

REVIEW

Umbilical cord blood transplantation for non-malignant diseases

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Many factors, including lower risk of GVHD, rapid availability of 4/6–6/6 matched cord blood (CB) units and incremental gains in the outcomes, have led to an increasing use of CB transplantation (CBT) to treat many patients who lack fully matched adult BM donors. A large electronically searchable worldwide inventory of publicly banked CB units allows for quicker donor identification and selection. In this review, we examine the current status and cumulative experience of related and unrelated donor CBT for the treatment of non-malignant diseases, including hemoglobinopathies, BM failure syndromes, primary immunodeficiency diseases (PIDs) and inherited metabolic disorders (IMDs), and conclude that CBT offers a promising and effective therapy for these diseases. Future strategies to facilitate earlier diagnosis and to decrease transplant-related risks should further improve the short- and long-term outcomes. Every effort should be made to perform transplantation early in the course of disease before extensive damage to various tissues and organs ensues.

Bone Marrow Transplantation advance online publication, 5 October 2009; doi:10.1038/bmt.2009.290

Keywords: inherited metabolic diseases; aplastic anemia; immunodeficiency; sickle cell anemia; thalassemia; umbilical cord blood transplantation

Introduction

Non-malignant diseases from a wide diagnostic spectrum, including hemoglobinopathies (for example, thalassemia and sickle cell disease), BM failure syndromes (for example, congenital or acquired aplastic anemia and Fanconi anemia), primary immunodeficiency diseases (PIDs; for example, SCID, chronic granulomatous disease and Wiskott–Aldrich syndrome (WAS)), inherited metabolic disorders (IMDs; for example, leukodystrophies and mucopolysaccharidoses) and others, can be successfully treated by allogeneic hematopoietic SCT (HSCT). In each of these diseases, donor-derived cells have the ability to

correct the underlying defect, either by direct repopulation of the hematopoietic and immune systems or by indirect delivery of the missing enzymes or other critical building blocks across the cellular membranes. The lower risk of GVHD and rapid availability of 4/6–6/6 matched cord blood (CB) units has led to a greater acceptance of CB transplantation (CBT).^{1–10} The majority of CBT, since the first one from a matched sibling in 1988¹¹ and from an unrelated donor in 1993,¹² have been performed for malignant diseases. However, for patients with non-malignant diseases, CBT offers unique advantages including broader donor access and rapid procurement. In addition, many studies have shown that hematopoietic progenitor cells derived from related or unrelated umbilical CB units are at least as effective as those derived from the BM or growth factor-mobilized peripheral blood.^{1,2,4,6,13} Biologically, transplantation in patients with non-malignant diseases facilitates the study of the effect of graft characteristics on transplant outcomes in an environment in which graft vs malignancy effect is not a competing risk factor. Currently, HLA typing by intermediate resolution for class I (A and B) loci and high resolution for HLA class II (DRB1) is considered optimal and CB units matching at $\geq 4/6$ loci are considered adequate. CB units with pre-cryopreservation cell counts of $\geq 2.5\text{--}3 \times 10^7$ nucleated cells (NCs)/kg are considered adequate for better matching grafts, but doses above 5×10^7 /kg yield superior results and can be achieved in most pediatric patients.^{1,2,4,10,14}

Cord blood transplantation (CBT) for patients with hemoglobinopathies

Hemoglobinopathies, such as thalassemia, sickle cell disease (SCD) and other complex defects, can cause major morbidity, poor quality of life and early death from the combined effects of anemia, hemolysis, iron overload and ineffective erythropoiesis. Early transplantation from a suitable donor prevents and reverses many of these problems. Because of different natural histories, the specific questions regarding the time of transplantation, criteria for patient selection and supportive care guidelines differ for patients with thalassemia and SCD. However, the overall concept and design of transplantation is similar. The curative potential of HSCT in hemoglobinopathies has been clearly shown. However, difficulties in defining the criteria for patient selection, limitations in donor

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Received 2 September 2009; accepted 2 September 2009

availability and risks of potentially serious toxicities have prevented HSCT from becoming the standard of care. To help define the patient selection criteria in thalassemia and an individual patient's risks from transplantation, Lucarelli *et al.*¹⁵ developed a scoring system on the basis of chelation therapy (regular or irregular), hepatomegaly and liver fibrosis. Patients with regular chelation and absence of hepatomegaly and fibrosis were Pesaro class 1, whereas those with irregular chelation, hepatomegaly and fibrosis were Pesaro class 3. Those with one or two risk factors were Pesaro class 2. Using these criteria and risk-based conditioning regimens, similar BMT outcomes can be achieved across all three Pesaro risk groups with OS in the 90% and disease-free survival in the 80% range.^{16–19} Similarly, SCD patients undergoing matched related donor BMT showed comparably good outcomes with OS and disease-free survival between 92–94% and 82–86%, respectively.^{20–23} These studies in thalassemia and SCD were very well reviewed recently in this journal.²⁴ However, a matched sibling or even an unrelated adult donor is not available for many patients in a timely manner and an unending wait to find one is not in the best interest of the patients. In the next two sections we review the status of CBT in hemoglobinopathies from published reports, using unrelated donor CB or matched sibling CB with or without BM from the same donor. Although the related donor experience is much larger than that from unrelated donors, they both point to a growing exploration and possibly acceptance of CB as a potential source of graft.

