach.

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4. The November 25, 2004 issue of the New England Journal of Medicine contains an editorial and two original articles on cord blood transplantation in adults. Also included in this issue is a "Perspective" on cord-blood-bank controversies.

A. In an editorial **Extract** (*N Engl J Med.* 2004;351:2328-2330) entitled, "**Cord-Blood Transplantation in Patients with Leukemia – A Real Alternative for Adults**", Dr. Miguel A. Sanz comments on the two original articles.

He points out that one important advance in allogeneic hematopoietic stem-cell transplantation is the use of sources of stem cells other than bone marrow from HLA-identical siblings, which is a resource available to only about 30 percent of potential recipients. For patients without an HLA-matched family member, searches are made for unrelated donors through international databases which contain more than 9 million potential volunteer stem-cell donors. However, only 30 percent of whites in the United States (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. For such patients, umbilical-cord blood has emerged as an attractive source of hematopoietic stem cells. (*For further data about availability of unrelated-donor units from international registries, see Annotated Bibliography VI. Availability and Time Required to Obtain Cord Blood Versus Bone Marrow.*)

There are now about 170,000 cryopreserved units in cord blood banks throughout the world, but the relatively small number of hematopoietic progenitor cells in a cord-blood unit has, in the past, discouraged widespread use of cord bloods for transplantation of adults. However, two groups of investigators now 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. The two investigations differ in their study populations and other methodologic issues that may have influenced their results.

Rocha et al. found 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 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 and other 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.* 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. 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.**

In attempting to reconcile the apparently different conclusions of these two reports, Sanz points out that 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. By contrast, Rocha et al. restricted their analysis to patients who received transplants after 1998, because they had previously identified substantially better outcomes after that date that probably were due to better selection of patients and cord-blood units.

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 Sanz strongly recommends a simultaneous search for an unrelated donor in both bone marrow and cord-blood registries. (*Indeed, some investigators recommend that if the transplant is deemed urgent (that is, required within 3 months of referral), a strong preference should be given to cord blood, provided that a unit with greater than 2.0×10^7 cells/kg can be identified. For further data about availability of unrelated-donor units from international registries, see Annotated Bibliography VI. Availability and Time Required to Obtain Cord Blood Versus Bone Marrow.*)

Sanz asks, "Can we imagine a scenario for adults with leukemia that is similar to the current situation with cord-blood transplantation in children?" He answers his own question by stating, "I think we can."

B. **Transplants of Umbilical-Cord Blood or Bone Marrow from Unrelated Donors in Adults with Acute Leukemia.** Rocha V, Labopin M, Sanz G, Arcese W, Schwerdtfeger R, Bosi A, Jacobsen N, Ruutu T, de Lima M, Finke J, Frassoni F, Gluckman E. *N Engl J Med.* 2004;351:2276-2285. **Abstract**

The investigators point out that advantages of cord blood are the immediate availability of cells, the absence of risk to the

donor, and a lower need for HLA compatibility between the donor and recipient. However, a limiting factor is the low number of hematopoietic stem cells in a unit of cord blood. For this reason, cord blood has been transplanted into few adults until recently, when cord-blood banks began a policy of selecting units with high numbers of nucleated and CD34+ cells.

In this study, the investigators compared outcomes in 682 adults with acute leukemia who received a hematopoietic stem-cell transplant from an unrelated donor: 98 received cord blood and 584 received bone marrow. The transplantations were performed from 1998 through 2002 and reported to Eurocord and the European Blood and Marrow Transplant Group.

Recipients of cord blood were younger than recipients of bone marrow (median, 24.5 vs. 32 years of age; $P < 0.001$), weighed less (median, 58 vs. 68 kg; $P < 0.001$), and had more advanced disease at the time of transplantation (52 percent vs. 33 percent, $P < 0.001$). All marrow transplants were HLA matched, whereas 94 percent of cord-blood grafts were HLA mismatched. The median number of nucleated cells that were infused was 0.23×10^8 per kilogram of the recipient's body weight for cord blood and 2.9×10^8 per kilogram for bone marrow. Multivariate analysis showed lower risks of grade II, III, or IV acute graft-versus-host disease (GVHD) after cord-blood transplantation (relative risk, 0.57; 95 percent confidence interval, 0.37 to 0.87; $P = 0.01$), but neutrophil recovery was significantly delayed (relative risk, 0.49; 95 percent confidence interval, 0.41 to 0.58; $P < 0.001$). The incidence of chronic GVHD, transplantation-related mortality, relapse rate, and leukemia-free survival were not significantly different in the two groups.

