UNRELATED DONOR HEMATOPOIETIC CELL TRANSPLANTATION: MARROW OR UMBILICAL CORD BLOOD?

Short title: Donor selection: Bone Marrow or Cord Blood?

Category: Review article

Authors: Satkiran S Grewal¹, Juliet N Barker², Stella M Davies¹*, and John E Wagner¹*

From the Blood and Marrow Transplantation Program, Departments of Pediatrics¹ and Medicine², the University of Minnesota, Minneapolis, MN, USA.

Corresponding author: Satkiran S Grewal, MD
University of Minnesota
420 Delaware St SE, MMC 477
Minneapolis, MN 55455
grewa002@umn.edu
Tel: 612 625 9428
Fax: 612 626 2815

*Co-senior authors

Word count: 5,718

This work was supported in part by Children’s Cancer Research Fund (JNB, JEW, SMD), and the National Institute of Health (P01 CA 21737 [JEW], N01 HB 67139 [JEW], and N01 HB 47095 [JEW, SMD])
INTRODUCTION

Hematopoietic cell transplantation (HCT) can be curative for selected malignant and non-malignant diseases\textsuperscript{1-13}. However, utilization and success of HCT are limited by several obstacles, primarily related to the importance of donor-recipient genetic match for favorable outcomes. While in most settings, best results are offered by human leukocyte antigen (HLA\textsuperscript{14,15}) identical sibling transplants, more than two thirds of patients awaiting HCT lack a suitable related donor. HCT with unrelated donor (URD) grafts are more frequently associated with severe graft-versus-host disease (GVHD\textsuperscript{16}) or graft rejection\textsuperscript{17-19}. T-cell depletion of URD grafts has substantially reduced the risk of GVHD and early transplant related mortality (TRM), but has not resulted in a concurrent survival benefit\textsuperscript{20-24}.

Despite the development of large international volunteer donor registries, still less than 50% of URD searches result in identification and availability of a suitably matched bone marrow (BM) graft\textsuperscript{25}. Donor searches for recipients not of Northern-European descent result in even lower success\textsuperscript{25}. These limitations have given impetus for the identification of alternative sources of hematopoietic stem cells (HSC).

In the last decade, HCT using umbilical cord blood (UCB) grafts has increasingly been utilized, particularly for pediatric patients\textsuperscript{26-35}. To date, it is estimated that more than 2000 unrelated umbilical cord blood transplants (UCBT) have been performed\textsuperscript{26-30,33,35}. The data indicate that UCB is a viable alternative source of HSC, and in certain situations, may
have advantages over URD marrow grafts. The aim of this review is to enumerate the advantages and disadvantages of each stem cell source, and explore the issues involved in the selection process of marrow versus UCB grafts for specific patient populations.

**CHALLENGES TO UNRELATED DONOR MARROW TRANSPLANTATION**

As of 2002, more than 7 million registered volunteer marrow donors exist in over 40 registries worldwide. The National Marrow Donor Program (NMDP), the single largest registry, now has more than 4 million potential donors listed (personal communication, R King, NMDP). Still, URD marrow is not readily available for all patients.

NMDP data indicate that a median of four months is required to complete searches that result in a transplant. Others have reported similar or considerably longer search times. An undefined number of patients succumb to their disease while awaiting identification of a suitable HLA-matched donor. In addition, about half of the initiated searches fail to provide a suitable donor marrow graft, even more so for ethnic/racial minority patients. Moreover, even if a donor is identified based on HLA-match criteria, not all donors are available when they are needed. Reasons for donor attrition include inability to contact the donor as a result of geographical movement or name change, loss of motivation over time, disqualification due to age or medical status, temporary unavailability, and death. The NMDP reports that about 30% of registered donors identified as potential matches, are not available for further evaluation at the time of request.
These challenges in the donor search process are being addressed at multiple levels. Traditionally, potential donors have been serologically typed for HLA-A and -B loci at recruitment. Registry studies indicate that HLA-A, -B, -DR typed donors are more likely to be available when needed, and constitute the more often utilized pool\textsuperscript{25,43}. This has given impetus to more extensively type volunteers at the time of recruitment. As reported recently, between 16-52\% of registered donors are HLA-A, -B, and -DR typed in the various registries worldwide\textsuperscript{36}. Another step has been to target ethnic minorities in an effort to increase availability of rare haplotypes, although with moderate success\textsuperscript{36}. The total number of donors recruited to registries has expanded rapidly in the last decade. However, the benefit of increasing registry size has perhaps reached its maximal impact. It is predicted that continuing focus on expanding the pool of registered donors, without attention to ethnicity, is likely to provide relatively little benefit\textsuperscript{44-46}.

**Outcomes with URD BMT**

With almost 35 years of human bone marrow transplantation (BMT) experience, several large studies have described outcomes with HLA-matched and mismatched URD marrow transplants. Table 1 summarizes results of selected large URD BMT series.

**Engraftment**

In a recent report of more than 5,000 URD marrow transplants facilitated by the NMDP, primary graft failure occurred in 4\%\textsuperscript{47}. However, with mismatched donor grafts, this risk increases significantly\textsuperscript{38,48-52}. In particular, disparity for HLA-C, or more than one allele-
level mismatch of class I determinants has been associated with increased risk of graft failure\textsuperscript{53,54}. Additional factors negatively influencing probability of marrow engraftment have been the use of T-cell depleted grafts\textsuperscript{38,50,55,56}, and diseases such as chronic myeloid leukemia (CML)\textsuperscript{40,41,57}, Fanconi anemia\textsuperscript{9,58}, aplastic anemia\textsuperscript{8,59,60}, and inherited metabolic storage disorders\textsuperscript{61,62}. Improved platelet engraftment has been associated with absence of severe acute GVHD and possibly higher marrow nucleated cell dose\textsuperscript{47,63,64}.

**GVHD**

Risk of GVHD is an important factor limiting HCT using an URD. With marrow transplants, many studies have shown histoincompatibility to be the greatest risk factor for the development of GVHD\textsuperscript{52,54,63,65-67}. Development of moderate to severe acute GVHD or extensive chronic GVHD is associated with diminished quality of life, as well as decreased overall survival, and is not regarded as desirable even in those with malignant disease where a graft versus leukemia (GVL\textsuperscript{68,69}) effect is sought\textsuperscript{68-71}. Grade II-IV GVHD is reported in 43 to 70\% of phenotypically-matched URD marrow transplants, and in 63-95\% of HLA one-antigen mismatched URD transplants\textsuperscript{38,41,51,63,72-76} (Table 1). Chronic GVHD affects more than 55\% of matched URD transplant recipients and as many as 80\% of those receiving one-antigen mismatched URD HCT\textsuperscript{77} 38,41,51,63. About 50\% of patients with extensive chronic GVHD will die secondary to severe immune dysfunction\textsuperscript{78}.