Related donor cord blood transplantation (CBT)

The first report of CBT leading to correction of hemoglobinopathy was published in 1995 by Issaragrisil *et al.*²⁵ They treated a 2½-year-old girl with Hb E-β-thalassemia disease with CB from her sibling who was pre-natally determined to be HLA identical and non-thalassemic. The patient was administered BU and CY for cytoreduction and CYA and MTX for GVHD prophylaxis. In 2000, Reed *et al.*²⁶ reported the use of CBT in three thalassemia patients, the CB of whose siblings were stored under the National Institutes of Health-funded sibling donor cord blood program based in Oakland, CA, USA. In 2005, Walters *et al.*²⁷ published the outcomes of a larger series of CBT performed under the sibling donor cord blood program. CBT using CB alone or in a small number of patients supplemented with BM or PBSC was performed in 14 thalassemia and 8 SCD patients. Of these 22 patients, 18 (12 thalassemia and 6 SCD patients) were alive and disease free with a median follow-up of 124 months (range 05–77 months). In 2003, Locatelli *et al.*²⁸ published the first large series documenting the retrospective analysis of the outcomes of related CBT in thalassemia ($n=33$) or SCD ($n=11$), performed at various centers around the world. Some of the sibling donor cord blood program patients were also included in this analysis. All CB donors were siblings and all but three were fully HLA matched. The median age was 5 years (1–20 years). All thalassemia patients were Pesaro class 1 ($n=20$) or 2 ($n=13$). Conditioning regimens included full-dose BU, cytoxan and antithymocyte globulin (ATG) or antilymphocyte

globulin (ALG) (BU + CY + ATG/ALG) in 73% of SCD and 30% of thalassemia whereas full-dose BU and CY without ATG or ALG (BU + CY) was used in 18% of SCD and thalassemics. One (9%) SCD and 21% of thalassemia patients received BU with fludarabine and thiopeta (BU + Flu + TT) whereas 27% of thalassemia patients received BU with CY and TT (BU + CY + TT). The majority ($n=30$, 68%) of patients received CYA A alone as GVHD prophylaxis. A median of 4×10^7 /kg total NC were administered. The actuarial OS in both thalassemia and SCD was 100%. The probability of EFS in thalassemia and SCD was 79 and 90% (Figure 1), respectively, with graft failure representing the major reason for failure. Among the thalassemics, BU + Flu + TT and BU + CY + TT preparative regimen was associated with a significantly higher probability of EFS when compared with BU + CY or BU + CY + ATG/ALG (94 vs 62%, respectively, $P=0.03$). The DFS in thalassemia patients who had class 1 and 2 features was 89 and 62%, respectively. DFS was significantly higher ($P=0.005$) if MTX was not used. Of the 38 patients who engrafted, only 4 developed grade 2 acute GVHD (aGVHD). Among those patients who developed aGVHD, two had received CB from an HLA-disparate donor. Limited chronic GVHD (cGVHD) was diagnosed in 2 of 36 evaluable patients, 1 of whom had aGVHD. The Kaplan–Meier estimate of the probability of developing aGVHD and cGVHD were 6 and 11%, respectively. In a smaller study of nine thalassemia patients with advanced disease (six and three patients were Pesaro class 2 and 3, respectively), EFS was not as good, particularly in patients receiving mismatched CB units.²⁹ Two single-patient reports describe successful use of related donor CBT for SCD.^{30,31} Thus, matched related donor CBT offers a low risk of GVHD and a high probability of engraftment and DFS in most patients with hemoglobinopathies. In addition, survival outcomes after matched related CBT are comparable to matched related BMT with a lower risk of GVHD.

Unrelated donor cord blood transplantation (CBT)

It is encouraging to note that in the last 5 years, a number of reports and abstracts, albeit with small number of

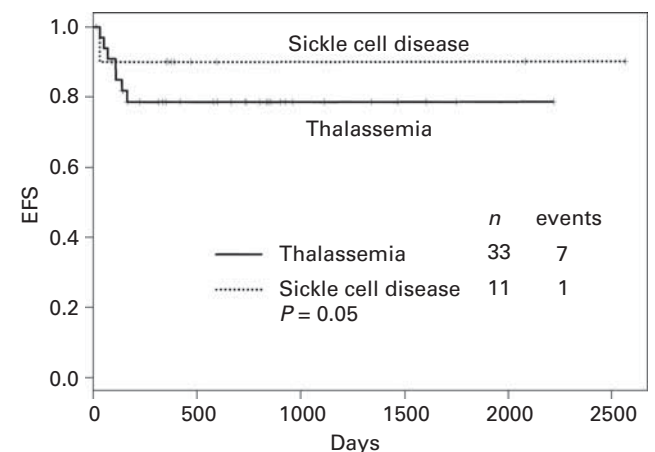


Figure 1 Kaplan–Meier estimates of probability of DFS in thalassemia and sickle cell disease patients undergoing related donor umbilical cord blood transplantation, as reported by Locatelli *et al.*²⁸

