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Unrelated donor umbilical cord blood transplantation for the treatment of hematologic malignancies

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Abstract

Purpose of review—This review summarizes the state of the art of unrelated donor (URD) umbilical cord blood transplantation (UCBT) for the treatment of hematologic malignancies and discusses the current issues associated with the use of this hematopoietic stem cell (HSC) source.

Recent findings—In contrast to the very high transplant-related mortality associated with the early experience of UCBT, recent series have been associated with comparable survival to that of human leucocyte antigen-matched URD transplantation in children with similarly promising results in adults with the use of double-unit grafts. In addition, utilization of reduced-intensity conditioning regimens has been successful extending access to patients unsuitable for myeloablation. Consequently, the use of umbilical cord blood as a HSC source and the global inventory of units in public banks is rapidly increasing although challenges associated with engraftment, unit quality, and infectious complications remain and will be discussed in this review.

Summary—URD umbilical cord blood is an alternative HSC source offering a unique set of advantages and disadvantages as compared with the transplantation of HSC from unrelated volunteers. Improved transplant outcomes are now making UCBT a rival to URD transplantation for the treatment of hematologic malignancies.

Keywords

allogeneic transplantation; cord blood; hematologic malignancy

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is indicated for the treatment of many high-risk hematologic malignancies. Unfortunately, application of this treatment is limited by a lack of suitable donors. Only 25% of patients have a HLA-matched sibling donor suitable for HSC donation and despite the many millions of volunteer donors registered in the unrelated donor (URD) pool, many patients do not have an adequately human leucocyte antigen (HLA)-matched URD using high-resolution donor–recipient HLA matching especially patients from racial and ethnic minorities [1]. Additionally, the procurement of an URD graft can often take months, whereas patients with hematologic malignancies frequently require urgent transplantation.

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Umbilical cord blood (UCB) can reconstitute hematopoiesis in adults following both myeloablative [2–8] and reduced-intensity/nonmyeloablative (NMA) [9,10•,11] conditioning and has the advantage of ready availability. Importantly, in marked contrast to the transplantation of URD HSC [12], the reduced stringency of the required HLA match with UCBT translates to the potential to extend allogeneic HSCT access to patients without other suitable donors (Table 1). This factor alone, along with multiple other attributes, frequently outweighs the disadvantages of UCBT as compared with URD HSCT (summarized in Table 2), thus accounting for the rapid expansion of use of this relatively new HSC source (Fig. 1). This review will outline the current status of UCBT as compared with URD HSC transplantation as well as discussing current issues associated with the transplantation of this HSC source.

Outcome of umbilical cord blood transplantation compared with unrelated donor bone marrow transplantation

Although no randomized controlled trials have compared UCBT and URD transplantation, retrospective studies have compared single-unit UCBT with URD bone marrow transplantation (BMT) using myeloablative conditioning in adults and children. In 2004, Laughlin *et al.* [5] and Rocha *et al.* [6] reported the first comparisons between UCBT and URD transplantation in adults. The American series found comparable survival after UCBT ($n = 150$) and one antigen-mismatched BMT ($n = 83$) [5], whereas the Europeans reported that HLA-mismatched adult UCBT ($n = 98$) was associated with comparable survival to 6/6 HLA antigen-matched BMT ($n = 584$) [6]. In contrast, a Japanese series reported by Takahashi *et al.* [7] demonstrated superior transplant-related mortality (TRM) and disease-free survival (DFS) in 68 adult UCBT as compared with 45 URD BMT recipients.

More recently, Eapen *et al.* [13••] have analyzed the outcomes of 503 UCBT recipients of 4–6/6 HLA-A, B antigen and DRB1 allele-matched single-unit UCBT as compared with those of URD BMT in children below 16 years of age with leukemia. Most notably, in a subset analysis comparing UCBT outcomes with the 116 recipients of the ‘gold standard’ of 8/8 HLA allele-matched bone marrow, the 35 6/6 HLA-matched UCBT recipients had significantly higher 5-year DFS, with 201 5/6 and 267 4/6 UCBT having comparable DFS with that of 8/8 allele-matched BMT recipients and demonstrated a robust protection against relapse (Table 3).