Attempts to decrease GVHD and early TRM by the use of T-cell depleted grafts have produced encouraging results, including in settings of mismatched unrelated and haplo-identical related donors\textsuperscript{20,79-85}. However, significant concerns remain with graft failure and
poor immune reconstitution resulting in opportunistic infections, post-transplant lymphoproliferative disease, and relapse\textsuperscript{21-24}. A large randomized, multi-center unrelated donor marrow transplant trial in the US, comparing T-cell depletion with pharmacologic GVHD prophylaxis, has recently concluded accrual\textsuperscript{86}. Analysis of this trial will include determination of GVHD prophylaxis on 3-year disease free survival (DFS).

**Immune reconstitution.**

Recovery of immune function after BMT has been characterized by several investigators, with unmanipulated as well as T-cell depleted marrow HCT\textsuperscript{87-91}. Reconstitution of T-cells occurs in two phases: an initial expansion of mature, previously antigen exposed T-cells infused with the donor graft, and a later thymus-dependent proliferation of T-cells, probably derived from HSC. Immune recovery is impaired by the development of severe GVHD, the risk of which is particularly high after URD transplants and in adult recipients\textsuperscript{72-76}. T-cell depletion can decrease the risk of GVHD, however, is still associated with delayed restoration of T-cell subsets and increased risk of infectious complications\textsuperscript{21-24,88,89}.

The immune response of the graft can also result in a GVL effect, potentially decreasing the risk of relapse in certain malignant disorders\textsuperscript{68-70}. With hematological malignancies, both in pediatric and adult recipients, the biology of the disease and disease status at HCT have been critical factors determining risk of relapse after transplant\textsuperscript{38-41,51,57,63} (Table 1).
Survival

URD transplant recipients are at increased risk for GVHD, graft failure, infections and decreased survival. BMT with HLA-mismatched grafts is associated with further increased morbidity and decreased survival, particularly in adult recipients.\(^{48,49,63,65-67,92}\) (Figure 1). Moreover, as molecular techniques have developed, previously unrecognized mismatches at HLA-A, -B, and -DRB1 have been identified, and shown to increase risk of graft rejection, GVHD, and mortality.\(^{53,54,67,93}\) Identification and study of additional transplant antigens such as HLA-C\(^{53}\), and -DQB1\(^{94}\) have suggested that outcome can be further optimized by higher levels of matching or matching across so called “ancestral haplotypes\(^{95}\)”. However, with the extraordinary polymorphism of HLA alleles, such extensively matched URD transplants will at best be limited to a minority of patients, particularly if allele-level matches at multiple loci are sought.

Better DFS and overall survival with URD transplants have been achieved when performed early in the course of the disease, both for malignant and non-malignant diseases such as immunodeficiencies, Fanconi anemia, and inborn errors of metabolism. Notably promising results have been achieved after HLA-A, -B, and -DRB1 matched URD marrow transplants for early CML in patients under 35-40 years\(^{40,41,57,96}\) (Table 1), and specific immunodeficiency states in young children.\(^{97-99}\) While URD transplants are associated with inferior transplant outcomes and survival as compared to matched-related donor BMT for better prognosis leukemia, the difference in survival is less evident with poor prognosis disease\(^{51}\).
Figure 1.

UMBILICAL CORD BLOOD TRANSPLANTATION (UCBT) EXPERIENCE

The first HLA-matched sibling UCBT was performed by Gluckman et al in 1988 in a child with Fanconi anemia. Subsequently, reports documented the feasibility and efficacy of mismatched related and unrelated UCBT. By 1993, repositories of unrelated donor UCB were established in New York, Dusseldorf, and Milan. Currently, private and publicly funded cord blood banks worldwide store an estimated 70,000 cryopreserved HLA-A, -B, and -DRB1 typed units, mostly for the purpose of URD transplants.
As limited HLA-mismatch appears to be better tolerated with UCB grafts, units are identified for most patients even with the size of current repositories. A significant advantage of UCB is the rapidity with which an acceptable HLA-matched unit, once identified, can be acquired\textsuperscript{26,107-109}. As UCB is cryopreserved, acquisition of an HLA-matched unit is quick. In addition, UCB units are typically intermediate, or high resolution typed at HLA-A, -B, and -DRB1 loci at collection, further shortening search time. In one study, the median time for a UCB unit to be identified and available was 13.5 days\textsuperscript{108}. Therefore this HSC source is particularly appealing for patients who need to proceed urgently to HCT. In addition, rescheduling the date of infusion of a cryopreserved UCB unit to fit the recipient’s needs is simple.

Total nucleated cell (TNC) dose of a UCB graft has proven to be a critical determinant of engraftment and survival with UCBT. Therefore, the fixed cell content of a UCB unit represents the major limiting factor, particularly for adult recipients. However, UCB has a higher frequency of progenitor cells as compared to adult peripheral blood or bone marrow\textsuperscript{110,111}. Laboratory data also suggest that UCB derived stem cells demonstrate an increased growth/engraftment potential as evidenced by larger size of colonies formed in cultures and efficient long-term, multi-lineage repopulation of immunodeficient mice by human UCB cells even in the absence of exogenous human cytokine support (in contrast to results with adult human BM grafts in the same mouse model)\textsuperscript{112-114}. In human HCT, while the number of nucleated cells infused with an UCB graft can frequently be one-log less than that infused with a BM graft, these features perhaps explain its comparable engraftment potential. Outcomes of human UCBT from larger series are described below and in Table 2.
Outcomes with unrelated UCBT

Engraftment

As with marrow transplants, several factors have been identified that predict successful engraftment with UCB grafts. The single most important factor influencing time to hematopoietic recovery appears to be the nucleated cell content of the graft relative to recipient size. The effect of HLA-mismatch on engraftment is less clear.

