Cellular Therapy and Transplantation (CTT), Vol. 2, No. 7
10.3205/ctt-2010-en-000069.01

Umbilical cord blood transplantation for treatment of non-malignant disorders

Mitchell E. Horwitz, MD, Nelson Chao, MD, MBA

Division of Cellular Therapy, Duke University Medical Center, Durham, North Carolina, USA

Correspondence: Mitchell E. Horwitz, MD, Division of Cellular Therapy, Duke University Medical Center, 2400 Pratt St. DUMC 3961, Durham, North Carolina 27710, USA
Phone: +1-919-668-1045, Fax: +1-919-668-1091, E-mail: Mitchell.horwitz@duke.edu

Abstract

As the outcomes of umbilical cord blood transplantation improve, the risk versus benefit considerations with respect to treatment of non-malignant disorders must be reassessed. Recent data would suggest that the outcome of umbilical cord blood transplantation is comparable to that of matched unrelated donor transplantation. Thus, patients felt not to be candidates for this potentially curative treatment modality due to lack of an available matched donor should be considered for matched or mismatched unrelated umbilical cord blood transplantation. This review will cover the most recent data pertaining to umbilical cord blood transplantation for the treatment of congenital immunodeficiency disorders, inborn errors of metabolism, bone marrow failure disorders, and hemoglobinopathies.

Keywords: stem cell transplantation, umbilical cord blood, outcomes, clinical results, immunodeficiency, non-malignant disorders, bone marrow failure, review

Introduction

Since the first related donor umbilical cord blood (UCB) transplant in 1988 for a patient with Fanconi anemia, and the first successful unrelated donor UCB transplant in 1993, an estimated 15,000 UCB transplantations have been performed [23]. Today, this approach is being applied to patients of all ages with a variety of diseases, including nonmalignant hematologic disorders and congenital metabolic disorders, as well as hematologic malignancies [2, 15, 16]. Between 2004 and 2007, the Center for International Blood and Marrow Transplant Research (CIBMTR) reported that for patients under age 20 years, 40% of unrelated donor stem cell grafts were collected from the bone marrow, 40% from umbilical cord blood, and 20% from peripheral blood. In contrast, for patients over age 20 years, only 7% of unrelated stem cell grafts were derived from UCB during the same time period. There are a number of factors contributing to increased usage of UCB stem cells. The most important factor is that results with UCB have improved progressively.

Furthermore, the cord blood banking infrastructure has improved, allowing for increased availability of high quality unrelated UCB. Compared to stem cell grafts obtained from unrelated adult donors, UCB stem cells can be procured more quickly, without risk or inconvenience to the donor. Finally, there is the possibility that contained within the UCB are totipotential stem cells with regenerative potential for non-hematopoietic tissues [23, 38]. This is particularly relevant when treating inborn errors of metabolism, which can result in damage to neuronal tissue.

This review will focus on the use of UCB transplantation to treat inherited or acquired hematopoietic disorders. Included are inborn errors of metabolism, in which promising outcomes have been demonstrated with allogeneic stem cell transplantation. As a group, bone marrow failure and congenital immunodeficiency disorders, as well as inborn errors of metabolism are rare. As a result, the worldwide experience with UCB transplantation is limited. Despite this, it is clear that UCB has proven to be a viable and effective stem cell source that will continue to play a major role in allogeneic stem cell therapy.

Use of UCB stem cell grafts for allogeneic transplantation; historical perspective

The 1988 report of successful engraftment and outcome of a patient with Fanconi anemia who was transplanted with cord blood

from a new-born HLA-identical sibling, generated considerable interest in further development of this novel transplant approach [15]. From 1988 until 1993, UCB transplants were limited to grafts collected from HLA-identical related donors. This early experience was important in that it confirmed the pre-clinical observation that contained within the UCB graft were true pluripotent long-term repopulating cells. What also became apparent from the early experience was that the graft vs host disease (GvHD)-inducing potential of HLA-matched related cord blood T-cells was less than been observed with similarly matched bone marrow grafts [37, 47]. The encouraging results in matched related donor cord blood transplantation prompted Kurtzberg and colleagues to perform the first mismatched cord blood transplantation [24]. This series of three patients and the larger series later reported by Wagner and colleagues were notable for the engraftment potential and low GvHD potential of these unrelated, cryopreserved cells [24, 48]. Due to the limited number of stem cells contained within the cord blood graft, early experience was restricted primarily to children where the UCB cell dose relative to body weight was more favorable. However, as promising outcome data began to emerge from large UCB bank and international registry studies, the experience in adult patients began to grow.