These findings support UCBT as an alternative to URD BMT in children. Further, if engraftment after UCBT is improved, it suggests that pediatric UCBT may be a superior HSC for the treatment of leukemia. In adults, the American and European comparisons, although establishing UCBT as a potential alternative to URD BMT, have highlighted that the poor engraftment and high TRM must be addressed for this HSC to be widely adopted. At the current time, whether UCBT will be offered to a patient will be frequently determined by the relative availability of a closely HLA-matched (7–8/8 alleles) URD versus an UCB graft of at least 4/6 HLA-A, B antigen and DRB1 allele match and adequate dose; and the experience and research bias of the transplant center.

Strategies to optimize engraftment and reduce transplant-related mortality

Graft failure is a major risk associated with UCBT and from early in the practice of UCBT it was recognized that the total nucleated cell (TNC) dose [2,3] and the infused CD34+ dose [4] per kilogram recipient body weight were significant determinants of sustained donor engraftment. Investigation of ex-vivo expansion [14], coinfusion of T-cell depleted haploidentical cells (to bridge the neutropenic period until the engraftment of a T-replete UCB unit) [15], infusion of mesenchymal stem cells [16], intra-bone marrow injection [17],

and agents to augment UCB homing [18] to improve both overall UCB engraftment and the speed of neutrophil recovery is ongoing. However, perhaps the simplest strategy to augment engraftment pioneered by the University of Minnesota is the infusion of a double-unit graft. Although traditionally thought of as being only needed for adult UCBT recipients this approach is equally as relevant to many children given graft failure is still a devastating feature of many pediatric UCBT series and many larger children will only have access to units of relatively low cell doses that similarly challenge adult UCBT recipients.

Initial investigation with double-unit UCBT following a total-body irradiation (TBI)-based myeloablative conditioning regimen yielded a DFS of 57% [95% confidence interval (CI) 35–79) in 23 leukemia patients (median age 24 years), with a DFS of 72% if transplanted in remission [19]. Updated survival data after myeloablative double-unit UCBT in high-risk hematologic malignancies is shown in Fig. 2. Interestingly, both engraftment and survival was improved after double-unit UCBT as compared with historical single-unit controls [4] despite only one of two relatively low cell dose units being responsible for sustained donor engraftment in the vast majority of patients. This raises the possibility that the ‘losing’ unit is somehow facilitating the engraftment of the engrafting or ‘winning’ unit. However, it is important to note that the single-unit historical controls were transplanted using cyclophosphamide and TBI with antithymocyte globulin (ATG) and cyclosporine-A (CSA)/methylprednisolone as immunosuppression. In contrast, though the double-unit transplants were also performed with cyclophosphamide/TBI and CSA, the ATG and MP were substituted with low-dose fludarabine (Flu) and mycophenolate mofetil (MMF). This raises the possibility that some of the advantage of double-unit UCBT was due to changes in the preparative regimen and immune suppression independent of the graft. This question is therefore being investigated in the Bone Marrow Transplant Clinical Trials Network (BMT CTN) single versus double-unit randomized trial in children in the United States utilizing the cyclophosphamide/Flu/TBI and CSA/MMF regimen. Importantly, however, this study may not fully answer the question of the utility of double-unit UCBT in adults. A major question for the field currently is how double-unit UCBT compares with URD peripheral blood stem cell (PBSC) transplantation in adult patients and should be studied in the near future.