In a report by Gluckman et al., a graft nucleated cell dose >3.7 x 10^7/kg was associated with shorter time to neutrophil recovery (25 days vs. 35 days). Wagner et al. (Table 2) analyzed the influence of graft CD34+ cell dose and observed significantly inferior speed and probability of engraftment with CD 34+ cell dose <1.7 x 10^5/kg. Rubinstein et al. showed that while a step-wise increasing graft nucleated cell dose progressively shortened the time to myeloid recovery, the final cumulative incidence of myeloid recovery was similar once the nucleated cell dose exceeded 2.5 x 10^7/kg, suggesting that a threshold number of nucleated cells are needed for engraftment. Analysis of HLA-mismatch in this study, and a more recent review-update with 861 unrelated UCBT, revealed a relationship between HLA-match and engraftment. The median time to neutrophil recovery with six-antigen matched grafts was 23 days in comparison to 28 days with mismatched grafts (p= .0027). However, no association between engraftment characteristics and number of HLA-mismatches (one vs. more than one HLA-mismatch) was observed.
Consequent to these studies, a consensus is emerging that UCB grafts with higher cell doses should be selected wherever possible to optimize engraftment. Particularly poor results are seen after UCBT when the nucleated cell dose infused is less than $1.5 \times 10^7$/kg$^{105,116,117}$. These data suggest that a minimum acceptable nucleated cell dose should be $1.5 \times 10^7$ nucleated cells/kg$^{117}$, to reduce time to myeloid recovery and increase probability of engraftment.

**GVHD**

UCBT series in the URD setting have reported 33-44% and 11-22% incidences of grade II-IV and grade III-IV acute GVHD respectively, and 0-25% incidence of chronic GVHD$^{28,29,31,35}$. 

These results are particularly notable since the majority of unrelated UCBT were performed using 1-2 HLA-mismatched grafts. It could be argued that a majority of the recipient population was young in these reports, however, the incidence of severe GVHD in adults receiving mismatched UCB grafts has also been low

HLA-mismatch has been the strongest risk factor for GVHD in recipients of marrow transplants. The association of histocompatibility with GVHD in the UCBT setting has only recently become apparent, and remains less clear. Many UCBT series have failed to observe an influence of 0-3 antigen-mismatch on the risk of acute or chronic GVHD\textsuperscript{28,32,33,35} (Table 2). Eurocord studies, while observing association of HLA-mismatch with risk of acute GVHD in the related UCBT setting, did not show an effect of HLA-mismatch on risk of acute GVHD after unrelated UCBT\textsuperscript{28,32}. However, in a large series of unrelated UCBT, subsequently updated to 861 patients, Rubinstein et al\textsuperscript{29,115}, reported significantly higher rates of acute GVHD with mismatched grafts, though no direct association of HLA-mismatch with chronic GVHD was observed.

\textit{Immune reconstitution}

The goal of HCT is the establishment of donor cell immune tolerance to recipient "self MHC antigens", with reconstitution of effective immune surveillance as well as response to foreign antigens including tumors and pathogens. With UCB grafts, it has been hypothesized that with its lower and previously unstimulated T-cell content, the early, thymus-independent expansion of T-lymphocytes maybe impaired. However, preliminary analyses show that the
recovery of immune-cell repertoire after UCBT is comparable to that after unmanipulated marrow HCT. NK-cell numbers are reconstituted promptly, and the recovery of B-lymphocytes and CD4+ T-cells may actually be faster after UCBT.

The functional naïveté of neonatal lymphocytes and the lower risk of GVHD with UCB grafts has raised concern for a reduced GVL effect after UCBT. The exact relationship between GVHD and GVL is unclear, even though the data suggest that development of GVHD is associated with decreased risk of relapse.

Initial experience with UCBT for leukemia suggests that similar to BMT, the biology of the disease and leukemia status at transplant are the major determinants of outcome. Wagner et al, in a study of 102 UCBT (median age, 7.4 years) from a single institution, reported a 37% cumulative incidence of relapse at 2 years, with age and malignancy risk group being the two factors associated with risk of relapse. Also, in a Eurocord report including 60 unrelated UCBT in children (<15 years) with acute leukemia, disease status at transplant was the most important factor predicting outcome. The 2-year incidence of relapse and 2-year probability of DFS in the poor risk and good risk groups were 31% vs. 75% and 7% vs. 40% respectively. Notably, cell dose and HLA-mismatch of the graft did not influence DFS in the latter series.

**Survival**

Several studies have analyzed factors influencing survival after UCBT. Locatelli et al reported outcomes in pediatric acute leukemia from the Eurocord registry. Fifty-four
of 60 unrelated UCB grafts were 1-4 loci HLA-disparate, with the majority being 1-2 loci HLA-mismatched. In univariate or multivariate analyses, number of HLA-mismatches did not influence survival. Similarly Gluckman et al\textsuperscript{28}, in a report of 65 unrelated UCBT (0-3 antigen HLA-mismatched) in pediatric recipients and Laughlin et al\textsuperscript{33} in a study of 68 adult recipients of 0-3 antigen HLA-mismatched UCBT, showed no association of degree of HLA-mismatch with overall survival in the unrelated setting. Of note, however, two larger series, by Wagner et al\textsuperscript{35} (102 UCBT, single institution) and Rubinstein et al\textsuperscript{29} (562 UCBT using grafts supplied by the New York Blood Center), have observed a significant association of HLA-mismatch with survival after unrelated UCBT.

Based on the UCBT experience reported thus far, UCB cell dose has been the most critical factor in determining speed of engraftment and survival after UCBT. HLA-disparity is also likely a major factor, although reports are contradictory\textsuperscript{28,29,31,32,35,115,129}. The challenge for transplant centers in selecting the optimal stem cell source for a recipient is defining the cell dose below which clinical outcomes become significantly inferior. At the University of Minnesota, local experience suggests that $1.5 \times 10^7$ nucleated cells/kg or $1.7 \times 10^5$ CD34$^+$ cells /kg defines that threshold below which outcomes are significantly poor\textsuperscript{35}, and routine use of units below this threshold is now not permitted. While patients receiving lower cell doses can engraft, risk of graft failure is exceedingly high and time to neutrophil recovery is prolonged\textsuperscript{28,33,35,116}.