In recent years, great strides have been made in identifying factors predictive of successful outcome. The two most important characteristics of an UCB graft are the cellular content and donor-recipient HLA-matching. It is generally accepted that a total nucleated cell dose under 2 x 10^7/kg recipient body weight results in an unacceptably high rate of graft failure. CD34+ cell content and colony forming unit potential of the donor graft have also proven to be predictive of donor cell engraftment [25]. However, practical issues surrounding accurate characterization of prospective units for their progenitor cell content remain to be worked out. For example, while CD34+ cell content is often enumerated by individual cord blood banks prior to cryopreservation, there remains considerable concern that inter-bank comparison of these values is not valid due to subtle differences in CD34+ quantification techniques. Therefore, choosing cord blood units based on CD34+ cell content as measured by different banks is not yet realistic.

As the outcome data are presented in this review, it is important to remember that earlier results were significantly compromised by lack of a clear understanding of the many factors that contribute to successful UCB transplantation. While advances in supportive care, patient selection, and transplantation techniques have improved outcomes of allogeneic stem cell transplantation as a whole, the advances are more pronounced with UCB transplantation.

Umbilical cord blood transplantation for inherited immunodeficiency disorders

Lymphoid immunodeficiency disorders

Severe Combined Immunodeficiency Disorders (SCID)

Included in this discussion of UCB transplantation for SCID will be the classical form of SCID characterized by an X-linked mutation of the common gamma-chain, adenosine deaminase deficient SCID, autosomal recessive SCID, and Omenn syndrome. Data on cord blood transplantation for treatment of these disorders remain scant. The largest single center series comes from Diaz de Heredia and colleagues who report the outcomes of 12 SCID patients (median age 11.6 months) transplanted with UCB at three Spanish hospitals between 1996 and 2002 [10]. All but 2 patients received a high dose busulfan/cyclophosphamide preparative regimen. Two patients received a reduced intensity melphalan/fludarabine preparative regimen. All patients achieved donor stem cell engraftment. The 5-year overall survival (which includes 3 additional patients with non-SCID immunodeficiency disorders) was 73%, with 3 patients dying from graft versus host disease, and one from progressive interstitial lung disease. Importantly, all surviving children had normal age-adjusted levels of T-cells, B-cells and NK cells by 24 months following transplantation. In contrast to what has been observed following stem cell transplantation without conditioning, quantitative and qualitative T-cell and B-cell functions are durable following UCB transplantation using high intensity transplant conditioning.

The outcomes of 16 children transplanted with UCB for treatment of SCID are reported in three separate retrospective reports [5, 22, 45]. One of 16 failed to engraft, and 13 of 16 are long-term survivors with normalization of immune function.

Wiscott-Aldrich Syndrome

Wiscott-Aldrich Syndrome (WAS) is due to an X-linked mutation in the WASP gene, with an incidence of 4 per million live male births. The role of stem cell transplantation for treatment of this disorder has been firmly established. The initial reports demonstrated cure rates as high as 89% when matched unrelated donor transplantation is performed before the age of 5 years [13]. The published experience of UCB transplantation for WAS has grown significantly in the past few years. In 2003, Knutsen and colleagues were among the first to demonstrate feasibility of UCB transplantation for WAS with successful treatment of 3 children age 2–8 yrs [21]. More recently, the Duke University group reported the outcome of 15 patients transplanted with UCB between 1998 and 2007 [42]. All patients achieved donor cell engraftment following a conditioning regimen consisting of busulfan, cyclophosphamide, +/- ATG. Six of 15 patients died from transplant-related complications, resulting in an overall survival of 60%. Chronic GvHD was observed in 11 of 12 surviving patients (limited in 10, extensive in 1). The authors found this incidence of chronic GvHD to be in excess of what has been observed in other patients with congenital immunodeficiency disorders transplanted with UCB. They postulate a potential link to pre-existing eczema, which is commonly seen in patients with WAS.

A recent review of registry data collected by the CIBMTR (unpublished) compared 113 WAS recipients of unrelated bone marrow with 65 WAS recipients of unrelated cord blood transplants carried out between 1995 and 2005. This analysis showed equivalent 3-year survival for recipients age <5 years at the time of transplantation (73% vs 75%). Taken together, these data support the use of UCB for stem cell transplantation of WAS.

The CIBMTR has received registration reports of UCB transplantation for other rare lymphoid immunodeficiency disorders. These include Cartilage Hair Hypoplasia, X-linked Lymphoproliferative syndrome, Common Variable Immunodeficiency, Reticular dysgenesis and Bare Lymphocyte syndrome. Unfortunately, the outcomes of these transplants are not available for review.

Myeloid immunodeficiency disorders

Chronic Granulomatous Disease (CGD)

CGD is a congenital neutrophil disorder that is a consequence of an X-linked or autosomal recessive mutation in the NADPH-oxidase complex. The curative potential of stem cell transplantation has been clearly demonstrated [17, 40]. There are 8 reported cases of UCB transplantation for CGD [4, 31, 32, 35, 43]. Reduced intensity conditioning was successfully used in the oldest patient of this compilation of reports (age 20 yrs). The others were conditioned with high intensity regimen; 2 experienced primary graft failure. Six of 8 patients are long-term survivors.