patients, have described the experience of unrelated CBT (UCBT) for the treatment of patients with hemoglobinopathies. The youngest patient was a 2-month-old boy who received a high cell dose, 4/6 HLA-matched unrelated CB units after BU/CY/ATG conditioning.³² He promptly engrafted with donor cells, is currently alive and well with 100% donor chimerism, almost 11 years after transplant. He developed autoimmune hemolytic anemia in the early post transplant course, which was treated with a short course of azathioprine and steroids and resolved completely by 2 years after transplant. Until 2007, a total of 16 patients with thalassemia and 7 patients with SCD had been reported to have undergone UCBT.^{32–39} The results from the first published series of unrelated donor CBT was very encouraging. In this Taiwanese report of five children (median age 3.7 years, range 2.3–11.4 years; all Pesaro class 1) with thalassemia major treated with unrelated donor CBT (median cell dose $8.8 \times 10^7/\text{kg}$) from 1-Ag ($n=3$) or 2-Ag ($n=2$) mismatched (high-resolution typing) units after BU (14 mg/kg), CY (200 mg/kg) and ATG cytoablation and CyA/methylprednisolone prophylaxis, all patients engrafted with full donor chimerism and became transfusion independent by 5 weeks after transplantation.⁴⁰ Four patients developed transient corticosteroid-responsive grade I–III aGVHD but there was no cGVHD. All patients were alive and well, with full donor hematopoietic chimerism and transfusion independence at a median follow-up of 303 days after transplant (range 120–360 days). In another report, the same group reported on five older children (median age 11.1 years, range 10–13.1 years) with thalassemia who received double CBT from unrelated mismatched donors after the same cytoablation.³⁶ One patient developed secondary graft failure and the other four developed transient corticosteroid-responsive grade I–III acute GVHD and later limited skin GVHD. At 18.5 months (range 11–32 months), three were alive, well and transfusion independent and one was alive but transfusion dependent. Results from other small and single case reports are similar to the above findings. A 2007 review of four previously published case reports summarized the experience of unrelated donor CBT in seven children with SCD all of whom had a history of stroke. HLA matching was 4/6 in five and 5/6 in two cases. Myeloablative cytoablation was used in four (BU + CY + ATG in three and BU + CY + ATG + Flu in one) and reduced-intensity conditioning in three patients. Unrelated donor CBT was curative in three of seven patients (two in myeloablative and one in reduced-intensity conditioning group) whereas three patients are alive with SCD after primary graft failure.

In an abstract at the annual meeting of the American Society of Blood and Marrow Transplantation in February 2009, Jaing *et al.*⁴¹ presented promising results with unrelated donor CBT in 30 children (median age 5 years, range 1–14 years) with β -thalassemia major (Pesaro 1–21, Pesaro 2–8) transplanted between 2003 and 2008 after myeloablative conditioning with BU + CY + ATG. Single CB unit was used for 21 and double for 9 patients, providing a high median cell dose of $10.9 \times 10^7/\text{kg}$. The CB units were 4/6 ($n=24$), 5/6 ($n=11$) or 6/6 ($n=4$) matched. The OS survivals at 1 and 3 years were $87 \pm 6\%$ and

$82 \pm 8\%$, whereas DFS at 1 and 3 years was $85 \pm 7\%$ and $78 \pm 9\%$, respectively. The risk of grade II–IV aGVHD and extensive cGVHD were $61 \pm 11\%$ and $4 \pm 4\%$, respectively. These results in patients who have been followed for a median of 16 months (range 0.3–58 months) are very encouraging with DFS rates similar to those after matched related transplants.

Despite recent advances, there is significant TRM and morbidity associated with myeloablative transplants for hemoglobinopathies. Various approaches, including improved cellular criteria for donor CB unit selection, pre-implantation genetic diagnosis and embryo selection as well as decreasing the toxicity of the transplant regimen, need to be undertaken in an effort to improve the risk–benefit ratio and to reach the ultimate goal of making transplants available to larger numbers of eligible patients. In an abstract at the American Society of Blood and Marrow Transplantation meeting, Bhatia *et al.*⁴² presented the results of reduced-intensity conditioning using BU ($3.2–4 \text{ mg/kg/day} \times 4$ days), Flu ($30 \text{ mg/m}^2/\text{day} \times 6$ days) and alemtuzumab ($2 \text{ mg/m}^2 \times 1$ day, $6 \text{ mg/m}^2 \times 2$ days and $20 \text{ mg/m}^2 \times 2$ days) in 14 patients with symptomatic SCD. The graft sources were matched sibling BM ($n=6$), matched sibling CB ($N=2$) and unrelated donor CB ($n=6$). Using a different RIC combination (alemtuzumab, Flu and melphalan) and a variety of graft sources (sibling BM $n=5$, sibling PBSC $n=5$, unrelated BM $n=3$ and unrelated CB $N=3$) in 16 children with non-malignant diseases, Shenoy *et al.*⁴³ achieved successful durable engraftment in 14 patients without significant GVHD. Engraftment with CB donors required a higher dose of melphalan (140 mg/m^2) as compared with engraftment with other stem cell sources. On the basis of these and other data, the Clinical Trials Network recently initiated a multicenter prospective study (CTN0601) of unrelated BM or CBT for the treatment of children with SCD.