Figure 3a and 3b show data from the University of Minnesota, illustrating the impact of CD34$^+$ cell dose on survival in recipients of 1 or 2 HLA-mismatched UCBT. Survival is
improved with the higher cell doses, suggesting that a higher cell dose can partially compensate for higher HLA-disparity. Notably, a study from the New York Blood Center concluded that raising the nucleated cell dose by approximately $3 \times 10^7$ per kg may offset the negative effect of one HLA-mismatch. As more data are collected, it will be possible to define with greater confidence an acceptable lower limit of cell dose for a given degree of HLA disparity.

Figure 3a

Figure 3b
Graft TNC dose has been used as a marker of graft “potency” in the majority of UCBT studies reported thus far, although, a few studies have also defined graft CD34+ cell dose as a predictor of speed of engraftment and survival with UCBT\textsuperscript{33,35}. The TNC count of any UCB unit includes a variable number of nucleated red cells. While TNC dose has consistently correlated with transplant outcomes, and the nucleated red cell count has been shown to correlate with progenitor cell numbers\textsuperscript{131}, a progenitor assay such as colony forming unit (CFU) or CD34+ content of a UCB graft may be a more precise predictor of engraftment and survival with any given UCB unit\textsuperscript{132}. In addition, CFU content (after thawing) is a measure of progenitor cell viability.

The contiguous integral segment of a cryopreserved UCB units is representative of the whole product and can be utilized to accurately estimate CFU content and viability after thawing (D. A. Wall, personal communication). Unfortunately, results of CFU assay are susceptible to minor variations in techniques and culture conditions used, and may not be accurately reproducible between different laboratories. While, CD34+ cell content of a UCB unit at harvest is not universally available at present, the authors’ bias is towards CD34+ cell content to quantify graft potency. Studies directly comparing the relative precision of TNC vs. CD34+ content to predict the various outcomes after UCBT are awaited.

**BMT vs. UCBT: COMPARATIVE ANALYSIS**

There are no prospective studies comparing outcomes in similar patient populations randomized to receive UCB or BM grafts. Three reports\textsuperscript{31,34,133} (and one study in abstract
form\textsuperscript{129} have retrospectively compared HCT outcomes with the two stem cell sources (Table 3).

**Engraftment**

In a matched pair analysis\textsuperscript{34} comparing HLA-A, -B, -DRB1 matched URD marrow transplants using either methotrexate (BM-MTX) or T-cell depletion (BM-TCD) for GVHD prophylaxis, with 0-3 loci HLA mismatched UCBT (Table 3[3]), the speed of neutrophil recovery was significantly slower after UCBT when compared to the BM-MTX group (median, 29 vs. 22 days) [p=.03], or the BM-TCD group (median, 27 vs. 14 days) [p<.01]. However by day 45, the overall myeloid engraftment rate was comparable in all groups.

Time to platelet engraftment, while slower with UCBT, was not statistically different from the BM-MTX group, perhaps due to small patient numbers [median, 66 days vs. 30 days: UCBT vs. BM-MTX (p=.12)]. However, at 6 months, there was no difference in platelet engraftment. In another registry report with larger numbers (Table 3[2]), Rocha et al\textsuperscript{31} also observed significant delay in speed of both neutrophil and platelet engraftment after UCBT when compared to URD marrow transplant in children with acute leukemia.

**GVHD**

Current data indicate that HLA-mismatch may be better tolerated in the UCBT setting. A registry study (Table 3[1]), comparing outcomes of HLA-identical sibling UCBT versus HLA-identical sibling BMT in pediatric recipients observed significantly lower incidence of acute and chronic GVHD in the UCBT group\textsuperscript{133}. This study is perhaps the clearest demonstration of a difference in biological properties between the two stem cell sources, as
interpretation of GVHD between unrelated UCBT and BMT is often complicated by different
levels of HLA histocompatibility and other recipient heterogeneity.

Two other reports have compared GVHD frequencies in unrelated donor BM and
UCB recipients. In a matched pair analysis from a single institution (Table 3[3]), risk of acute
and chronic GVHD was similar when comparing outcomes in recipients of HLA-A, -B, -
DRB1 matched unmanipulated BM and mostly 1-2 antigen mismatched unrelated UCB
transplants\(^3^4\). In another registry study (Table 3[2]), 0-3 antigen mismatched UCBT
transplants were associated with a significantly lower risk acute and chronic GVHD as
compared to unmanipulated, mostly HLA-matched marrow transplants\(^3^1\). Taken together
these data indicate that despite the greater degrees of HLA-disparity accepted in UCBT, the
risk of developing acute and chronic GVHD after 1-2 antigen HLA-mismatched unrelated
UCBT\(^2^7,3^1,3^4,3^5\) is similar, or even lower than that reported with HLA-matched bone marrow
transplant\(^3^8,5^4,6^3,6^5,1^3^4\).

The reason(s) for this lower risk of GVHD after UCBT is not clear. Functional and
phenotypic immaturity of UCB lymphocytes\(^1^3^5-1^3^9\) and/or a reduced T-cell dose infused with
UCB grafts\(^3^5,1^0^5,1^4^0\) may contribute to its reduced alloreactivity. Mature T-cells present in the
donor graft are the chief contributor to repopulating T-cells in the first year after HCT\(^1^4^1\).
Large numbers of mature, antigen specific T-cells are infused in a BM graft, and can initiate
GVHD due to recognition of cross-reactive alloantigens\(^1^3^6\). In contrast, characterization of
the UCB \(\alpha\beta\) T-cell repertoire reveals a naïve T-cell population unexposed to prior antigenic
stimulation. It has been suggested that absence of clonal expansion in response to alloantigens by UCB T-cells contributes to its enhanced tolerance.

Relapse and GVL effect

Current experience comparing risk of relapse after UCBT vs. BMT is limited. In an analysis of HLA-matched sibling transplants (Table 3[1]), the 3-year survival in patients with malignant diagnosis was comparable after UCBT or BMT (p=0.69). Notably, in another study of HCT for acute leukemia in children by Rocha et al (Table 3[2]), a larger proportion of recipients (18-20%) in the unmanipulated BMT (UBMT) and UCBT groups had advanced stage leukemia compared to the T-cell depleted BMT (T-UBMT) group (9%). Interestingly, while in both T-UBMT and UCBT groups a lower incidence of acute and chronic GVHD was noted relative to the UBMT recipients, the T-UBMT group, but not the UCBT group had an increased risk of early relapse when compared to UBMT group (p=.02).