Leukocyte adhesion deficiency is another life-threatening myeloid immune disorder. To date, there are no published reports of UCB transplantation for treatment of this disorder.

Immune/Inflammatory disorders

Hemophagocytic Lymphohistiocytosis (HLH)

The familial or inherited form of HLH as well as the EBV-associated HLH will be considered together in this review. In general, the outcomes of allogeneic stem cell transplantation following high dose conditioning, regardless of the stem cell source, are not as favorable as that observed for other inherited immunodeficiencies. This has prompted a movement toward the use of reduced intensity preparative regimens for this disorder [8]. Ohga and colleagues recently reviewed data from the Japanese Society of Pediatric Hematology [34]. Outcomes of 57 patients (familial HLA-43, EBV-associated HLH-14), 21 of whom received UCB grafts, are reported. The overall survival by log-rank analysis of the UCB transplant recipients was 66%, which did not differ from recipients of related or unrelated bone marrow or peripheral blood stem cell transplantation.

Chediak-Higashi

The team from the University of California at Los Angeles has reported in abstract form successful UCB transplantation of 3 patients with Chediak-Higashi. Limited information is available on long-term outcome [50].

Umbilical cord blood transplantation for inborn errors of metabolism

Current data supports the use of allogeneic stem cell transplantation for the treatment of lysosomal and peroxisomal storage disorders. Enzyme replacement therapies are currently available, but questions remain as to the long-term efficacy of these therapies and their ability to positively impact the natural history of the disorder. Stem cell transplantation provides the opportunity for enzyme replacement via "cross correction" of enzyme-deficient cells by neighboring donor derived, enzyme-replete cells [9, 20]. Furthermore, stem cell transplantation (and UCB transplantation in particular) provides the potential for repair of damaged non-hematopoietic tissue such as microglial cells in the brain and Kupffer cells in the liver via differentiation of tissue-specific progenitor cells or transdifferentiation.

Lysosomal and peroxisomal storage diseases affect multiple organ systems, with the central and peripheral nervous system particularly impacted. Depending on the extent of damage at the time of stem cell transplantation, the impact of allogeneic SCT may require extensive and sophisticated neurocognitive testing to objectively measure response. It is clear that many of the neurocognitive deficits incurred by the patients will not be corrected by stem cell transplantation. However, a plateau in survival appears to be evident from a large, single center series of UCB transplants for inherited metabolic disorders [36, Fig. 3]. Longer follow-up and more experience will be required to optimize the timing and impact of this treatment modality.

Krabbe's disease

The potential for UCB transplantation to favorably impact on the natural history of inborn errors of metabolism was elegantly demonstrated by Escolar and colleagues in patients with Krabbe's disease [11]. Children born with Krabbe's disease are deficient of the lysosomal enzyme galactocerebrosidase. As a result, the children experience rapidly progressive neurologic deterioration and death at an early age. Escolar et al found that when children undergo UCB transplantation prior to the onset of symptoms, most will go on to have age-appropriate cognitive and motor function, along with 100% overall survival. Those who underwent UCB transplantation after the onset of symptoms showed little improvement in neurologic function and had an overall survival of only 43%. The study demonstrates the importance of early recognition of inborn errors along with early intervention with stem cell transplantation before irreversible damage occurs.

Hurler's syndrome

Hurler's syndrome is an autosomal recessive mucopolysaccharidosis caused by deficiency of alpha-L-iduronidase. Multiple organs, including the central nervous system, heart, bone, eyes, and liver are affected. Although enzyme replacement therapy has been available since 2003, due to poor CNS penetration, it does not completely prevent neurologic deterioration. Therefore, allogeneic stem cell transplantation remains the treatment of choice. Both European and North American registry data suggest that over 500 patients with Hurler's syndrome have been treated with allogeneic stem cell transplantation. Staba and colleagues reported the Duke University experience with UCB transplantation for 20 children with Hurler's syndrome [41]. The patients were prepared with high dose conditioning and received UCB units from mismatched unrelated donors. The median cell dose was $8.8x10^7$ nucleated cells/kg. Only one patient failed to engraft with donor cells. Long-term survival was achieved in 17 of 20 patients with all surviving patients having normal alpha-L-iduronidase activity. Many of the surviving children continue to have neurocognitive impairment. Despite this, 81% of the surviving school-age children attend school in age-appropriate classrooms [36]. However, many Hurler's patients continue to have problems with skeletal deformities that require corrective surgery.

Boelens and colleagues reviewed data from the European Blood and Marrow Transplant Registry regarding outcome of patients with Hurler's syndrome undergoing allogeneic transplantation [6]. While overall survival was not affected by cell source selection, the data suggested that UCB grafts significantly improved

the chance for achieving full donor chimerism and, as a result, normal circulating enzyme levels compared to patients receiving peripheral blood or bone marrow grafts.