The double-unit UCBT experience has raised unique questions about transplant biology especially given that preliminary University of Minnesota data have suggested that this strategy has also been associated with a reduced risk of relapse as compared with single-unit UCBT [20]. To date, no reliable factor has been able to predict which unit will predominate in engraftment after double-unit transplantation. Interestingly, Scaradavou *et al.* [21] have recently demonstrated an association between UCB unit CD34+ cell viability after thaw [as measured by flow cytometric 7-amino-actinomycin D (7-AAD) staining] and unit predominance. In this analysis of 26 double-unit UCBTs, although the factor determining unit predominance when both units of a double-unit graft have high viability was unclear, units with low viability did not engraft ($P = 0.007$). Such data suggest that the reason that double-unit UCBT is efficacious may simply be because it increases the chance that the patient will receive at least one unit of high viability and thus with engraftment potential. This introduces the concept that postthaw CD34+ cell viability could be an effective measure of unit quality and has the advantage that, unlike colony-forming assays, is available on the day of transplant. Postthaw unit quality is a relatively new variable to be considered in the field of UCBT and will be a critical area of investigation for the future. If these findings are confirmed it would suggest that double-unit UCBT may be indicated even in children given the viability of a unit that appears satisfactory from the standpoint of HLA-matched and TNC dose cannot be predicted prior to thaw.

Although the poor engraftment and high TRM associated with low-infused TNC dose in single-unit UCBT has understandably led to a focus on strategies to augment graft cell dose,

unit selection is complicated by the fact that both engraftment and TRM are also influenced by HLA match. For example, in an analysis of 989 single-unit myeloablative UCBT recipients facilitated by the National Cord Blood Program of the New York Blood Center (NYBC), HLA-A, B antigen and DRB1 allele match was associated with significantly improved engraftment, a lower incidence of severe acute graft-versus-host disease (GVHD), lower TRM, and improved DFS [22]. Eurocord analyses have also found that HLA match is associated with significantly improved engraftment and lower TRM [8].

These findings lead to the question of how to 'trade-off' HLA match with TNC dose when selecting UCB units for transplantation. Although this issue is yet to be fully resolved it is intriguing that in the NYBC analysis referenced above [22] 6/6 HLA-matched UCBT recipients (any dose) had superior DFS to recipients of either 5/6 units at least 2.5×10^7 TNC/kg or 4/6 units at least 5×10^7 TNC/kg. Further, recipients of 5/6 at least 2.5×10^7 TNC/kg units had a comparable DFS to those of 4/6 HLA-matched units with a TNC at least 5.0×10^7/kg [although with less severe acute GVHD (aGVHD)]. This raises the concept of a 'sliding scale' in unit selection with HLA-matched compensating for lesser cell dose (or conversely that the greater the HLA mismatch the greater the cell dose required), and prompts a unit selection algorithm of 6/6 units followed by 5/6 units above 2.5×10^7/kg, and 4/6 units above 5.0×10^7/kg. However, many patients will not have access to such units, and some patients with such optimal units will still not engraft. One strategy to address this limitation that is being investigated in a Center for Bone Marrow Transplant Research (CIBMTR) sponsored study is to prioritize HLA match above a cell dose threshold of 1.5×10^7/kg but to augment engraftment by the infusion of two units.

Graft-versus-host disease after umbilical cord blood transplantation

Although GVHD remains one of the leading causes of TRM in allogeneic HSCT, UCBT has consistently demonstrated a lower than expected incidence of acute and chronic GVHD (cGVHD) [2–8] especially given the considerable degree of HLA mismatch if high-resolution typing is considered [23]. In comparison with URD BMT Eapen *et al.* [13••] reported a similar incidence of grade 2–4 acute and chronic GVHD in pediatric 8/8 allele-matched BMT and 4–6/6 A, B antigen, DRB1-matched UCBT. In adult recipients, Laughlin *et al.* [5] found a similar incidence of grade 2–4 aGVHD and a lesser incidence of extensive cGVHD as compared with HLA-matched BMT recipients. In contrast, Rocha *et al.* [6] reported a lower risk of grade 2–4 aGVHD in adult UCBT as compared with HLA-matched BMT recipients with a relative risk of cGVHD of 0.64 after UCBT although this did not reach significance ($P = 0.11$). Takahashi *et al.* [7] have reported similar findings to the Rocha *et al.* study [6], and more recently these investigators have even reported a significantly lower incidence of grade 3–4 aGVHD and extensive cGVHD after predominantly HLA-matched-related donor HSC transplantation and mismatched URD donor UCBT in adults [24•].