Overall, there is no evidence thus far to suggest a higher risk of leukemia relapse after UCBT. The observations of (1) better donor cell immune tolerance of recipient MHC-antigens, evidenced by acceptable risk of GVHD despite up to two HLA-mismatched grafts, and (2) preserved GVL effect after UCBT, might be explained by intact UCB NK-cell function combined with immaturity of umbilical B- and T-cells. In laboratory studies, NK-like cytotoxicity has not been linked with pathogenesis of GVHD, but has been shown to mediate a GVL effect.
A recent study of HCT in mice and humans showed that infusion of donor-derived alloreactive NK-cells not only provides a GVL effect, but may also protect against GVHD by targeting recipient antigen presenting cells\textsuperscript{145}. UCB contains levels of NK-cells and inducible NK-like cytotoxic activity similar to those in adult peripheral blood\textsuperscript{135,146,147}, which might explain a preserved GVL effect. Prospective studies comparing similar patient populations receiving UCB or marrow graft are needed for reliable conclusions, although, it remains to be seen if such studies will be feasible, or ever performed. Randomization will be difficult as UCB grafts are typically available much faster than URD marrow. Hence high-risk patients (e.g. leukemia in tenuous remission) may be more likely to receive UCBT. Strict control of patient risk factors will be critical for any reliable comparison between UCB and marrow transplants.

\textbf{Survival}

Three retrospective reports have compared survival between URD UCB and marrow HCT. A registry report comparing HLA-mismatched UCBT with unmanipulated marrow in children with leukemia (Table 3[2]), noted a significantly higher early (<100 days) TRM in the UCBT group, although, overall survival between 0-2 HLA-mismatched UCBT and mostly HLA-matched URD marrow transplants was comparable\textsuperscript{31}. UCB recipients were more likely to have adverse prognostic factors in this study. Other groups have not reported increased early TRM with UCBT.
A second study from the International Bone Marrow Transplant registry (IBMTR), reported in abstract form, compared 296 UCBT (94% with at least 1 mismatch at HLA-A, -B or -DRB1) with 210 URD BMT (62% matched at HLA-A, -B and -DRB1) in children with hematological malignancy\textsuperscript{129}. This study reported similar survival rates in recipients of BMT and 0 or 1 HLA-mismatched UCBT, with reduced GVHD in the UCBT recipients. In this study survival was reduced in recipients of 2 HLA-mismatched UCBT compared with recipients of better-matched UCBT and BMT recipients. Also, a matched pair case control study (Table 3\textsuperscript{3}) showed comparable outcomes in recipients of HLA-A, -B, -DRB1 matched marrow and mismatched UCB\textsuperscript{34}. Taken together, these results suggest that UCB with limited HLA-mismatch is an acceptable alternative to marrow, at least in children.

**OUTCOMES IN ADULT RECIPIENTS**

BMT for acute leukemia in adults, from donors other than HLA-identical siblings, is associated with a high risk of GVHD and treatment failure\textsuperscript{38,51,148,149}. UCBT may have an advantage in adult recipients due to potentially decreased risk of GVHD. However, as cell dose is associated with survival, this considerably limits the pool of eligible UCB grafts for adult recipients.

Laughlin et al\textsuperscript{33} reported the first major adult UCBT series from five US centers. The recipients (n=68) weighed a median of 69.2 kg (range, 40.9-115.5 kg), and 54 had a hematological cancer, of which 50 were considered intermediate/high risk. 97% grafts were 1-3 antigen HLA-mismatched with their recipient. The median nucleated cell dose infused
was 2.1 x 10^7 per kg of recipient (range, 1 - 6.3 x 10^7 per kg). Engraftment frequency was similar to pediatric series with an estimated probability of myeloid recovery by day 42 of 90% (median time to engraftment, 28 days). Time to neutrophil count >0.5 x 10^9/L was associated with nucleated cell dose (<1.87 x 10^7 vs. >1.87 x 10^7; p=0.003). Despite a high frequency of HLA-mismatched grafts, the probabilities of grade II-IV and grade III-IV GVHD were 60% and 20% respectively. Nineteen [18 disease free (26%)] of 68 recipients were alive at 22 months of follow-up. Speed of myeloid recovery and DFS were linked with higher nucleated cell and CD34+ cell dose. There was no significant association between the kinetics of myeloid recovery, graft failure, or acute GVHD with extent of HLA-mismatch. Of note, the risk of severe acute and chronic GVHD was lower than typically reported after URD marrow transplants\textsuperscript{38,40,57,150}.

In another report\textsuperscript{151} of 22 adult patients weighing 41-85 kg, who received unrelated UCBT with TNC dose ranging from 1.01-4.96 x 10^7/kg, all 20 patients who survived more than 30 days showed myeloid engraftment at a median of 22 days. One patient who received the lowest cell dose experienced secondary graft failure. Also, in a separate Eurocord report of 42 adult recipients of UCBT\textsuperscript{116}, median time to neutrophil recovery (>0.5 x 10^9/L) was 35 days, and no patient who received less than 1.0 x 10^7 nucleated cells/kg survived. These results combined, once again underscore the importance of graft cell dose relative to recipient size for optimal results after UCBT, and support a minimum nucleated cell dose limit of 1.5 x 10^7 nucleated cells/kg.
Several strategies to increase the nucleated/CD34+ cell dose of the graft are being investigated, including ex-vivo expansion of UCB hematopoietic cells\textsuperscript{152,153}. The hematopoietic cells in UCB have an immense capacity to expand ex-vivo in the presence of an appropriate cytokine cocktail\textsuperscript{111,154,155}. However, while the yield of more mature hematopoietic progenitor cells is extensive, it is not yet clear if actual expansion of the pluripotent, long-term repopulating HSC is possible or required\textsuperscript{111,154,155}. It will be important however, to demonstrate that HSC are at least maintained, and safety studies are currently underway.

Alternative approaches to optimize outcomes are being explored such as multiunit UCB transplant\textsuperscript{156}, UCBT combined with infusion of mesenchymal stem cells, or UCBT after a nonmyeloablative preparative regimen\textsuperscript{157}. Barker et al\textsuperscript{158} reported short-term outcomes in 8 adults (median weight, 81 kg) with advanced hematological malignancy, using two unrelated 1-2 HLA-mismatched UCB grafts. Initial results are encouraging, however, further study is required to show if double UCBT is associated with improved engraftment and survival as compared to single UCBT in larger sized recipients.