X-linked Adrenoleukodystrophy (X-ALD)

X-ALD is a peroxisomal disorder stemming from a defective ABCD1 gene. This results in accumulation of long chain fatty acids, which has devastating neurologic consequences. The therapeutic potential of UCB transplantation was best described by Beam and colleagues who report the outcomes of 12 boys, 3 of whom were transplanted early in life, before symptoms of the disease developed [3]. All patients received high dose conditioning with busulfan, cyclophosphamide, and anti-thymocyte globulin followed by partially matched unrelated UCB transplantation. Extensive baseline neurophysiologic, neuroimaging and neurodevelopmental testing was performed prior to transplantation and followed serially after the transplantation. One patient died early from toxicity and another experienced primary graft failure, but was rescued with a second transplant. Overall survival at 6 months was 67%. The authors found that the degree of pre-transplant ALD-associated brain involvement (Loes score) was a strong predictor of post-transplantation cognitive and motor outcome. Many of the patients with severe neurocognitive impairment at the time of transplantation experienced disease progression despite transplantation. In contrast, the 3 boys who were asymptomatic at the time of transplant had excellent outcomes.

Composite reports of UCB transplantation for rare inborn errors

Disease-specific reports of allogeneic transplantation for rare inborn errors of metabolism lack the detail or sample size to draw definitive conclusions about outcomes [30, 36, 44]. Table 1 lists the disorders that have been treated with UCB transplantation. Questions remain as to the appropriate timing for the transplant as well as the therapeutic benefit. It is for this reason that use of allogeneic SCT for treatment of many of these disorders remains investigational.

Hurler syndrome
Krabbe‘s disease
Sanfilippo syndrome
Metachromatic leukodystrophy
Adrenoleukodystrophy
Tay Sachs disease
Hunter syndrome
Lesch-Nyhan disease
Sandhoff disease
Hurler Scheie
Neimann-Pick
Alpha mannosidosis
GM1 gangliosidosis
I-cell disease
Maroteaux-Lamy syndrome
Pelizaeus-Merzbacher disease
Fucosidosis
Wolman disease (Acid Lipase Deficiency)

Table 1. Inborn metabolism errors treated with umbilical cord blood transplantation

The common theme among all the reports is that the earlier the transplant is done, the better the outcome. In the largest of these composite reports from the Duke University group, 159 children representing 16 different inborn errors of metabolism were transplanted following high dose conditioning (busulfan, cyclophosphamide, and equine anti-thymocyte globulin) over a 12-year period, ending in 2007. The probability of engraftment, acute and chronic GvHD, overall survival and factors influencing survival has been shown [36, Fig. 1]. Of note, the 1 and 5 year overall survivals for the most common disorders treated on the study (Hurler, Hunter, and Sanfilippo syndrome, metachromatic leukodystrophy, and adrenoleukodystrophy) were all similar. This suggests that timing of the transplant, not the underlying disease, is most important in predicting outcome.

Umbilical cord blood transplantation for hemoglobinopathies

Related UCB transplantation for β-thalassemia and sickle cell disease

Unlike the situation with inborn errors of metabolism, there is an established role for allogeneic stem cell transplantation for the treatment of β-thalassemia and sickle cell disease [27, 28, 49]. The published experience of UCB transplantation for β-thalassemia remains quite limited [12, 26]. The largest report comes from the Eurocord registry data describing the outcome of 33 β-thalassemia patients transplanted with matched related UCB grafts [26]. All patients had a low disease severity (Pesaro 1 in 20 pts, Pesaro 2 in 13 pts). All patients received high dose e conditioning and GvHD prophylaxis with cyclosporine alone or combined with methotrexate. Seven of 33 patients experienced graft failure, but were rescued with either autologous stem cells or bone marrow from the original matched sibling cord blood donor at a later date. With a median follow-up of 24 months, all 33 patients were alive and well, but 4 retained the β-thalassemia phenotype.

The Locatelli report also included outcomes of 11 patients with sickle cell disease transplanted with UCB from related donors matched 6/6 (9 pts) or 5/6 (2 pts) [26]. The conditioning and GvHD prophylaxis regimens were similar to those used for the β-thalassemia patients. Primary engraftment was achieved in 10 of 11 patients, and all 11 patients are alive and well (1 with sickle cell disease) with a median follow-up of 24 months.

Unrelated UCB transplantation for β-thalassemia and sickle cell disease

There has yet to be enough published experience with unrelated UCB transplantation for β-thalassemia or sickle cell disease to fully assess the risk versus benefit considerations. The relative dearth of reports in the literature likely portrays unresolved challenges that remain with this mode of therapy. The few available reports suggest feasibility of unrelated UCB transplantation for hemoglobinopathies [1, 18, 19, 46]. However, it appears that establishment of stable donor engraftment is more challenging in this population of patients [1]. This may be related to the chemotherapy naïve status of the patients combined with a highly proliferative, cellular bone marrow milieu.