Cord blood transplantation (CBT) for patients with primary immunodeficiency disorders (PIDs)

HSCT is curative in most children with a variety of PIDs if a suitable donor is available in a timely manner. However, a majority of patients will not have a suitable matched sibling BM donor because of the limitations posed by a combination of Mendelian inheritance of HLA and the genetic nature of these diseases. Alternative donor transplants using T-cell-depleted grafts from haploidentical parents have been used successfully in many patients with SCID; however, many patients will fail to reconstitute B-cell function.⁴⁴ Furthermore, anecdotal reports of late graft failure, more than a decade after transplant, are emerging as longer follow-up is available. CB offers an attractive option because of ready availability and less stringent HLA matching requirements. The low risk of GVHD after CBT is additionally useful as many patients with PID, such as Wiskott–Aldrich syndrome (WAS), Omen syndrome and sometimes SCID, have inherent dermatological problems. In addition, CB units with good cell dose are more easily available for PID patients because of their young age and low body weight.

A number of reports in the past 15 years support the use of CB as a graft source in patients with PID. In the original report of 562 UCBTs performed between 1992 and 1998, at least 31 patients were treated for PID (SCID 24 patients and WAS 7 patients),⁹ but because of the small numbers their outcomes were not reported separately. However, it is noteworthy that PID was not identified as having outcomes worse than the overall group. In a 2007 review by Cairo *et al.*,⁴⁵ outcomes of CBT in 93 UCBT in children with severe PID were reported from the Eurocord data. They were transplanted in 40 different centers and had a median age of 0.9 years (range 0–26) and median weight of 8 kg (range 3–39). Diagnosis included SCID ($n = 61$), WAS ($n = 20$) and others ($n = 12$). Fifty-six patients were matched or had one HLA difference with the CB unit. BU/CY was the most common regimen ($n = 44$, 46%) followed by Flu-containing regimen ($n = 24$, 26%). A radiation-containing regimen was used in 7 (8%) patients whereas 11 patients (12%) did not receive any conditioning. The median number of NCs infused was $8.3 \times 10^7/\text{kg}$ (range 0.1–94), and the median CD34⁺ cell number was $3.4 \times 10^5/\text{kg}$ (0.4–33). Seventy-four patients (80%) received CYA/steroids as GVHD prophylaxis. The cumulative incidences (CI) for neutrophil and platelet recoveries were 85 and 77%, respectively. CIs for acute grades II–IV and cGVHD were 41 and 23%, respectively. TRM at 2 years was 31%. Overall survival at 2 years was 68% for all patients, 78% for those receiving matched or one HLA-disparate CB and 58% for 2–3 HLA-mismatched grafts (multivariate analysis, $P = 0.04$). In a recent report, chronic granulomatous disease was corrected successfully in two patients with UCBT.⁴⁶ Both patients received BU/CY/ATG cytoreduction for the initial grafts, but rejected and were retransplanted with a second UCB graft after either Flu/CY/alemtuzumab or Flu/CY/TBI200 for the second transplant. Both are alive and well 52 and 40 months later. We have subsequently used Flu/BU/CY/ATG for two patients treated with UCBT and one with related CBT with successful primary engraftment.

In an abstract at the 2009 American Society of Blood and Marrow Transplantation meeting, 15 boys (median age 12 months, range 6–51 months) with WAS treated between 1998 and 2007 with UCBT after myeloablative conditioning with BU/CY/ATG \pm Flu were reported.⁴⁷ The CB units were matched at 4/6 ($n = 10$), 5/6 ($n = 3$) or 6/6 ($n = 2$) HLA loci and provided a median infused total NC of $8.31 \times 10^7/\text{kg}$ (range 4.87–16.40). GVHD prophylaxis was methylprednisone and CYA in 12 (80%) patients. All patients engrafted with donor cells reaching ANC of 500 and platelet of 50k in a median of 21 (10–38) and 67 (46–139) days, respectively. One patient has mixed chimerism but all others maintained complete donor chimerism after transplant. Four patients experienced grade II–IV acute GVHD and 11 of 12 evaluable patients experienced limited ($n = 10$) or extensive ($n = 1$) cGVHD. One patient died from post transplant complications including gut GVHD with adenovirus, extensive cGVHD and another from EBV lymphoproliferative disorder and multisystem organ failure, whereas three patients died from infection alone (klebsiella, parainfluenza and adenovirus). Nine patients are surviving with a median follow-up of 89 months (range

9–127), an overall survival of 60%. Survivors have normal platelets, minimal eczema or other medical issues. All school-age children are attending school. These data suggest that CBT should be considered in patients with PID if they lack a suitable matched related donor.