**CONCLUSIONS AND RECOMMENDATIONS**

As noted earlier, there are a number of logistical and biological differences between the two stem cell sources, which may make one more advantageous over the other. A comparison of issues involved in the selection of BM vs. UCB grafts is outlined in Table 4.
For URD BMT, suitable donors have previously been accepted as HLA matched at -A and -B loci by serology, and at -DRB1 by molecular techniques, with one mismatch allowed by some centers in recipients younger than 36 years. Additionally, allele level matching at HLA-A, -B, and -C is increasingly being sought, in conjunction with matching at additional class II loci. This practice may however further restrict availability of suitably matched donors. Cell dose is generally not a limiting factor in identifying a marrow donor, although data indicate improved survival when higher cell doses are obtained.

For UCBT, cell dose is the most critical determinant of outcome, and currently, 4-6 antigen HLA-matched grafts are considered acceptable. While the minimum acceptable UCB graft cell dose is yet to be unanimously agreed upon, a minimum threshold of 1.5 x 10⁷ nucleated cells/kg or 1.7 x 10⁵ CD 34+ cells/kg has been suggested. Among 0-2 antigen HLA-mismatched grafts, current data suggest that for the same cell dose, survival is superior with better-matched grafts, although, the negative effect of HLA-mismatch can be at least partially overcome by a higher cell dose. Hence, higher cell doses are even more important with HLA-mismatched grafts. While it has become obvious that both HLA-match and cell dose must be considered in the algorithm for UCB graft selection, future studies are awaited to delineate their relative importance.

When URD HCT is indicated, initiating a simultaneous search of UCB and marrow donor registries is justifiable, as it will maximize the chance of finding an acceptable source of HSC, particularly for children. When both a suitable UCB and marrow graft are available on preliminary search, the urgency for HCT and recipient’s diagnosis may dictate the best
stem cell source for the specific patient. The time required to acquire an identified UCB graft is significantly shorter. Also, since UCB grafts are banked, rescheduling the date of HSC infusion is simple. Hence, in situations where the patient requires urgent transplant, or when the patient’s disease or medical status may require rescheduling the date of transplant at short notice, an UCB graft has obvious advantages.

In comparison to BMT, experience with UCBT is relatively less. However, sufficient data are becoming available to suggest at least comparable efficacy between HLA-matched marrow and UCB for pediatric patients with acute leukemia\textsuperscript{28,29,31,32,34,35}. Some investigators have also reported encouraging preliminary results after UCBT in young children (<2.5 years) with leukemia, immunodeficiency or inborn errors of metabolism\textsuperscript{164,165}. Of note, available UCB grafts for children this age typically deliver a high TNC dose.

Experience with UCBT for most non-malignant disorders such as aplastic anemia, and for adults with hematological malignancies is more limited at present. In diagnoses where HCT is associated with higher rates of graft rejection, or where need for donor lymphocytes may arise after transplant e.g. in chronic myeloid leukemia (CML), marrow grafts may be a better option. Moreover, in certain diseases such as CML in chronic phase (<40 years) or Wiskott-Aldrich syndrome in young children, disease free survival after HLA-A, -B, -DRB1 matched URD BMT is very good\textsuperscript{40,57,96,98,99}. For such patients, at present, UCB might be considered, but only if HLA-A, -B, -DRB1 matched URD marrow is not available.
With certain inherited diseases, such as mucopolysaccharidoses or X-linked cerebral adrenoleukodystrophy, the disease manifestations can be rapidly progressive, potentially limiting the usefulness of HCT\textsuperscript{11-13}. Hence, the decision to wait for a marrow graft needs to be carefully weighed against the disease stage at presentation, and the predicted rate of progression. In adult patients, while cell dose restricts the use of UCBT, results with URD BMT for acute leukemia are sufficiently poor to warrant investigation of UCB in an attempt to reduce non-relapse mortality\textsuperscript{38,51,148,149}. A suggested approach to select an URD graft is shown in Figure 4.

---

**Figure 4.**
Efforts to more rapidly identify and increase the availability of allele-level HLA-matched URD marrow grafts are ongoing by marrow donor registries worldwide. Alternatively, the majority of UCB searches are likely to identify a 0-2 antigen-mismatched graft for pediatric and many adult patients, even within the currently accessible UCB pool. With growing awareness and public interest, the number of UCB units being harvested and stored is rapidly expanding. Also, programs aimed at increasing the pool of uncommon haplotypes by recruiting ethnic/racial minority donors might meet with higher success for UCB "donors" as compared to marrow donors. In the future, with a larger pool of stored UCB units, and with possibly increased representation of minority haplotypes, there will be an increased likelihood of identifying UCB units with 0-1 HLA-mismatch. Unfortunately, currently a UCB search requires initiation of separate queries with individual cord blood banks, and different banks have diverse policies on methods of HLA-typing and cell content assessment at harvest. This can make comparisons between different search reports difficult. The development of a unified system that will allow for a single search, with access to all available UCB units worldwide, that have been stored by banks using uniform standards, will make the search process faster, more accurate, and comparisons of results after UCBT more reliable.

Acknowledgements

The authors would like to acknowledge and thank the National Marrow Donor Program (NMDP) for providing registry data. We thank the staff at the University of Minnesota Blood and Marrow Transplant Program for their assistance in the investigation of the clinical role of
UCBT. The authors also acknowledge Dr. Norma KC Ramsay for her critical review of the manuscript and helpful suggestions.