Of further interest beyond the incidence of GVHD is the nature of this disease after UCBT and its response to therapy. Although this has not yet been examined for aGVHD, Arora *et al.* [25•] found more frequent responses of cGVHD to therapy in 47 UCBT as compared with predominantly HLA-matched URD BMT recipients at 2 months (74 versus 48%, $P = 0.005$), 6 months (78 versus 49%, $P = 0.001$) and 1 year (72 versus 51%, $P = 0.03$) following cGVHD diagnosis. UCBT cGVHD was also associated with a lower TRM (11 versus 27% with URD BMT). It is likely that the findings in this study in favor of UCBT may have even been more pronounced if the URD transplant recipients had received PBSC as the HSC source rather than bone marrow, and given the wide adoption of PBSC (Fig. 1) comparisons of both aGVHD and cGVHD after UCBT to recipients of URD PBSC should be a priority for the future.

The exact reasons for the relatively low incidence of GVHD after UCBT are unknown but likely result from the functional immaturity of the infused lymphocytes including decreased cytotoxicity, an altered cytokine profile, decreased HLA expression and increased regulatory T cells. Of even more interest is to understand the biology of why UCBT is associated with a retained graft-versus-leukemia effect despite the GVHD reduction.

Infectious complications after umbilical cord blood transplantation and immune recovery

Opportunistic infections are a significant cause of TRM in HSCT regardless of graft source. However, studies have revealed varying results in the assessment of infection risk after UCBT as compared with other HSC sources. A University of Minnesota analysis revealed equal incidences of one or more serious infections in unmodified bone marrow [81% (95% CI 65–97)], T-cell depleted [83% (95% CI 60–100)] and UCB [90% (95% CI 74–100)] pediatric transplant recipients ($P = 0.48$) in the first 2 years after transplant, with no significant differences overall when taking all serious infections into account [26]. Further, more recently this group has reported a similar risk of cytomegalovirus (CMV) infection in recipients of UCB, bone marrow and PBSC grafts [27]. Another study [28] has reported increased incidences of severe infection in 48 adult UCBT (85% risk) as compared with 144 adults URD HSC transplant (69% risk) recipients, although day 100 and 3-year infection-related mortality did not differ between HSC sources.

Regardless of the specifics of such comparisons infection is a major challenge in UCBT and at many centers infection-related mortality is now the most frequent cause of death in UCBT with the majority of deaths occurring within the first 3–4 months [29•]. Although improved engraftment with new preparative regimens and double-unit grafts, and aggressive supportive care to abrogate neutropenic sepsis and prevent fungal infections by the use of extended spectrum azoles have led to decreased infection-related TRM, viral infections remain a critical challenge in the early postengraftment period. For example, Duke University analyzed 330 pediatric patients undergoing UCBT and reported most deaths within the first 6 months after transplant being attributable to opportunistic infection, of which more than half were secondary to CMV or adenovirus [29•].

Important in interpreting the infectious complications and immune recovery seen after UCBT is not only considering patient and unit characteristics but also what preparative regimen and immune suppression was used. The use of ATG [30,31], corticosteroids, or both for GVHD prophylaxis, for example, appears to be associated with impaired immune recovery and increased risk of severe infection. How to augment immune reconstitution is a major question in the field of UCBT today and assume even greater importance with the recognition that improved immune recovery has also been associated with protection against leukemic relapse [32]. Cellular therapy approaches, although clearly challenging given the naïve neonatal immune system, may yet show promise in the future. In the interim, improved preparative regimens/immune suppression and aggressive supportive care including surveillance for viral reactivation is mandatory in the care of UCBT patients in the early posttransplant period.