Cord blood transplantation (CBT) for patients with BM failure syndromes

Collective experience in the use of CBT for the treatment of various congenital and acquired BM failure syndromes and recognition of critical elements in the cytoreduction for some of these diseases points to the possibility of increasing use and greater acceptance. Interestingly, the longest surviving recipient of CBT, who is also the world's first patient to undergo CBT, was treated for Fanconi anemia. He is alive and well, more than 20 years after transplant.¹¹ Eurocord retrospectively analyzed the outcomes of 93 UCBTs that were performed worldwide from 1994 to 2005 for patients with Fanconi anemia who were a median of 8.6 years (range 1–45) old.⁴⁸ CB units were 6/6 ($n = 12$), 5/6 ($n = 35$) and 4/6 or lower ($n = 45$) matched. The median total NC and CD34⁺ cells infused were $4.9 \times 10^7/\text{kg}$ and $1.9 \times 10^5/\text{kg}$, respectively. The choice of preparative regimen reflected institutional preferences, although 57 patients (61%) received a Flu-containing combination. The most frequently used regimen was a combination of Flu (25 mg/m² \times 4 days), CY (10 mg/kg/day \times 4 days), and TBI (200 cGy \times 1 day). Most of the patients received CYA with prednisone for GVHD prophylaxis. The CI of neutrophil recovery was $60 \pm 5\%$ at day +60. CI of grade II–IV aGVHD and cGVHD was $32 \pm 5\%$ and $16 \pm 4\%$, respectively. With a median follow-up of 22 months (range 3–121 months), OS was $40 \pm 5\%$. In multivariate analysis, the factors associated with a favorable outcome were use of Flu-containing cytoreduction, number of NCs infused $\geq 4.9 \times 10^7/\text{kg}$ and negative CMV serology in the recipient (Figures 2a and b). Further analyses led researchers to recommend UCB units containing higher cell dose, 4/6 or higher HLA match and use of Flu-based conditioning regimen for Fanconi anemia patients. The benefits of Flu in the conditioning has been described in various reports, including an analysis by Wagner *et al.*⁴⁹ of 98 unrelated donor BMT cases.

Outcomes of unrelated donor CBT for acquired severe aplastic anemia have historically been poor, mainly due to primary graft failure.^{9,50} The high risks of graft rejection likely stem from a combination of inadequate donor hematopoietic cell number in low cell dose of CB units, relative immune competence of the host and previous exposure to multiple blood and platelet transfusions. However, recent reports of improved survival and lower graft failure rates are encouraging. In a Japanese study of 31 patients with a median age of 28 years (range 0.9–72) followed for a median of 33.7 months (range 6–77) the probability of OS in the entire group at 2 years was 41.1%.⁵¹ However, improved outcomes were observed in a subgroup of five patients who received TBI (2–5 cGy), Flu and CY, in which the probability of overall survival was 80% ($P = 0.02$). The risk of aGVHD and cGVHD was low. In a recent report in pediatric patients undergoing