References


<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Age (median) in years</th>
<th>Myeloid engraftment* (median time)</th>
<th>Acute GVHD II-IV (III-IV)</th>
<th>Chronic GVHD (extensive)</th>
<th>Disease free survival (DFS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1] NMDP (1987-1990), 462 patients, malignant and non-malignant diagnoses</td>
<td>0.3-54.5 (26.0)</td>
<td>94% (22 days)</td>
<td>64% (47%)</td>
<td>55% (35%)</td>
<td>2-year DFS for leukemia (n=352) Low risk = 40% High Risk = 19%</td>
</tr>
<tr>
<td>[2] IBMTR (1985-1991), Leukemia only</td>
<td>1.0-57.0 (32)</td>
<td>99%</td>
<td>29% (13%)</td>
<td>42%</td>
<td>3-year DFS Low risk: 66% High risk: 12%</td>
</tr>
<tr>
<td>HLA-6/6 sibling donor (n=1,224)</td>
<td>1.0-53.0 (25)</td>
<td>HLA-5/6: 91% HLA-4/6: 84%</td>
<td>HLA-5/6: 52%</td>
<td>HLA-5/6: 60%</td>
<td></td>
</tr>
<tr>
<td>HLA-5/6 or 4/6, related donor (n=340)</td>
<td>1.0-56.0 (31)</td>
<td>91%</td>
<td>HLA-6/6: 54% (35%) HLA-5/6: 63% (47%)</td>
<td>HLA-6/6: 62% HLA-5/6: 73%</td>
<td></td>
</tr>
<tr>
<td>[3] Seattle (1985-1993), 88 pediatric patients, malignant and non-malignant diagnoses</td>
<td>0.5-17.8 (9.1)</td>
<td>93% (21 days)</td>
<td>HLA-6/6: 83% (37%) HLA-5/6: 98% (62%)</td>
<td>HLA-6/6: 60% HLA-5/6: 69% (37%)</td>
<td></td>
</tr>
<tr>
<td>[4] NMDP (1988-1996), 1423 patients, chronic myeloid leukemia only</td>
<td>Age in years 0-20: 11% 21-40: 54% &gt;40: 35%</td>
<td>92% (20 days)</td>
<td>43% (33%)</td>
<td>73% (60%)</td>
<td>3-year DFS: all patients in CP: 43% &lt;35 years, CP, &gt;1 year after diagnosis: 63%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Age (Median)</th>
<th>Donor-recipient HLA-mismatch</th>
<th>Myeloid engraftment (median time)</th>
<th>Platelet engraftment (median time)</th>
<th>Favorable factors associated with engraftment (multivariate analysis)</th>
<th>Grade II-IV (III-IV) acute GVHD</th>
<th>Factors associated with acute GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1] Analysis of 562 patients receiving UCB grafts from New York Blood Center between 1992-1998</td>
<td>82% patients: ≤ 17 years 18% patients: ≥ 18 years</td>
<td>7% of grafts: 6/6 HLA-match 39% of grafts: 1 HLA-mm 54% of grafts: 2-3 HLA-mm</td>
<td>At day 60 91% (28 days)</td>
<td>At day 180† 85% (90 days)</td>
<td>1. Higher nucleated cell dose, HLA-match, US center, and diagnosis other than Chronic myeloid leukemia &amp; Aplastic anemia were associated with successful myeloid engraftment 2. Younger age, absence of infection after HCT, and absence of acute GVHD were associated with platelet engraftment</td>
<td>6/6 HLA-match: 27% (9%) 1 HLA-mm: 48% (22%) 2-3 HLA-mm: 49% (25%)</td>
<td>1. Older age (≤12Vs ≥12) 2. Non-US center location 3. HLA mismatch (0 Vs &gt;1) approached significance (p=0.06), but no correlation with number of mismatches was seen</td>
</tr>
<tr>
<td>[2] Multi-center (Eurocord and others) between 1988-1996. Results of unrelated UCBT group (n=65) are shown</td>
<td>0.3-45.0 (9) years</td>
<td>14% of grafts: 6/6 HLA-match 83% of grafts: 1-2 HLA-mm</td>
<td>At day 60 87%</td>
<td>At day 60‡ 39%</td>
<td>Recovery of neutrophil count and platelet engraftment associated with 1. Higher number of nucleated cells infused 2. HLA-identity</td>
<td>32% (20%)</td>
<td>1. No association of acute GVHD with number of HLA mismatches 2. CMV seronegative status was associated with a lower risk of acute GVHD</td>
</tr>
<tr>
<td>[3] 102 UCBT at the University of Minnesota between 1994-2001</td>
<td>0.2-56.9 (7.4) years</td>
<td>14% of grafts: no HLA-mm 84% of grafts: 1-2 HLA-mm</td>
<td>At day 42 88% (23 days)</td>
<td>At day 180† 65% (86 days)</td>
<td>1. Neutrophil recovery: higher CD34+ cell dose infused (&gt;1.7x10^6/kg) 2. Platelet recovery: higher CD34+ cell dose infused and absence of severe acute GVHD 3. No association of either with HLA match was observed</td>
<td>39% (11%)</td>
<td>No association with CD3 cell dose, HLA disparity or class of HLA-mismatch.</td>
</tr>
</tbody>
</table>

Table 2. Engraftment and acute GVHD after unrelated umbilical cord blood transplantation (UCBT). Results of three large peer-reviewed studies of unrelated UCBT are shown. [1] N Engl J Med 1998;339:1565-77. Malignant and non-malignant diagnoses; [2] N Engl J Med 1997;337:373-381. Malignant and non-malignant diagnoses; [3] Blood 2002;100:1611-1618. Malignant and non-malignant diagnoses; Abbreviations: 1, 2 or 3 HLA-mm, HLA-mismatch at 1, 2 or 3 HLA-A, -B, or -DRB1; Myeloid engraftment: neutrophil count ≥0.5 x 10^9/L, first of 3 consecutive days. Platelet engraftment: ≥ 50 x 10^9† or ≥ 20 x 10^9‡ (untransfused) platelets/L, first of 7 days.
<table>
<thead>
<tr>
<th>Type of HCT and patient numbers</th>
<th>Age (median) in years</th>
<th>Donor-recipient HLA-mismatch</th>
<th>Myeloid engraftment (median days)</th>
<th>Platelet engraftment (median days)</th>
<th>Acute GVHD grade II-IV (III-IV) [chronic GVHD]</th>
<th>Survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1] Type of HCT: patient numbers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCBT: 113</td>
<td>&lt;1-15 (5)</td>
<td>HLA-identical sibling</td>
<td>89% (26)</td>
<td>86% (44)</td>
<td>14% (2%) [5%]</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>BMT: 2052</td>
<td>&lt;1-15 (8)</td>
<td>HLA-identical sibling</td>
<td>98% (18)</td>
<td>96% (24)</td>
<td>24% (10%) [14%]</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>[2] Type of HCT: patient numbers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UBMT: 262</td>
<td>5-12 (8)</td>
<td>18%: 1 HLA-mm</td>
<td>96% (18)</td>
<td>85% (29)</td>
<td>56% (29%) [46%]</td>
<td>43% (39%)</td>
<td></td>
</tr>
<tr>
<td>T-UBMT: 180</td>
<td>6-12 (8)</td>
<td>40%: 1-2 HLA-mm</td>
<td>90% (16)</td>
<td>85% (29)</td>
<td>19% (8%) [12%]</td>
<td>37% (47%)</td>
<td></td>
</tr>
<tr>
<td>UCBT: 99</td>
<td>2.5-10 (6)</td>
<td>89%: 1-3 HLA-mm</td>
<td>80% (32)</td>
<td>90% (81)</td>
<td>33% (21%) [25%]</td>
<td>31% (38%)</td>
<td></td>
</tr>
<tr>
<td>[3] Comparison groups (patient numbers)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCB vs. BM-MTX (n=26 each)</td>
<td>(4.5) vs. (4.7)</td>
<td>19% vs. 100%</td>
<td>88% (29) vs. 96% (22)</td>
<td>72% (66) vs. 76% (30)</td>
<td>42% (19%) vs. 35% (8%)</td>
<td>53% vs. 41%</td>
<td></td>
</tr>
<tr>
<td>UCB vs. BM-TCD (n=31 each)</td>
<td>(5.8) vs. (6.8)</td>
<td>13% vs. 100%</td>
<td>85% (27) vs. 90% (14)</td>
<td>84% (61) vs. 84% (59)</td>
<td>36% (10%) vs. 35% (13%)</td>
<td>52% vs. 56%</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of UCBT and BMT from HLA-identical sibling donors.
1. There was a significantly longer time to platelet recovery in the early transplant period (<35 days) with UCBT.
2. Risk of acute and chronic GVHD was significantly lower with UCBT.
3. No significant difference in 100 day or 3-year survival observed between UCBT or BMT groups for either malignant or non-malignant diseases.