Reduced-intensity or nonmyeloablative conditioning

Reduced-intensity conditioning (RIC) or NMA HSCT has been investigated as a method to offer the potential benefit of a graft-versus-malignancy effect to older, more heavily pretreated, more infirm patients, or all with less toxicity. Early series from the University of Minnesota demonstrated that UCBT after NMA conditioning was feasible [9]. However, it was observed that there was a strong association between recent exposure to combination

chemotherapy or a prior autologous transplant and the likelihood of sustained donor engraftment (Fig. 3) [33]. This group has recently updated their NMA UCBT experience [10•]. One-hundred and ten patients (median age 51 years) with high-risk or advanced leukemias, myelodysplasia and Hodgkin's or non-Hodgkin's lymphoma unsuitable for myeloablative conditioning received cyclophosphamide 50 mg/kg, Flu 200 mg/m^2, and TBI 200 cGy with immune suppression of CSA/MMF. Eighty-five percentage of patients received double-unit grafts to attain a target TNC dose of at least 3.0×10^7/kg. In this high-risk patient group, TRM was 26% (95% CI 18–34) at 3 years with an overall survival of 45% (95% CI 34–56) and progression-free survival (PFS) of 38% (95% CI 28–48) at 3 years. Interestingly, the PFS was significantly higher in recipients of double-unit [39% (95% CI 27–51)] as compared with single-unit [24% (95% CI 4–44)] grafts. Further to these findings, the Minnesota group has also reported comparable PFS after RIC allograft in recipients older than 55 years of matched-related donor ($n = 47$) or UCB ($n = 43$) grafts with 3-year PFS of 30% (95% CI 16–44) and 34% (95% CI 19–48), respectively [34].

Ballen *et al.* [11] have also investigated double-unit UCBT utilizing a RIC regimen of Flu 180 mg/m^2 with melphalan 100 mg/m^2, rabbit ATG, and CSA/MMF in advanced hematologic malignancies or severe aplastic anemia reporting a 100-day TRM of 14% and a promising 1-year DFS of 67% in 21 patients. The outcomes from these series appear comparable to previously published series of RIC/NMA transplantation using volunteer donors but this will need to be studied formerly in randomized studies in the future. For the meantime, major questions in the field of RIC/NMA UCBT are: how to ensure engraftment in patients (such as those with myelodysplasia, myelofibrosis and acute myelogenous leukemia who have only received a single induction) without intensive prior chemotherapy (especially given the addition of ATG to the NMA preparative regimen as a strategy to augment engraftment is associated with a high incidence of Epstein–Barr virus posttransplant lymphoproliferative disease [30]); and what is the efficacy of RIC/NMA UCBT in specific disease entities.

Umbilical cord blood banking

As a counterpart to the increased adoption of UCB as an alternative HSC source, the number of units banked worldwide continues to increase with at least 250 000 units for unrelated recipient use banked to date. However, the UCB search continues to be a challenge with no centralized search mechanism to access all units in the global inventory (Fig. 4) and no international regulation to ensure uniform standards from bank to bank. Notably, it is not known how many units would be needed to ensure, for example, a 5/6 HLA-A, B antigen and DRB1 allele-matched unit for the majority of patients of any race or ethnicity. Such projections, although complicated, are important in the consideration of the future funding needed for public UCB banks. A further issue is that of unit quality including: what are the critical determinants of a quality product; and how this should be regulated. McCullough *et al.* [35] investigated the quality of 268 units from banks in the United States and Europe and discovered that quality issues existed in 56% of units, with 10% likely and 35% potentially associated with patient risk. The major issues associated with UCB banking are discussed by Atlas [36] and Rubinstein [37].

Conclusion

UCB is a promising alternative HSC source although reaching its full potential will likely require a significant increase in the size of the global UCB inventory. If that can be achieved, this combined with measures such as improved preparative regimens, double-unit grafts, improved supportive care, measures to augment immune recovery will likely improve

TRM and thus extend the adoption of UCBT to treat patients with high-risk hematologic malignancies.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 640).