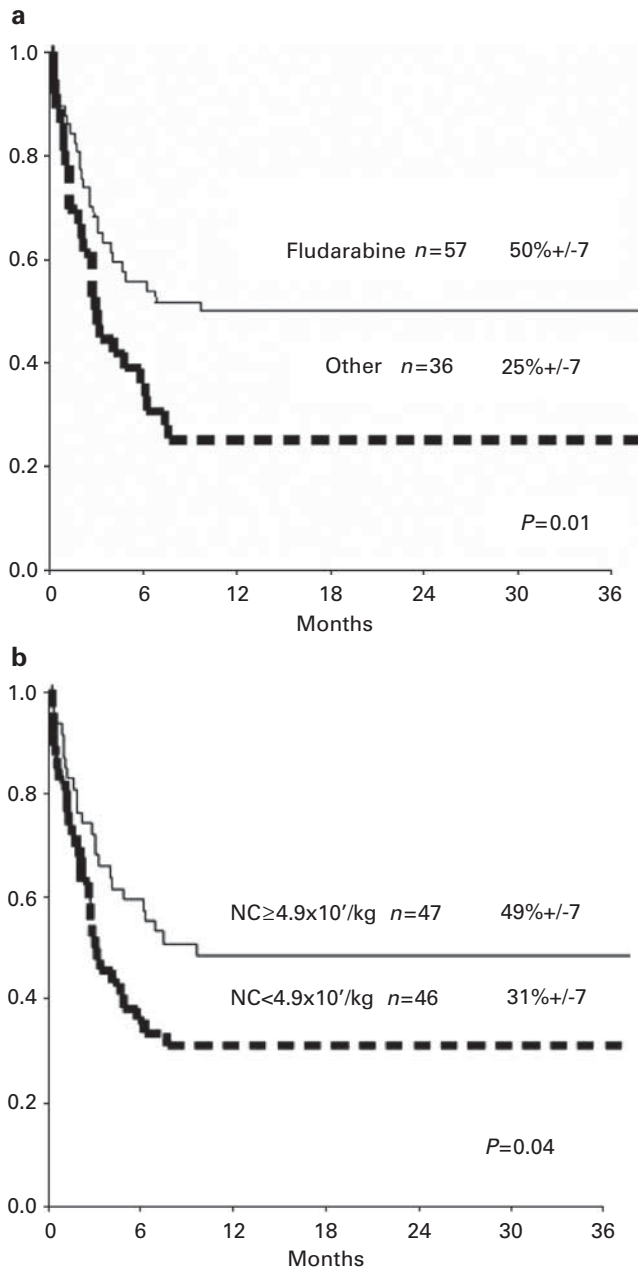


Figure 2 Survival of 93 Fanconi anemia patients treated with unrelated cord blood transplantation (CBT): the results of multivariate analysis, as reported by Gluckman *et al.*⁴⁸ (a) Use of fludarabine in the conditioning regimen and (b) the effect of the number of nucleated cells (NCs) infused.

unrelated donor CBT after failure of immunosuppressive therapy, durable engraftment was observed after Flu 35 mg/m²/day × 5 days, cytoxan > 120 mg/kg divided over 2 or 3 days, rabbit ATG 3 mg/kg/day × 3 days and 200 cGy TBI. The OS was observed in 7 of 9 (78%) patients.⁵² Encouraging results in this and other studies^{53,54} with small numbers of patients offer hope that CBT could be attempted if other suitable donors are unavailable. Furthermore, it is possible that selection of CB units with higher cell dose, use of double CB units and escalation of cytoreductive regimen intensity will likely improve outcomes.

Cord blood transplantation (CBT) for inherited metabolic disorders (IMDs)

Allogeneic HSCT is the only currently available clinical treatment for IMDs that has the ability to induce a long-term metabolic correction and to ameliorate neuro-cognitive and functional problems.⁵⁵ The overall goal of any therapy used to treat patients with IMD is improvement in the quality of life, preservation of functional abilities, potential for neuro-cognitive gains and prolongation of life. Enzyme replacement and gene therapies hold promise, but to date, they have failed to affect the natural history of disease in the central nervous system. It is important to clarify that the evidence and potential usefulness of HSCT in IMD predominantly relate to lysosomal and peroxisomal storage disorders. The biochemical and clinical consequences of IMD, a disease group that in most cases does not have any direct or indirect hematopoietic problems, are corrected by HSCT because of two important factors. The first is the ability of hematopoietic cells to differentiate and become an integral part of non-hematological organs, such as microglial cells in the brain, alveolar macrophages in the lungs and Kupffer cells in the liver. The second is the ability of donor-derived cells to induce ‘cross-correction’, a phenomenon by which the close proximity of normal cells can correct the biochemical consequences of enzymatic deficiency within the neighboring cells.^{56–58} Many cellular^{59–61} and animal^{62,63} studies have defined the scientific basis for HSCT in IMD. In addition, the ability of donor-derived cells to reach the brain was directly shown in the post-mortem analysis of an advanced Krabbe’s disease baby who died 1 year after UCBT from a donor of the opposite sex.⁶⁴ There was evidence of extensive distribution of donor cells in the blood vessels, peri-ventricular tissues, cerebral white matter, cerebellum, choroid plexus and forebrain parenchyma.

Our group recently published the results of 159 young patients with IMD (Hurler’s syndrome, *n* = 45; Hunter’s syndrome, *n* = 6; Sanfilippo syndrome, *n* = 19; Krabbe’s disease, *n* = 36; adrenoleukodystrophy, *n* = 13; metachromatic leukodystrophy, *n* = 15; and others) consecutively transplanted between 1995 and 2007 mostly with HLA-mismatched unrelated donor UCB grafts.⁴ All patients received myeloablative conditioning with BU, CY and horse (ATG). GVHD prophylaxis was administered with CYA combined with either steroids or mycophenolate. CBU cell doses were high (9.37 × 10⁷/kg cryopreserved and 7.57 × 10⁷/kg infused). The patients were young (median age 1.5 years) and small (median weight 12 kg) and their median follow-up was 4.2 years (range 1–11). The cumulative incidences of neutrophil and platelet engraftment were 87.1% (95% CI 81.8–92.4%) and 71.0% (95% CI 63.7–78.3%) and total graft failure rate was low at 8.2% (Figures 3a and b). The cumulative incidence of full donor chimerism (>90%) in engrafting patients was very high (97%). Serum enzyme normalized in 97% of the patients with diseases for which testing exists. The risk of GVHD was low (Figure 3c). Grade III–IV aGVHD occurred in 10.3% (95% CI 5.4–15.2%). Overall 1-year risk of any cGVHD was 20.9% (95% CI 14.2–27.6%) and that of extensive