In previous studies the authors had found that transplant-related mortality at 100 days was higher after transplantation of cord blood than after transplantation of bone marrow in children with acute leukemia, because of delayed neutrophil recovery and a higher incidence of infections. In the present study, however, the risk of transplantation-related mortality was similar in the two groups, perhaps because transplantation centers have improved their criteria for selecting patients and units of cord blood. The authors stated that they expected more deaths related to infections in the cord-blood group owing to delayed neutrophil recovery and probably delayed immune recovery. However, causes of death were more frequently related to the toxicity of treatment, since cord-blood recipients underwent transplantation in a more advanced phase of leukemia than did recipients of bone marrow.

The authors concluded that cord blood from an unrelated donor is an alternative source of hematopoietic stem cells for adults with acute leukemia who lack an HLA-matched bone marrow donor. They state that there is a consensus that a unit of cord blood should have at least 2.0×10^7 nucleated cells per kilogram of patient's body weight at the time of freezing and no more than two disparities in the matching for HLA-A,B, or DRB1, alone or in combination, with the recipient.

C. Outcomes after Transplantation of Cord Blood or Bone Marrow from Unrelated Donors in Adults with Leukemia. Laughlin MJ, Eapen M, Rubinstein P, Wagner JE, Zhang MJ, Champlin RE, Stevens C, Barker JN, Gale RP, Lazarus HM, Marks DI, van Rood JJ, Scaradavou A, Horowitz MM. *N Engl J Med.* 2004;351:2265-2275. [Abstract](#)

The investigators compared the outcomes of the transplantation of hematopoietic stem cells from unrelated donors in adults with leukemia who had received cord blood that was mismatched for one HLA antigen (34 patients) or two antigens (116 patients), bone marrow that had one HLA mismatch (83 patients), and HLA-matched bone marrow (367 patients).

The results indicated that cord-blood recipients were younger and more likely to have advanced leukemia than were bone marrow recipients, and they received lower doses of nucleated cells. Hematopoietic recovery was slower with transplantation of mismatched bone marrow and cord blood than with matched marrow transplantations. Acute graft-versus-host disease (GVHD) was more likely to occur after mismatched marrow transplantation, and chronic GVHD was more likely to occur after cord-blood transplantation. The rates of treatment-related mortality, treatment failure, and overall mortality were lowest among patients who received matched marrow transplants. Patients who received mismatched bone marrow transplants and those who received mismatched cord-blood transplants had similar rates of treatment-related mortality ($P = 0.96$), treatment failure ($P = 0.69$), and overall mortality ($P = 0.62$). There were no differences in the rate of recurrence of leukemia among the groups. There were no differences in outcome after cord-blood transplantation between patients with one HLA mismatch and those with two HLA mismatches.

The authors concluded that HLA-mismatched cord blood should be considered an acceptable source of hematopoietic stem-cell grafts for adults in the absence of an HLA-matched adult donor.

D. The Cord-Blood-Bank Controversies. Steinbrook R. *N Engl J Med.* 2004;351:2255-2257. [Extract](#)

In this "Perspective" the author provides a brief history of cord-blood transplantation and then describes both private and public cord blood banks. He points out that cord-blood banks are currently mired in a patent dispute (*mistakenly indicating that this involves only private cord-blood banks*), and that such litigation is ongoing in the federal courts. He comments that public banks have seen their growth hindered by insufficient funding for additional collection and storage. He adds that not all parents have the opportunity to donate because public banks usually collect cord blood only at affiliated hospitals. He comments on the fact that Congress has approved \$9 million for additional cord-blood collection but that the structure of a national cord-blood program in the United States remains uncertain and that the funds will not be spent until the conclusion of an Institute of Medicine study for which an additional \$1 million has been allocated.

5. Unrelated cord blood transplants in adults with hematologic malignancies. Arcese W, Rocha V, Labopin M, Sanz G, Iori AP, de Lima M, Sirvent A, Busca A, Asano S, Ionescu I, Wernet P, Gluckman E; Eurocord-Netcord Transplant group. *Haematologica.* 2006;91:223-30. [Full Text](#)

The authors point out that umbilical cord blood from unrelated donors represents a clear alternative source of hematopoietic progenitor cells to bone marrow for **children** lacking an HLA identical sibling. The lower risk of GVHD in the cord blood transplant (CBT) setting than in BMT permits less stringent criteria for donor-recipient HLA matching. Moreover, cord blood units are acquired faster than bone marrow from unrelated donors, which is particularly relevant for patients who require an urgent transplant. They cite two recent independent studies which compared results of unrelated CBT and BMT in **adults with acute leukemia**. In both studies, the main outcomes (relapse, transplant-related mortality, leukemia-free survival) were similar in the patients receiving the two different types of transplants.