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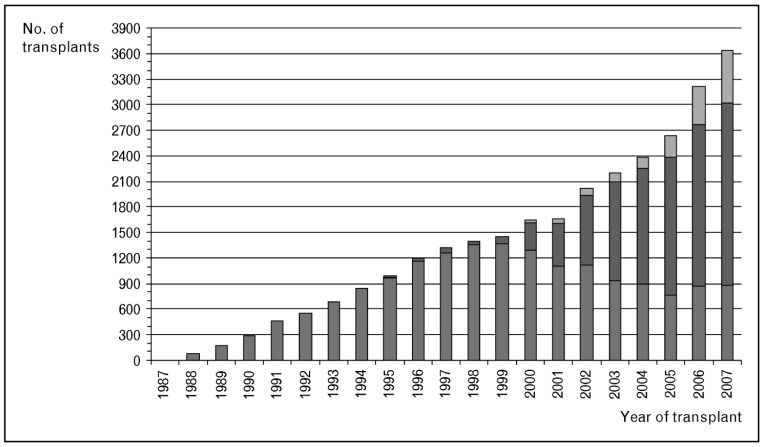

Figure 1. National Marrow Donor Program-facilitated transplants by fiscal year 1987–2007
Since the year 2000, UCBT has been rapidly increasing. Bone marrow, PBSC, UCB. PBSC, peripheral blood stem cell; UCB, umbilical cord blood; UCBT, umbilical cord blood transplantation. Reproduced with permission from Mary Halet, NMDP.

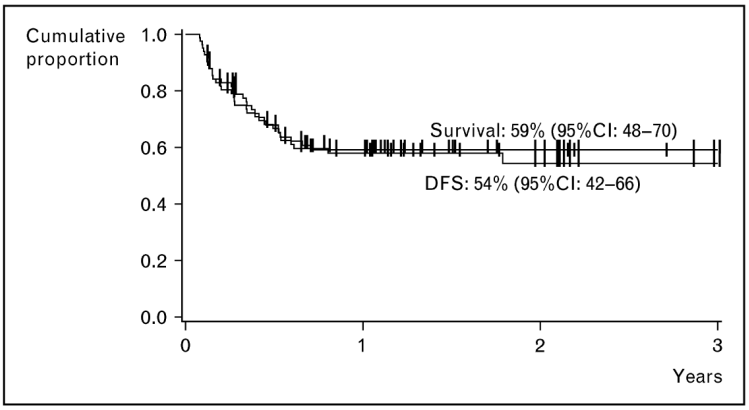

Figure 2. Survival after myeloablative double-unit umbilical cord blood transplantation (*n* = 83)
Patients were conditioned with cyclophosphamide 120 mg/kg, TBI 1320 cGy, fludarabine 75 mg/m^2 with CSA/MMF. CI, confidence interval; CSF, cyclosporine-A; DFS, disease-free survival; MMF, mycophenolate mofetil; TBI, total-body irradiation. University of Minnesota data (reproduced with permission from Professor John Wagner, University of Minnesota, 2007).

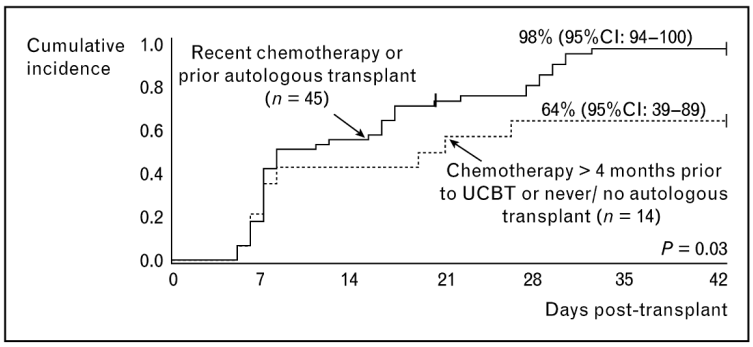

Figure 3. Association between prior chemotherapy exposure and sustained donor engraftment after nonmyeloablative umbilical cord blood transplantation

CI, confidence interval; UCBT, umbilical cord blood transplantation. University of Minnesota data.