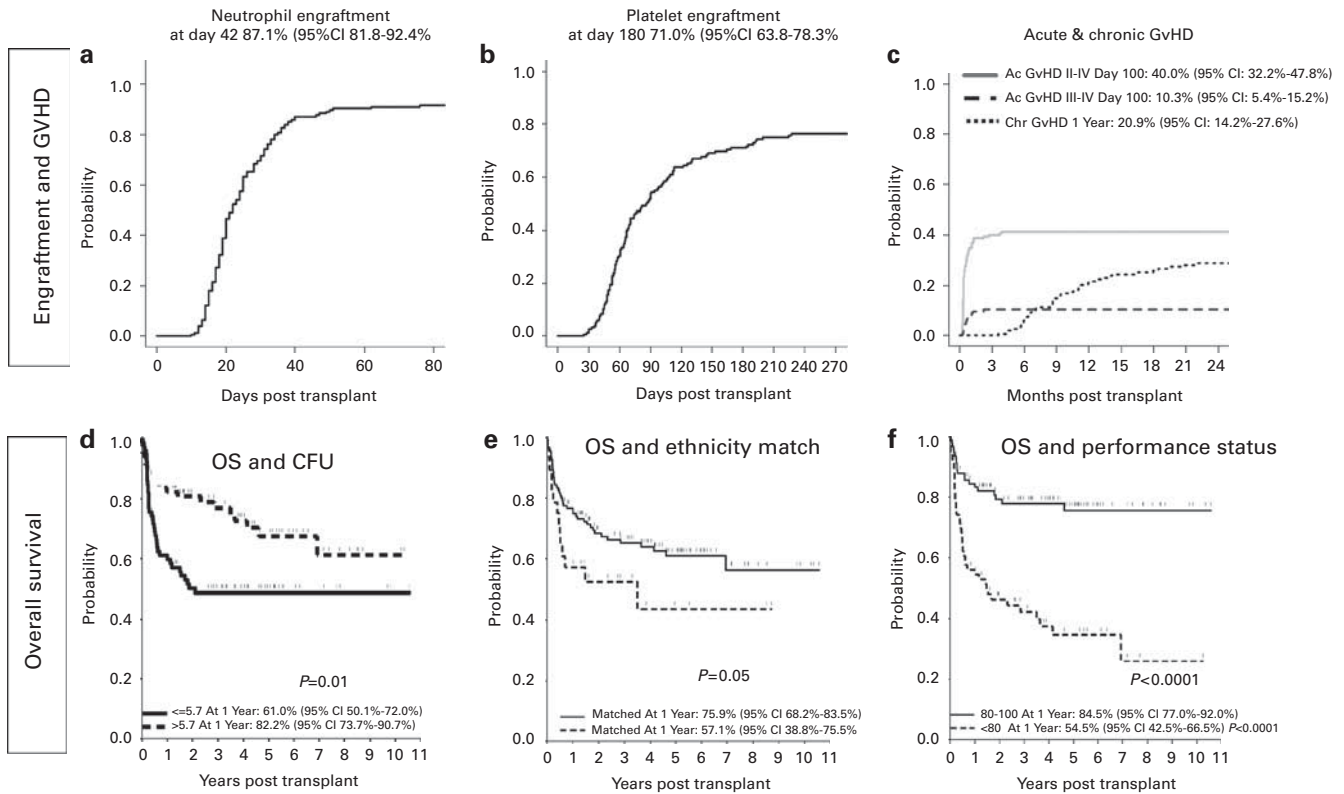


Figure 3 Unrelated cord blood transplantation for 159 patients with inherited metabolic diseases, as reported by Prasad *et al.*⁴ (a) the probability of neutrophil engraftment; (b) the probability of platelet engraftment (50 k); (c) the probability of grade II–IV acute GVHD, grade III–IV acute GVHD and chronic GVHD; (d) the effect of colony-forming units infused ($\times 10^4$ /kg of recipient weight) on *P* of OS; (e) the effect of the donor–patient ethnicity matching on the OS; and (f) the effect of performance status (80–100 vs <80) on the OS.