Umbilical cord blood transplantation for bone marrow failure disorders

The published experience with UCB for treatment of acquired bone marrow failure disorders is outlined in Table 2. Most investigators have relegated UCB transplantation to a treatment of last resort. Thus, those transplanted with UCB represent an extremely high-risk subset of patients who have failed prior therapy. Interpretation of the data is further compromised by the heterogeneous transplantation techniques. The data suggests that UCB transplantation for severe aplastic anemia is feasible. Larger studies will be needed to garner a better understanding of the relative risk of graft failure compared to patients with other non-malignant or malignant disorders.

References

1. Adamkiewicz, T.V., Mehta, P.S., Boyer, M.W., Kedar, A., Olson, T.A., Olson, E., Chiang, K.Y., Maurer, D., Mogul, M.J., Wingard, J.R. & Yeager, A.M. (2004) Transplantation of unrelated placental blood cells in children with high-risk sickle cell disease. Bone Marrow Transplant, 34, 405-411.

2. Barker, J.N., Krepski, T.P., DeFor, T.E., Davies, S.M., Wagner, J.E. & Weisdorf, D.J. (2002) Searching for unrelated donor hematopoietic stem cells: availability and speed of umbilical cord blood versus bone marrow. Biol Blood Marrow Transplant, 8, 257-260.

3. Beam, D., Poe, M.D., Provenzale, J.M., Szabolcs, P., Martin, P.L., Prasad, V., Parikh, S., Driscoll, T., Mukundan, S., Kurtzberg, J. & Escolar, M.L. (2007) Outcomes of unrelated umbilical cord blood transplantation for X-linked adrenoleukodystrophy. Biol Blood Marrow Transplant, 13, 665-674.

4. Bhattacharya, A., Slatter, M., Curtis, A., Chapman, C.E., Barge, D., Jackson, A., Flood, T.J., Abinun, M., Cant, A.J. & Gennery, A.R. (2003) Successful umbilical cord blood stem cell transplantation for chronic granulomatous disease. Bone Marrow Transplant, 31, 403-405.

5. Bhattacharya, A., Slatter, M.A., Chapman, C.E., Barge, D., Jackson, A., Flood, T.J., Abinun, M., Cant, A.J. & Gennery, A.R. (2005) Single centre experience of umbilical cord stem cell transplantation for primary immunodeficiency. Bone Marrow Transplant, 36, 295-299.

6. Boelens, J.J., Wynn, R.F., O'Meara, A., Veys, P., Bertrand, Y., Souillet, G., Wraith, J.E., Fischer, A., Cavazzana-Calvo, M., Sykora, K.W., Sedlacek, P., Rovelli, A., Uiterwaal, C.S. & Wulffraat, N. (2007) Outcomes of hematopoietic stem cell transplantation for Hurler's syndrome in Europe: a risk factor analysis for graft failure. Bone Marrow Transplant, 40, 225-233.

7. Chan, K.W., McDonald, L., Lim, D., Grimley, M.S., Grayson, G. & Wall, D.A. (2008) Unrelated cord blood transplantation in children with idiopathic severe aplastic anemia. Bone Marrow Transplant, 42, 589-595.

8. Cooper, N., Rao, K., Goulden, N., Webb, D., Amrolia, P. & Veys, P. (2008) The use of reduced-intensity stem cell transplantation in haemophagocytic lymphohistiocytosis and Langerhans cell histiocytosis. Bone Marrow Transplant, 42 Suppl 2, S47-50.

9. Di Ferrante, N., Nichols, B.L., Donnelly, P.V., Neri, G., Hrgovcic, R. & Berglund, R.K. (1971) Induced degradation of glycosaminoglycans in Hurler's and Hunter's syndromes by plasma infusion. Proc Natl Acad Sci U S A, 68, 303-307.

10. Diaz de Heredia, C., Ortega, J.J., Diaz, M.A., Olive, T., Badell, I., Gonzalez-Vicent, M. & Sanchez de Toledo, J. (2008) Unrelated cord blood transplantation for severe combined immunodeficiency and other primary immunodeficiencies. Bone Marrow Transplant, 41, 627-633.

11. Escolar, M.L., Poe, M.D., Provenzale, J.M., Richards, K.C., Allison, J., Wood, S., Wenger, D.A., Pietryga, D., Wall, D., Champagne, M., Morse, R., Krivit, W. & Kurtzberg, J. (2005) Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med, 352, 2069-2081.

12. Fang, J., Huang, S., Chen, C., Zhou, D., Li, C.K., Li, Y. & Huang, K. (2004) Umbilical cord blood transplantation in Chinese children with beta-thalassemia. J Pediatr Hematol Oncol, 26, 185-189.