In this study the authors analyzed outcomes and risk factors after **unrelated CBT in adults with hematologic malignancies**. One hundred and seventy-one patients were transplanted after 1997. Their median age was 29 years (15-55), and the median follow-up time was 18 months (1-71). Most patients had acute or chronic leukemia ($n = 142$, 83%), 91 (53%) were transplanted in advanced phase and an autologous transplant had failed in 32 (19%). Most patients (87%) received an HLA-mismatched cord blood unit with 1-2 HLA disparities. At infusion, the median number of nucleated cells and CD34(+) cells was 2.1×10^7 /kg and 1×10^5 /kg, respectively.

The cumulative incidence of neutrophil recovery at day 60 was 72+/-3% with a median of 28 days (11-57). A higher neutrophil

count and use of hematopoietic growth factors were independently associated with faster neutrophil recovery. The cumulative incidence of grade II-IV acute graft-versus-host disease was 32+/-4% and this complication was not associated with the number of HLA mismatches. The 2-year cumulative incidence of chronic graft-versus-host disease, transplant related-mortality and relapse were 36+/-10%, 51+/-4% and 22+/-4%, respectively. At 2-years, disease-free-survival for patients transplanted in early, intermediate and advanced phases of disease was 41+/-9%, 34+/-10% and 18+/-4%, respectively. In multivariate analyses, advanced disease status was an adverse factor for relapse and disease-free survival.

The authors concluded that **unrelated CBT is a clear alternative for adults with hematological malignancies lacking an HLA-matched related or unrelated donor**. The choice of units containing a higher neutrophil count and a policy of earlier transplantation are likely to provide better results.

6. **Unrelated cord blood transplantation after myeloablative conditioning in patients with acute leukemia aged between 50 and 55 years.** Konuma T, Ooi J, Takahashi S, Tomonari A, Uchiyama M, Fukuno K, Tsukada N, Iseki T, Tojo A, Asano S. Bone Marrow Transplant. 2006; 37:803-804.

The authors report a retrospective analysis of results of unrelated CBT after myeloablative conditioning in 11 patients with acute leukemia aged between 50 and 55 years. The median age of patients was 51 years, the median weight was 59 kg, and the median number of cryopreserved nucleated cells was $2.50 \times 10^7/\text{kg}$ (range, $2.05\text{-}3.53 \times 10^7/\text{kg}$).

All but one patient had myeloid reconstitution and median time to more than $0.5 \times 10^9/\text{l}$ was achieved in nine patients at a median time of 42 days (range, 33-88 days). A self-sustained platelet count $>50 \times 10^9/\text{l}$ was achieved in nine patients at a median time of 42 days (range, 33-88 days). Acute GVHD (grade I or II) occurred in nine of 10 evaluable patients. Among four grade II acute GVHD patients, only 2 required steroid therapy. Chronic GVHD occurred in six of 8 evaluable patients and was extensive in two. No patient died of transplantation-related toxicity at day 100. Three patients experienced relapse on days 78, 76 and 53, and died of relapse on days 380, 145 and 368, respectively.

Eight patients are alive and free of disease at between 126 and 749 days; **the probability of DFS at 2 years was 72.7%**. The low transplant-related mortality may be associated with a low incidence of severe acute GVHD in these patients. The authors suggest that this may possibly be explained by the lower genetic diversity of the Japanese population.

Although the number of patients was small and the observation period limited, **these results suggest that CBT after myeloablative conditioning may be feasible in patients with acute leukemia aged between 50 and 55 years**.

7. **Cord blood transplantation for acute myelogenous leukemia using a conditioning regimen consisting of granulocyte colony-stimulating factor-combined high-dose cytarabine, fludarabine, and total body irradiation.** Tomonari A, Takahashi S, Ooi J, Nakaoka T, Takasugi K, Uchiyama M, Tsukada N, Konuma T, Iseki, Tojo A, Asano S. Eur J Haematol. 2006; 77:46-50. [Abstract](#)

The cytotoxic effect of the cell-cycle-dependent agent cytarabine (Ara-C) on myeloid leukemic cells is enhanced by concomitant use of granulocyte colony stimulating factor (G-CSF) *in-vitro*. The feasibility of a conditioning regimen consisting of G-CSF combined with 24 g/m^2 Ara-C, 90 mg/m^2 fludarabine, and 12 Gy total body irradiation was studied for 5 patients with AML (ages 35-47 years) who received cord blood transplants. GVHD prophylaxis consisted of cyclosporine and methotrexate. After the conditioning regimen 2.48×10^7 cord blood nucleated cells (range, $2.28\text{-}3.53$) were infused.