cGVHD was 10.8% (95% CI 5.7–15.9%). OS at 1 and 5 years were 71.8% (95% CI 64.7–78.9%) and 58.2% (95% CI 49.7–66.6%) in all patients and 84.5% (95% CI 77.0–92.0%) and 75.7% (95% CI 66.1–85.3%) in patients with high (Lansky or Karnofsky 80–100) performance score. In multivariate analysis, favorable factors for OS were high pre-transplant performance status, matched donor/recipient ethnicity and higher infused colony-forming units (Figures 3d–f). In addition to the above study, a previously published multi-institutional trial of UCBT for IMD as a part of the Cord Blood Transplantation Study sponsored by the National Heart, Lung, and Blood Institute,³ publications from the European Group for Blood and Marrow Transplantation registry,⁶⁵ data from a Japanese report⁶⁶ and a number of disease-specific reports^{65,67–69} provide support to the argument that UCBT is an appropriate and viable option for HSCT in infants and children with IMD. In a retrospective European Group for Blood and Marrow Transplantation study of risk factor analysis in 146 Hurler’s syndrome patients, use of UCB graft and shorter interval between diagnosis and transplant were associated with improved survivals.⁶⁵ The probability of overall survival at 1 and 5 years for Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy, Hurler’s syndrome, Hunter’s syndrome and Sanfilippo syndrome were similar, suggesting that it is not the diagnosis but the timing of transplant in relation to the

clinical deterioration that has more affect on the overall success of UCBT. In an effort to decrease the transplant-related toxicity, Hansen *et al.*⁷⁰ recently published their results of HSCT in Hurler’s syndrome patients using unrelated CB ($n=1$), unrelated BM ($n=5$) and related PBSC ($N=1$). One patient died (BM) and one failed to achieve the duration of donor chimerism (PB). A Japanese group used non-ATG-containing regimen and UCB grafts in five IMD patients with encouraging results.⁶⁶

The Duke study showed that UCBT provides high levels of near-total chimerism, enzyme recovery in the blood and ‘engrafted and alive’ rates coupled with low risks of graft failure as well as aGVHD and cGVHD despite significant donor–recipient HLA mismatching. In addition, CBT could be performed quickly in most cases and it took a median of only 35 days to proceed with the transplant after the child was first evaluated at the transplant centre. This is of critical importance because it allows for speedy transplantation in young infants with rapidly progressing forms of these diseases. The advantages of UCBT include its ready availability, quick search and procurement process, less stringent HLA matching requirement, higher probability of finding a UCB donor for racial and ethnic minority patients and those with rarer HLA types, potentially less risk of graft-transmitted infections, lower incidences of GVHD and no risk to the donor.

General principles: related and unrelated donor cord blood transplantation (CBT) for non-malignant diseases

1. Transplantation in early stages of disease before significant organ and tissue damage, exposure to multiple transfusions and/or infective complications leads to less graft failure, lower TRM and better survival.
2. If transplant is indicated and a matched related donor is unavailable, the search for alternative donors, including CB units, should be carried out as soon as possible. If an adequate CB unit is available ($\geq 4/6$ match, $> 3 \times 10^7$ cells/kg), proceed to transplant. Do not wait for an unrelated adult match to become available on the registry.
3. Inquire if a sibling CB unit was stored and what is the degree of HLA matching? Matched and partially mismatched CB units should be used alone if their cell dose is adequate ($\geq 2.5 \times 10^7$ /kg) or with supplemental BM from the same donor if the donor and patient are matched.
4. Consider 9/10 or 10/10 HLA-matched (high resolution for A, B, C, DRB1 and DQB1) unrelated BM donors for all patients except those with inherited metabolic diseases. If no such donor is available, or if the patient is diagnosed with an IMD, unrelated CB should be used.
5. For patients considering CBT:
 - 5.1. Refer to a transplant center experienced in CBT and the particular disease group.
 - 5.2. Identify unrelated CB donors and screen them appropriately (for example, carrier state for IMD transplants or autologous donation from the patient).
 - 5.3. The CB units should minimally:
 1. Contain a pre-cryopreservation total NC dose of $\geq 3 \times 10^7$ /kg.
 2. Match at $\geq 4/6$ HLA loci.
 3. Target a higher cell dose ($> 5 \times 10^7$ /kg) for any 4/6 match and patients with severe aplastic anemia.
6. IMD:
 - 6.1. Establish diagnosis as early as possible. If patient has infantile or severe phenotype forms of disease, refer immediately for CBT.
 - 6.2. Carrier HSCT donors should not be used.
 - 6.3. CB is preferred over adult unrelated donor sources.
 - 6.4. Evaluate patient for disease and performance status.
 1. If patient has central nervous system involvement, pursue CBT if disease manifestations are early.
 2. The patient should have a good performance status, disease should not be rapidly progressing, organ function should not preclude administration of high-dose chemotherapy, and the patient should not have any uncontrolled co-morbidities such as seizures, aspiration, infections and so on.

Conclusions

In summary, transplantation of CB from related and unrelated donors offers promising and effective therapy for many patients with non-malignant disorders. The use of CB increases access to transplantation for almost all patients in need and allows for quicker donor identification and selection. Future strategies to facilitate earlier diagnosis and to decrease transplant-related risks should further improve the short- and long-term outcomes. Every effort should be made to perform transplantation early in the course of disease before extensive damage to various tissues and organs ensues. Continued efforts in this and related fields may lead to even better outcomes for these children in the future.

Conflict of interest

The authors declare no conflict of interest.

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