13. Filipovich, A.H., Stone, J.V., Tomany, S.C., Ireland, M., Kollman, C., Pelz, C.J., Casper, J.T., Cowan, M.J., Edwards, J.R., Fasth, A., Gale, R.P., Junker, A., Kamani, N.R., Loechelt, B.J., Pietryga, D.W., Ringden, O., Vowels, M., Hegland, J., Williams, A.V., Klein, J.P., Sobocinski, K.A., Rowlings, P.A. & Horowitz, M.M. (2001) Impact of donor type on outcome of bone marrow transplantation for Wiskott-Aldrich syndrome: collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program. Blood, 97, 1598-1603.

Reference	Disorder-number of patients	Median Age (yrs)	Preparative Regimen	Median Cryopreserved Cell Dose (x 10^7/kg)	Percent donor engraftment (%)	Outcome (%)
(Mao, et al 2005)	AA-9	25	Cy/ATG	2.19 (1.6-10.7)*	78	EFS-78 OS-78
(Ohga, et al 2006)	AA-1	11	TBI-5Gy Melphalan 120mg/m^2 Fludarabine 120mg/m^2	3.9	100	EFS-100 OS-100
(Chan, et al 2008)	AA-9	9	Cy/ATG-2 Cy/Flu/ATG-7	5.4 (3.5-20)	67	EFS-67 OS-78
(Yoshimi, et al 2008)	AA-31	28	TBI (4-5Gy)/Flu/Mel-12 TBI (4-5Gy)/Flu/Cy-5 TBI (10-12Gy)/Cy/ ATG-3 Other-11	NA	55	OS (2yrs)-41
(Ruggeri, et al 2008)	SAA-4 PNH-1	19	Bu/Cy/Flu-3 Flu/Cy-1 Flu/Cy/TBI(2Gy)	4.7 (2.9-9.7) (Dual Cord Blood Graft)	80	EFS-60 OS-80

*Post-thaw cell dose (cryopreserved cell dose not reported)

Table 2. Umbilical cord blood transplantation for treatment of severe aplastic anemia and paroxysmal nocturnal hemoglobinurea

15. Gluckman, E., Broxmeyer, H.A., Auerbach, A.D., Friedman, H.S., Douglas, G.W., Devergie, A., Esperou, H., Thierry, D., Socie, G., Lehn, P. & et al. (1989, now open access in this issue of CTT) Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. N Engl J Med, 321, 1174-1178.

16. Gluckman, E.G., Roch, V.V. & Chastang, C. (1997) Use of Cord Blood Cells for Banking and Transplant. Oncologist, 2, 340-343.

17. Horwitz ME, B.A., Brown BS, Carter CS, Childs R, Gallin J, Holland S, Linton GF, Miller JA, Leitman SF, Read EJ, Malech HL (2001) Treatment of Chronic Granulomatous Disease with Nonmyeloablative Conditioning and a T-cell Depleted Hematopoietic Allograft. N Engl J Med, 344, 881.

18. Jaing, T.H., Hung, I.J., Yang, C.P., Chen, S.H., Sun, C.F. & Chow, R. (2005) Rapid and complete donor chimerism after unrelated mismatched cord blood transplantation in 5 children with beta-thalassemia major. Biol Blood Marrow Transplant, 11, 349-353.

19. Jaing, T.H., Yang, C.P., Hung, I.J., Chen, S.H., Sun, C.F. & Chow, R. (2007) Transplantation of unrelated donor umbilical cord blood utilizing double-unit grafts for five teenagers with transfusion-dependent thalassemia. Bone Marrow Transplant, 40, 307-311.

20. Knudson, A.G., Jr., Di Ferrante, N. & Curtis, J.E. (1971) Effect of leukocyte transfusion in a child with type II mucopolysaccharidosis. Proc Natl Acad Sci U S A, 68, 1738-1741.

21. Knutsen, A.P., Steffen, M., Wassmer, K. & Wall, D.A. (2003) Umbilical cord blood transplantation in Wiskott Aldrich syndrome. J Pediatr, 142, 519-523.

22. Knutsen, A.P. & Wall, D.A. (2000) Umbilical cord blood transplantation in severe T-cell immunodeficiency disorders: two-year experience. J Clin Immunol, 20, 466-476.

23. Kurtzberg, J. (2009) Update on umbilical cord blood transplantation. Curr Opin Pediatr, 21, 22-29.

24. Kurtzberg, J., Graham, M., Casey, J., Olson, J., Stevens, C.E. & Rubinstein, P. (1994) The use of umbilical cord blood in mismatched related and unrelated hemopoietic stem cell transplantation. Blood Cells, 20, 275-283; discussion 284.

25. Kurtzberg, J., Prasad, V.K., Carter, S.L., Wagner, J.E., Baxter-Lowe, L.A., Wall, D., Kapoor, N., Guinan, E.C., Feig, S.A., Wagner, E.L. & Kernan, N.A. (2008) Results of the Cord Blood Transplantation Study (COBLT): clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies. Blood, 112, 4318-4327.