1. Significant delay of neutrophil & platelet engraftment in UCBT group.
2. Neutrophil and platelet recovery correlated with nucleated cell dose (< 3.7 vs. >3.7x10^7 cells/kg) but not with HLA-disparity for UCBT.
3. Decreased acute GVHD in the UCBT and T-UBMT groups as compared to UBMT group.

Matched-pair analysis.
1. No difference in graft failure among comparison groups.
2. Neutrophil recovery was significantly delayed in UCBT group vs. BM-MTX or BM-TCD.
3. No difference in acute/chronic GVHD in comparison groups.
4. Survival at 100 days/2-years was comparable between BM and UCB pairs.
Table 3. Engraftment, GVHD, and survival in series comparing UCBT with BMT. All series shown are in pediatric recipients only. [1], N Engl J Med 2000;342:1846-54. From Eurocord, University of Minnesota, and IBMTR. Malignant and non-malignant diagnoses; [2], Blood 2001; 97: 2962-2971. Eurocord and other centers, with pediatric acute leukemia patients only; [3], Blood 2001;97:2957-61. University of Minnesota. Malignant and non-malignant diagnoses; Abbreviations: HLA-mm, HLA-mismatch; UBMT, Unmanipulated (unrelated) bone marrow transplantation; BM-MTX, T-replete bone marrow transplantation with methotrexate GVHD prophylaxis; T-UBMT or BM-TCD, T-cell depleted unrelated bone marrow transplantation; myeloid engraftment: neutrophil count ≥0.5 x 10^9/L, first of 3 consecutive days. Platelet engraftment: ≥20 x 10^9† (untransfused) platelets/L, first of 7 days or 14 days free of platelet transfusions‡.
<table>
<thead>
<tr>
<th></th>
<th>Marrow graft</th>
<th>UCB graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available pool</td>
<td>Living, volunteer donors, currently ~7 million</td>
<td>Pre-harvested, cryopreserved units, currently ~ 70,000</td>
</tr>
<tr>
<td>Typical donor HLA-type information in database</td>
<td>HLA-A, -B ± -DRB1</td>
<td>HLA-A, -B, and -DRB1</td>
</tr>
<tr>
<td>Acceptable donor-recipient HLA-match</td>
<td>HLA-A, -B (serologic), and DRB1 match, with 1 mismatch permitted for recipients &lt;36 years</td>
<td>4 of 6 loci match at HLA-A, -B, and -DRB1</td>
</tr>
<tr>
<td>Median search time</td>
<td>Longer, ~4 months</td>
<td>Shorter, &lt;1 month</td>
</tr>
<tr>
<td>Major limiting factors to graft acquisition</td>
<td>-HLA-match</td>
<td>Fixed UCB cell content</td>
</tr>
<tr>
<td></td>
<td>-Donor attrition/availability</td>
<td>(especially for larger sized recipients)</td>
</tr>
<tr>
<td>Ease of rearranging date of stem cell infusion</td>
<td>Can be difficult</td>
<td>Easy</td>
</tr>
<tr>
<td>Potential for second HSC graft or DLI from same donor</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Potential for disease transmission to recipient</td>
<td>-Yes</td>
<td>-No</td>
</tr>
<tr>
<td></td>
<td>-CMV/EBV</td>
<td>-Yes</td>
</tr>
<tr>
<td></td>
<td>-Congenital disease*</td>
<td></td>
</tr>
<tr>
<td>Risk to donor</td>
<td>Uncommon</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>-anesthesia related</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-surgical complication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-emergent blood transfusion</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Comparison of issues involved in URD marrow and UCB graft selection. HSC, hematopoietic stem cells; DLI, donor lymphocyte infusion; * such as hereditary spherocytosis, thalassemia or infant leukemia.
Figure legends


Figure 2. Association of umbilical cord blood nucleated cell dose with speed of myeloid engraftment. Higher graft nucleated cell doses result in shorter time to neutrophil recovery. However, the three highest cell doses have similar Kaplan-Meier probability of achieving engraftment. (Reproduced by permission from Rubinstein P, Carrier C, Scaradavou A, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. N Engl J Med 1998:339:1565-77. Copyright, 1988 Massachusetts Medical Society. All rights reserved)

Figure 3. Association of umbilical cord blood graft CD34+ cell dose with overall survival. (University of Minnesota data:102 consecutive unrelated umbilical cord blood transplants between 1994-2001).

Figure 4. Approach to unrelated donor search for HCT. HLA-mm, HLA-mismatch; TNC, total nucleated cells; *, see text “Conclusions and Recommendations”.
Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood?

Satkiran S Grewal, Juliet N Barker, Stella M Davies and John E Wagner