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REVIEW

Emerging trends in transplantation of inherited metabolic diseases

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Allogeneic hematopoietic stem cell transplantation (HSCT) can prolong life and improve its quality in patients with inherited metabolic diseases. HSCT offers a permanent source of enzyme replacement therapy and also might mediate nonhematopoietic cell regeneration or repair. Unrelated cord blood is an exciting newer graft source for treatment of patients with these fatal disorders, providing increased access to donors and significant clinical efficacy, particularly when transplantation is performed in early stages. Pre-transplant performance status is highly predictive of overall survival.
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Introduction

Hematopoietic stem cell transplantation (HSCT), in its various forms has emerged as a viable option for the long-term treatment of young patients with selected inherited metabolic disorders (IMD).[1–10] Recent reports from European and American collaborative studies suggest that there is growing acceptance of this form of therapy.[3,11,12] In this report, we review the published literature using HSCT to treat IMD and also review recent results of umbilical cord blood transplantation for this indication. In addition, we define the current status of the field, the scientific basis for efficacy of transplantation therapy, areas of debate, and future directions.

The first HSCT for IMD was performed in a patient with Hurler syndrome (mucopolysaccharidosis I, MPS I) in 1980 utilizing a bone marrow graft from a matched sibling donor which led to clinical and biochemical improvement.[13] Since that time, >1000 transplants from carrier and noncarrier, related and unrelated donors have been performed throughout the world. More recently, some patients have received unrelated donor (URD) umbilical cord blood transplants (UCBT).[11,12,14–17]

In the short term, HSCT has favorably impacted the clinical outcomes of patients with IMD. However, because of limited follow-up, the long-term effects of treatment on the natural history of these disorders and the impact of myeloablative therapy are unknown. Recent reports, particularly from UCBT, suggest that there will be tremendous benefit if the transplants are performed early in the course of these diseases, prior to the development of neurologic and other deficits. Specific host and donor characteristics have impact on immediate transplant outcomes (for example, engraftment, GVHD and survival) but the final measures of success must be benchmarked against clinical development, neurocognitive abilities and non-hematopoietic organ function.

Scientific basis of HSCT

HSCT has primarily been used to treat IMDs belonging to the family of lysosomal and peroxisomal storage disorders (PSD) (Table 1). Lysosomal storage disorders (LSD) consist of many different rare diseases each caused by a single gene defect, inherited in an autosomal recessive pattern (except Hunter, Fabry and Danon syndromes), leading to specific enzyme deficiencies which result in defective lysosomal acid hydrolysis of endogenous macromolecules and consequent accumulation of a toxic substrate. The PSD like adrenoleukodystrophy (ALD) stems from a defect in the membrane transporter protein ABCD1 leading to defects in the metabolism of long-chain fatty acids. Most LSD and PSD affect multiple organs and involve both the central and peripheral nervous systems. They are progressive in nature and frequently fatal in childhood from a combined effect of accumulation of toxic substrate(s) as well as a deficiency of the product of the enzyme reaction. Many also cause pathology within the reticuloendothelial system leading to hepatosplenomegaly with or without accompanying hematological abnormalities.

Lysosomal enzymes are glycoproteins synthesized in the endoplasmic reticulum, which migrate to the Golgi complex where they undergo further chemical modification. They are then incorporated into the endosomes and finally mature in the lysosomes following proteolysis, folding and aggregation. In the presence of cofactors, the lysosomal enzymes degrade their substrates that may be intracellular

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Table 1 Lysosomal and peroxisomal storage disorders: nomenclature, enzyme defects and chromosomal localization of the gene defects