26. Locatelli, F., Rocha, V., Reed, W., Bernaudin, F., Ertem, M., Grafakos, S., Brichard, B., Li, X., Nagler, A., Giorgiani, G., Haut, P.R., Brochstein, J.A., Nugent, D.J., Blatt, J., Woodard, P., Kurtzberg, J., Rubin, C.M., Miniero, R., Lutz, P., Raja, T., Roberts, I., Will, A.M., Yaniv, I., Vermylen, C., Tannoia, N., Garnier, F., Ionescu, I., Walters, M.C., Lubin, B.H. & Gluckman, E. (2003) Related umbilical cord blood transplantation in patients with thalassemia and sickle cell disease. Blood, 101, 2137-2143.

27. Lucarelli, G., Clift, R.A., Galimberti, M., Polchi, P., Angelucci, E., Baronciani, D., Giardini, C., Andreani, M., Manna, M., Nesci, S., Agostinelli, F., Rapa, S., Ripalti, M. & Albertini, F. (1996) Marrow transplantation for patients with thalassemia: results in class 3 patients. Blood, 87, 2082-2088.

28. Lucarelli, G., Galimberti, M., Polchi, P., Angelucci, E., Baronciani, D., Giardini, C., Politi, P., Durazzi, S.M., Muretto, P. & Albertini, F. (1990) Bone marrow transplantation in patients with thalassemia. N Engl J Med, 322, 417-421.

29. Mao, P., Zhu, Z., Wang, H., Wang, S., Mo, W., Ying, Y., Li, Q. & Xu, Y. (2005) Sustained and stable hematopoietic donor-recipient mixed chimerism after unrelated cord blood transplantation for adult patients with severe aplastic anemia. Eur J Haematol, 75, 430-435.

30. Martin, P.L., Carter, S.L., Kernan, N.A., Sahdev, I., Wall, D., Pietryga, D., Wagner, J.E. & Kurtzberg, J. (2006) Results of the cord blood transplantation study (COBLT): outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with lysosomal and peroxisomal storage diseases. Biol Blood Marrow Transplant, 12, 184-194.

31. Mochizuki, K., Kikuta, A., Ito, M., Akaihata, M., Sano, H., Ohto, H. & Hosoya, M. (2009) Successful unrelated cord blood transplantation for chronic granulomatous disease: a case report and review of the literature. Pediatr Transplant, 13, 384-389.

32. Nakano, T., Boku, E., Yoshioka, A. & Fujimura, Y. (1999) A Case of McLeod Phenotype Chronic Granulomatous Disease who Received Unrelated Cord Blood Transplantation. Journal of Pediatric Hematology, 12, 264.

33. Ohga, S., Ichino, K., Goto, K., Hattori, S., Nomura, A., Takada, H., Nakamura, K. & Hara, T. (2006) Unrelated donor cord blood transplantation for childhood severe aplastic anemia after a modified conditioning. Pediatr Transplant, 10, 497-500.

34. Ohga, S., Kudo, K., Ishii, E., Honjo, S., Morimoto, A., Osugi, Y., Sawada, A., Inoue, M., Tabuchi, K., Suzuki, N., Ishida, Y., Imashuku, S., Kato, S. & Hara, T. (2009) Hematopoietic stem cell transplantation for familial hemophagocytic lymphohistiocytosis and Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in Japan. Pediatr Blood Cancer, 54, 299-306.

35. Parikh, S.H., Szabolcs, P., Prasad, V.K., Lakshminarayanan, S., Martin, P.L., Driscoll, T.A. & Kurtzberg, J. (2007) Correction of chronic granulomatous disease after second unrelated-donor umbilical cord blood transplantation. Pediatr Blood Cancer, 49, 982-984.

36. Prasad, V.K., Mendizabal, A., Parikh, S.H., Szabolcs, P., Driscoll, T.A., Page, K., Lakshminarayanan, S., Allison, J., Wood, S., Semmel, D., Escolar, M.L., Martin, P.L., Carter, S. & Kurtzberg, J. (2008) Unrelated donor umbilical cord blood transplantation for inherited metabolic disorders in 159 pediatric patients from a single center: influence of cellular composition of the graft on transplantation outcomes. Blood, 112, 2979-2989. Figure 3. Figure 1.

37. Rocha, V., Wagner, J.E., Jr., Sobocinski, K.A., Klein, J.P., Zhang, M.J., Horowitz, M.M. & Gluckman, E. (2000) Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. Eurocord and International Bone Marrow Transplant Registry Working Committee on Alternative Donor and Stem Cell Sources. N Engl J Med, 342, 1846-1854.

38. Rogers, I., Yamanaka, N., Bielecki, R., Wong, C.J., Chua, S., Yuen, S. & Casper, R.F. (2007) Identification and analysis of in vitro cultured CD45-positive cells capable of multi-lineage differentiation. Exp Cell Res, 313, 1839-1852.