Neutrophil counts consistently $>0.5 \times 10^9/\text{L}$ were achieved at 24 days (22-32) after CBT. Grade I stomatitis and gastrointestinal toxicities occurred in all patients. Grade I and II aGVHD occurred in one and four patients, respectively, which resolved without steroid therapy. Sepsis and aspergillosis occurred in two and one patients, respectively. **All patients were alive without leukemia relapse at a follow up of 15 months (12-43) after CBT.**

This conditioning regimen could avoid the toxicities of high-dose cyclophosphamide but might enhance the cytotoxic effect of Ara-C. More studies are needed to determine its efficacy and safety.

8. **The efficacy of unrelated cord blood transplantation for adult myelodysplastic syndrome.** Ooi J. Leuk Lymphoma. 2006;47:599-602. [Abstract](#)

The authors have previously reported an initial series of patients with myelodysplastic syndrome (MDS) who were treated with unrelated cord blood transplantation (CBT) after myeloablative conditioning. (see [Citation #14](#)) Here, they update the results with this report of unrelated cord blood transplantation (CBT) for 22 adult patients with MDS. Diagnosis at transplantation included refractory anemia (RA) (n = 3), refractory anemia with excess blasts (RAEB) (n = 2), RAEB-t (n = 2), and MDS-related secondary acute myeloid leukemia (AML) (n = 15). All patients were treated with total body irradiation (12 Gy), cytosine arabinoside Ara-C) and cyclophosphamide followed by unrelated HLA-mismatched CBT. The (median age was 40 years (range, 19 - 51 years), the median weight was 54.5 kg (range, 43 - 75 kg), and the median number of cryopreserved nucleated cells was $2.43 \times 10^7/\text{kg}$ (range, $1.82 - 4.10 \times 10^7/\text{kg}$). Twenty one patients had myeloid reconstitution and the median time to more than $0.5 \times 10^9/\text{l}$ absolute neutrophil count was 22.5 days. A self-sustained platelet count more than $50 \times 10^9/\text{l}$ was achieved in 19 patients at a median time of 49 days. Acute GVHD above grade II occurred in seven of 21 evaluable patients and chronic GVHD in 16 of 19 evaluable patients. Among 16 chronic GVHD patients, in eight patients the disease was extensive.

Seventeen of the 22 patients are alive and free of disease at between 371 and 2562 days after transplantation. With a median follow-up of 1505 days, the probability of disease-free survival at 4 years was 76.0%. These results suggest that adult MDS patients without suitable related or unrelated bone marrow donors should be considered as candidates for CBT.

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9. **Unrelated CB allogeneic stem cell transplantation for MDS.** A commentary on the paper of Ooi (see [citation 8](#)) Laughlin, MJ. *Leuk Lymphoma*. 2006; 47:569-570.

With conventional HLA matched grafting after administration of reduced intensity conditioning, disease free survival (DFS) rates are only 35-40%, with disease relapse the most common cause of treatment failure. The patients reported by Ooi were treated with fully ablative conditioning and single unit non-expanded allogeneic unrelated cord blood transplantation. In the 21 patients demonstrating myeloid reconstitution, chimerism analyses confirmed full donor engraftment. Only 4 patients relapsed despite the majority of patients having advanced disease at the time of transplant. The probability of DFS at four years was an impressive 76%.

The report by Ooi identifies the use of banked unrelated cord blood as a suitable alternative allogeneic graft source that results in durable remissions for adults with MDS and emerging AML, with low rates of GVHD, and excellent survival rates. Further studies are warranted to determine the impact of improved HLA matching and higher graft cell dose threshold (>2.5 x 10⁷/kg).

10. **Unrelated umbilical cord blood transplantation for adults with haematological malignancies: results from a single Australian centre.** Bradstock KF, Hertzberg MS, Kerridge IH, Svenilsson J, McGurgan M, Huang G, Antonenas V, Gottlieb DJ. *Intern Med J*. 2006;36:355-61. [Abstract](#)

Favorable results are reported in this small study from Australia. Nine adult patients (median age 32 years, median weight 68 kg) with haematological malignancies (five with acute myeloid leukaemia, one with acute lymphoblastic leukaemia, one with Hodgkin lymphoma and two with non-Hodgkin lymphomas) received transplants of cryopreserved cord blood after conditioning therapy with high-dose cyclophosphamide, total body irradiation and antithymocyte globulin. Cord units contained a median 2.6 x 10⁷ nucleated cells/kg recipient bodyweight and were matched for four (seven cases) or five (two cases) major histocompatibility complex class 1 and 2 antigens. Patients were given post-transplant immunosuppression with cyclosporin and methylprednisolone.