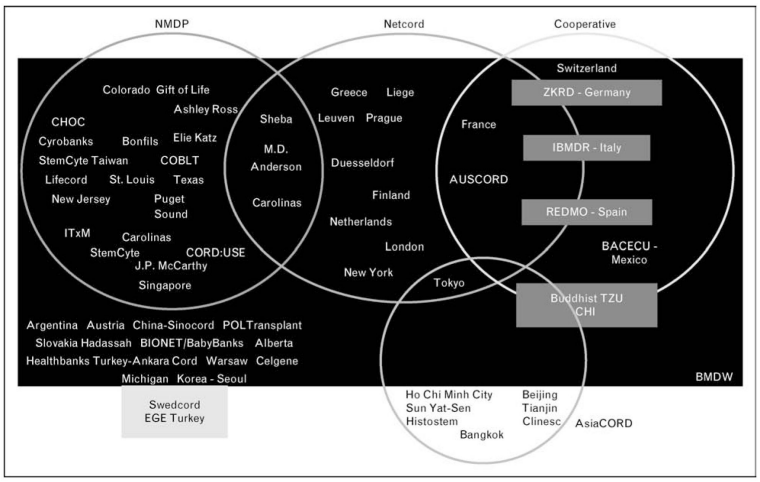

Figure 4. A schema representing the relationships between current umbilical cord blood banks
BMDW, bone marrow donors worldwide; NMDP, National Marrow Donor Program
Reproduced with permission from Mary Halet, NMDP, April 2008.

Table 1

Ancestry of 48 umbilical cord blood transplantation recipients at Memorial Sloan-Kettering Cancer Center October 2005–April 2008

Patient ancestry	UCBT recipients, *n*
Northwest Europe	4
Eastern Europe	6
Southern Europe	7
European Mix	7
Asian	9
African	6
Middle Eastern	1
Hispanic/Latino	8
Total	48

Patients were offered UCBT if allogeneic transplant was indicated and no suitably HLA-matched-related or unrelated volunteer donor was available. Notably, 42% of patients were of non-North Western European ancestry with 50% of patients being non-European. In addition, the four patients of North-Western European ancestry had proven or potential 9–10/10 HLA-A, B, C, DRB1, DQ allele-matched-unrelated volunteer donors but received UCB due to transplant urgency ($n = 1$) or patient preference ($n = 3$). UCB grafts were 4–6/6 HLA-matched at A and B antigens and DRB1 alleles. HLA, human leucocyte antigen; UCB, umbilical cord blood; UCBT, umbilical cord blood transplantation.

Table 2

Relative advantages and limitations of unrelated umbilical cord blood as a hematopoietic stem cell source as compared with transplantation with unrelated volunteer donors

Advantage of UCB	Comparison with URD
Rapid access without the problem of donor availability (admit revolves around patient)	Major advantage over URD
Ability to reschedule easily	Advantage over URD
Reduced requirement for HLA match at high resolution	Major advantage over URD
Less severe GVHD with chronic GVHD easier to treat[a]	Major advantage over URD
Preserved graft-versus-leukemia effect	Similar to URD
Potential to build inventory from all racial groups	Major advantage over URD
Limitation of UCB	**Comparison with URD**
Limited cell dose	Major disadvantage over URD
Limited inventory to enable at least 4/6 HLA matches of adequate dose for patients of all races	URD transplantation also has limited availability to minorities
Potential for variable unit quality at thaw	Disadvantage over URD
Inability to obtain additional collections from donor and naive immune system	Disadvantage over URD for cellular therapies

GVHD, graft-versus-host disease; HLA human leucocyte antigen; UCB, umbilical cord blood; URD, unrelated donor.

[a]Not yet examined for acute GVHD.

Table 3

Comparison of outcomes after 8/8 HLA allele-matched unrelated donor bone marrow transplantation and 4–6 A, B antigen, DRB1 allele-matched umbilical cord blood transplantation in children with acute leukemia [13••]

HSC source	TRM (%)	Relapse (%)	DFS (%)	Overall survival (%)
8/8-matched bone marrow (n = 116)	19	41	38	45
UCB (n = 503)				
6/6	6	34	60	63
5/6 > 3.0×10^7 NC/kg	29	31	41	45
5/6 < 3.0×10^7 NC/kg	43	21	37	36
4/6	49	20	33	33

Survival data are reported at 5 years after transplant. DFS, disease-free survival; HSC, hematopoietic stem cell; TRM, transplant-related mortality; UCB, umbilical cord blood.