Category	*Diagnosis*	*Other names*	*Gene*	*Enzyme defect*[a]
Mucopolysaccharidosis				
	MPS I	Hurler, Scheie, H–S	4p16.3	α-L-iduronidase
	MPS II	Hunter	Xq28	Iduronate sulfatase
	MPS III A–D	Sanfilippo A–D	17q25.3 (A)	Heparan N-sulfatase,
			17q21 (B)	α-*N*-acetylglucosaminidase,
			8p11.1 (C)	Acetyl CoA:α-glucosaminide acetyltransferase,
			12q14 (D)	*N*-acetylglucosamine 6-sulfatase
	MPS IV A–B	Morquio A–B	16q24.3 (A)	*N*-acetylgalactosamine-6-sulfatase (galactose-6-sulfatase)
			3p21.33 (B)	β-galactosidase
	MPS VI	Maroteaux–Lamy	5q11-q13	*N*-acetylgalactosamine 4-sulfatase (arylsulfatase B)
	MPS VII	Sly	7q21.11	β-Glucuronidase
Glycoproteinosis				
	Aspartylglucosaminuria		4q32-q33	*N*-aspartyl-β-glucosaminidase
	Fucosidosis		1p34	α-L-fucosidase
	α-Mannosidosis		19cen-q12	α-Mannosidase
	β-Mannosidosis		4q22-q25	β-Mannosidase
	Mucolipidosis III and IV	Sialidosis	16p, 12q23.3	*N*-acetylglucosamine-1-phosphotransferase (type III)
	Schindler disease		22q11	α-*N*-acetylgalactosaminidase
Sphingolipidosis				
	Fabry's		Xq22	α-Galactosidase A
	Farber's	Lipogranulomatosis	8p22-p21.3	*N*-Laurylsphingosine deacylase (ceramidase)
	Gaucher's I–III		1q21	β-Glucocerebrosidase
	GM_1 gangliosidosis		3p21.33	β-Galactosidase-1
	Niemann-Pick disease A and B		11p15.4-p15.1	Acid sphingomyelinase
	Tay-Sachs disease		15q23-q24	Hexosaminidase A
	Sandhoff's disease		5q13	Hexosaminidase A and B
	Globoid leukodystrophy	Krabbe disease	14q31	Galactocerebrosidase (galactosylceramide β-galactosidase)
	Metachromatic leukodystrophy	MLD	22q13.31-qter	Arylsulfatase A
Other lipidosis				
	Niemann-Pick disease C		18q11-q12	NPC1
	Wolman disease		10q24-q25	Acid lipase (cholesteryl ester hydrolase)
	Ceroid lipofuscinosis	Type III—Batten ds	16p12.1 (type III)	Palmitoyl-protein thioesterase-1
Glycogen storage				
	GSD type II	Pompe	17q25.2-q25.3	Acid α-glucosidase (acid maltase)
Multiple enzyme deficiency				
	Galactosialidosis			β-Galactosidase and neuraminidase
	Mucolipidosis type II	I-cell disease	12q23.3	Mutation in the GNPTAB gene leads to multiple enzyme deficiency
	Other mucolipidoses			
Lysosomal transport defects				
	Cystinosis		17p13	Cysteine transporter (cystinosin)
	Sialic acid storage disease		6q14-q15	Sialic acid transporter
	Salla disease		6q14-q15	Sialic acid transporter
Peroxisomal storage disorders (PSD)				
	Adrenoleukodystrophy	ALD	Xq28	ABCD1 transporter protein
	Adrenomyeloneuropathy	AMN	Xq28	ABCD1 transporter protein

[a]Alternate names are in parenthesis.
Source: OMIM database of Pubmed as of 12 November 2007.

or extracellular in origin. From the Golgi apparatus, a large portion of the newly synthesized enzyme is secreted into the cytoplasm, rather than being encapsulated into the lysosomes. This 'free' enzyme can be endocytosed by neighboring cells, generally via mannose 6 phosphate receptors on the plasma membranes. This intercellular transport enabled cross-correction of metabolic defects in coculture of healthy cells with fibroblasts from enzyme-deficient patients.[18] Cross-correction was also seen in cultures supplemented with lymphocytes extracts or serum.[19,20] Exogenous enzyme replacement therapy (ERT) and HSCT primarily utilize this cross-correction effect for therapeutic benefit. ERT has to be administered throughout the life of the patient and does not cross the blood–brain barrier. This results in ineffective treatment of the central nervous system in affected patients. In addition, ERT is currently only available for a limited number of diseases (MPS I, MPS II, MPS VI, Gaucher, Pompe, Fabry). Long-term ERT has also been associated with clinical hypersensitivity reactions and the development of antibodies against the synthetic enzyme.

HSCT provides a constant source of enzyme replacement through the engraftment of donor cells. In addition, the donor cells are not impeded by the blood–brain barrier allowing for enzyme delivery to the central nervous system. Following HSCT, donor-derived cells can migrate to and engraft in many organ systems. For example, donor-derived macrophages can give rise to Kupffer cells in the liver, alveolar macrophages in the lung and microglial cells in the brain. Continuous production of microglia, from donor-derived monocytes, provides a constant supply of the deficient enzyme and the close proximity of the microglial cells to the neurons allows for enzyme to be utilized by adjacent cells. This is supported by observations of decreased storage materials in neurons of cats with α-mannosidosis treated with bone marrow transplantation[21] and MPS VII mice treated with genetically modified fibroblasts.[22] In addition, in 2002, Passini *et al.*[23] demonstrated evidence of axonal transport of enzyme to distal areas of the brain in mice.