Neutrophil recovery to 0.5 x 10⁹/L was seen by median day 30 after transplant in all seven patients who survived more than 1 month post-transplant. Platelet recovery to 50 x 10⁹/L occurred by median day 81 in five evaluable patients. Acute graft versus host disease (GVHD) grades II-IV was seen in four of seven evaluable patients and limited chronic GVHD was seen in four of five. Infection was the most common complication. Four patients died before day 100 of infection (methicillin-resistant *Staphylococcus aureus* septicaemia, respiratory syncytial virus pneumonia), GVHD and multi-organ failure, and intracranial bleeding. Five patients survived 7-69 months post-transplant, without evidence of relapse of the underlying malignancy. The authors concluded that transplantation of unrelated cord blood is a feasible strategy for adult patients with poor-risk haematological malignancies, with infection relating to immunocompromise being the major limitation.

11. **Phase II study of unrelated cord blood transplantation for adults with high-risk hematologic malignancies.** Lekakis L, Giralt S, Couriel D, Shpall EJ, Hosing C, Khouri IF, Anderlini P, Korbling M, Martin T, Champlin RE, de Lima M. *Bone Marrow Transplant*. 2006; 38:421-6. [Abstract](#)

The authors investigated a strategy in which CB units should contain at least 2 x 10⁷ total nucleated cells/kg of recipient weight, otherwise a second unit had to be added.

Patients with **advanced hematologic malignancies** without a human leukocyte antigen-matched sibling or unrelated donor were eligible. Conditioning regimen consisted of fludarabine and 12 Gy of total body irradiation (n=11), or melphalan (n=4), with antithymocyte globulin. Graft-versus-host disease prophylaxis was tacrolimus and methotrexate. Fifteen patients with acute leukemia (n=9), chronic myelogenous leukemia (n=2), multiple myeloma (n=2) and lymphoma (n=2) were treated; **60% had relapsed disease at transplantation**. Three patients received double CB transplants. **The 100-day and 1-year treatment-related mortality rates were 40 and 53%, respectively.** Median time to neutrophil and platelet engraftment was 22 days (n=10) and 37 days (n=10), respectively. One patient had secondary graft failure and five patients failed to engraft. Two patients are alive and disease free; **4-year actuarial survival is 33 versus 0% for patients transplanted in remission versus in relapse.**

The early mortality and engraftment failure rates were deemed excessive and led to premature trial discontinuation.

Explanations for these results include the following: The most important variable was disease status at transplantation, associated with extensive prior treatment and poor tolerance to transplant-associated toxicities, factors that likely increased TRM. It is possible that a diagnosis of CML was an added risk factor in two of the cases.

The 100 day mortality rate of 40% was similar to that observed in two other studies published in 2001 and 2005 with data collected throughout the earlier experience of CB transplants. Lower 100 day mortality has since been reported by several single-center studies. This may indicate the influence of growing experience using CB units, but one cannot underestimate the effect of patient selection on outcomes. At the time the authors' trial was initiated, they allowed the use of units with three HLA mismatches (3 patients were so treated). Other factors of possible significance was the GVHD prophylaxis regimen that employed "mini" methotrexate, the use of fludarabine and melphalan in the preparative regimen in 4 cases, and high dose ATG.

The authors concluded that CB carries the potential to extend hematopoietic transplantation to a variety of patients otherwise not

eligible for this form of treatment but high-risk patients have an increased probability of TRM even with the use of units containing higher TNC counts. Thus, **treatment of relapsed patients should only be pursued under controlled clinical trials.**

12. **Outcomes among 562 recipients of placental-blood transplants from unrelated donors.** Rubinstein P, Carrier C, Scaradavou A, Kurtzberg J, Adamson J, Migliaccio AR et al. N Engl J Med 1998; 339:1565-1577. [Abstract](#)

In this landmark article reporting outcomes among 562 recipients of placental blood transplants from unrelated donors, 18% of the patients were over the age of 18 years and 17% were over 60 kg in weight. The authors concluded that placental blood transplantations from unrelated donors regularly engraft, cause GVHD at a relatively low rate, and produce *survival rates similar to those with transplantation of bone marrow from unrelated donors. In multivariate analysis age was not independently predictive of engraftment.*

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