39. Ruggeri, A., de Latour, R.P., Rocha, V., Larghero, J., Robin, M., Rodrigues, C.A., Traineau, R., Ribaud, P., Ferry, C., Devergie, A., Gluckman, E. & Socie, G. (2008) Double cord blood transplantation in patients with high risk bone marrow failure syndromes. Br J Haematol, 143, 404-408.

40. Seger, R.A., Gungor, T., Belohradsky, B.H., Blanche, S., Bordigoni, P., Di Bartolomeo, P., Flood, T., Landais, P., Muller, S., Ozsahin, H., Passwell, J.H., Porta, F., Slavin, S., Wulffraat, N., Zintl, F., Nagler, A., Cant, A. & Fischer, A. (2002) Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985-2000. Blood, 100, 4344-4350.

41. Staba, S.L., Escolar, M.L., Poe, M., Kim, Y., Martin, P.L., Szabolcs, P., Allison-Thacker, J., Wood, S., Wenger, D.A., Rubinstein, P., Hopwood, J.J., Krivit, W. & Kurtzberg, J. (2004) Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. N Engl J Med, 350, 1960-1969.

42. Sun, J.M., Driscoll, T., Prasad, V.K., Parikh, S.H., Szabolcs, P., Kurtzberg, J. & Martin, P. (2009) Unrelated Umbilical Cord Blood Transplantation is an Effective Therapy for Wiskott-Aldrich Syndrome. Biol Blood Marrow Transplant, 15, 76.

43. Suzuki, N., Hatakeyama, N., Yamamoto, M., Mizue, N., Kuroiwa, Y., Yoda, M., Takahashi, J., Tani, Y. & Tsutsumi, H. (2007) Treatment of McLeod phenotype chronic granulomatous disease with reduced-intensity conditioning and unrelated-donor umbilical cord blood transplantation. Int J Hematol, 85, 70-72.

44. Tokimasa, S., Ohta, H., Takizawa, S., Kusuki, S., Hashii, Y., Sakai, N., Taniike, M., Ozono, K. & Hara, J. (2008) Umbilical cord-blood transplantations from unrelated donors in patients with inherited metabolic diseases: Single-institute experience. Pediatr Transplant, 12, 672-676.

45. Tsuji, Y., Imai, K., Kajiwara, M., Aoki, Y., Isoda, T., Tomizawa, D., Imai, M., Ito, S., Maeda, H., Minegishi, Y., Ohkawa, H., Yata, J., Sasaki, N., Kogawa, K., Nagasawa, M., Morio, T., Nonoyama, S. & Mizutani, S. (2006) Hematopoietic stem cell transplantation for 30 patients with primary immunodeficiency diseases: 20 years experience of a single team. Bone Marrow Transplant, 37, 469-477.

46. Vanichsetakul, P., Wacharaprechanont, T., R, O.C., Seksarn, P. & Kupatawintu, P. (2004) Umbilical cord blood transplantation in children with beta-thalassemia diseases. J Med Assoc Thai, 87 Suppl 2, S62-67.

47. Wagner, J.E., Kernan, N.A., Steinbuch, M., Broxmeyer, H.E. & Gluckman, E. (1995) Allogeneic sibling umbilical-cord-blood transplantation in children with malignant and non-malignant disease.[see comment]. Lancet, 346, 214-219.

48. Wagner, J.E., Rosenthal, J., Sweetman, R., Shu, X.O., Davies, S.M., Ramsay, N.K., McGlave, P.B., Sender, L. & Cairo, M.S. (1996) Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. Blood, 88, 795-802.

49. Walters, M.C., Storb, R., Patience, M., Leisenring, W., Taylor, T., Sanders, J.E., Buchanan, G.E., Rogers, Z.R., Dinndorf, P., Davies, S.C., Roberts, I.A., Dickerhoff, R., Yeager, A.M., Hsu, L., Kurtzberg, J., Ohene-Frempong, K., Bunin, N., Bernaudin, F., Wong, W.Y., Scott, J.P., Margolis, D., Vichinsky, E., Wall, D.A., Wayne, A.S., Pegelow, C., Redding-Lallinger, R., Wiley, J., Klemperer, M., Mentzer, W.C., Smith, F.O. & Sullivan, K.M. (2000) Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. Blood, 95, 1918-1924.

50. Wang, K., Lin, E., Moore, T. & Roberts, R. (2009) Cord Blood Transplantation for Treatment of Chediak-Higashi Syndrome. Clinical Immunology, 131, S77-S78.

51. Yoshimi, A., Kojima, S., Taniguchi, S., Hara, J., Matsui, T., Takahashi, Y., Azuma, H., Kato, K., Nagamura-Inoue, T., Kai, S. & Kato, S. (2008) Unrelated cord blood transplantation for severe apastic anemia. Biol Blood Marrow Transplant, 14, 1057-1063.