In recent years, there has been increasing interest in the potential uses of HSCT particularly with regards to their capacity for transdifferentiation, cellular repair and regeneration. In 2004, Kogler *et al.*[24] isolated 'unrestricted somatic stem cells' from unfractionated, fresh umbilical cord blood (UCB). They showed that these cells can be expanded and differentiated into neural cells (astrocytes and neurons), liver cells, pancreatic cells, osteoclasts, chondrocytes and cardiac myocytes in tissue culture. Other examples of donor-derived nonhematopoietic cell engraftment and differentiation have been seen after allogeneic bone marrow (BM) and cardiac transplantation.[25] Table 2 summarizes the likely processes responsible for the effectiveness of HSCT for IMD.

Table 2 Hematopoietic stem cell transplant in inborn metabolic diseases (IMD)

- Cytoreduction ablates myeloid and immune elements
- Engraftment of donor-derived hematopoietic and immune system
- Donor leukocytes produce enzyme
- Enzyme distributed through blood circulation
- Cells migrate to brain, cross blood–brain barrier, many develop microglia)
- Replace enzyme in the brain by 'cross-correction'
- Nonhematopoietic cell engraftment

Disease-specific applications

In the past 25 years, HSCT has emerged as a viable option for the treatment of many IMD that cause disorders of lysosomal and peroxisomal storage. HSCT has been performed in almost 20 of ~40 known LSD and PSD. However, the majority of transplant experience to date is in patients with MPS I (Hurler syndrome), other MPS syndromes (MPS II, MPS III A and B, MPS VI), ALD, metachromatic leukodystrophy (MLD) and globoid leukodystrophy (Krabbe disease) accounting for more than 80% of the cases (Table 3). ERT is also available for some of these disorders (Table 3). It is important to note that the response to HSCT varies from disease to disease, within patients with the same disease, and within different organ systems in the same patient. The factors affecting these variations will be further discussed in later sections.

Bone marrow transplantation

In the past 25 years, approximately 1000 HSCT for IMD have been reported.[1] The majority of this experience utilized matched related BM donors. The literature on BMT for IMD is well reviewed.[1,3,5,9] A smaller number of patients, presumably those lacking matched related donors, have received transplantation from T-cell-depleted mismatched related or matched unrelated adult BM or PBPC donors. The rates of engraftment and overall survival (OS) at 2 years in a group of 40 Hurler syndrome patients transplanted from unrelated BM donors at 14 different centers were 62.5 and 49%, respectively.[6] Of the survivors, approximately 30% had no donor cell engraftment. A retrospective analysis of 74 transplants for Hurler syndrome from URD BM or PBSC performed at 16 centers revealed an 'alive and engrafted' rate of $<55\%$ at 3.7 years follow-up with a higher engraftment rate for UCBT patients.[26] In a retrospective questionnaire-based analysis of 94 patients with ALD at 43 centers, of whom 52 received URD (83% BM) transplantation, the probability of OS following URD transplant was 53%.[8] In another study of haploidentical bone marrow transplant for Hurler disease, only 9 of 26 (35%) were engrafted and alive at a median follow-up of 4.6 years.

Umbilical cord blood transplantation

Recognition that UCB contains sufficient numbers of hematopoietic stem cells to reconstitute an allogeneic recipient and subsequent demonstration of clinical efficacy in humans has greatly increased the access to HSCT, particularly for patients lacking fully matched marrow donors. Currently, there are $>200\,000$ publicly banked cord blood units that have been collected from healthy

Table 3 Lysosomal and peroxisomal storage disorders: reports of bone marrow transplantation (BMT), umbilical cord blood transplantation (UCBT), and enzyme replacement therapy (ERT)

Category	*Diagnosis*	*BMT*	*UCBT*	*ERT*
Mucopolysaccharidosis				
	MPS I	Refs.[2,6,7,11,27]	Refs.[11,12,17]	Yes
	MPS II	SCR	Refs.[12]	Yes
	MPS III A–D	SCR	Refs.[12]	
	MPS IV A–B	SCR		
	MPS VI	SCR		Yes
	MPS VII			
Glycoproteinosis				
	Aspartylglucosaminuria	SCR		
	Fucosidosis	SCR		
	Mannosidosis α and β	SCR		
	β-Mannosidosis			
	Mucolipidosis I and II			
	Schindler disease			
Sphingolipidosis				
	Fabry's			Yes
	Farber's	SCR		
	Gaucher's I–III	SCR		Yes
	GM_1 gangliosidosis	SCR		
	Niemann-Pick disease A and B	SCR	SCR	
	Tay-Sachs disease	SCR		
	Sandhoff's disease			
	Krabbe disease	Refs.[2]	Refs.[12,15]	
	Metachromatic Leukodystrophy	Refs.[2]	Refs.[12]	
Other lipidosis				
	Niemann-Pick disease C			
	Wolman's disease	SCR		
	Ceroid lipofuscinosis	SCR		
Glycogen storage				
	GSD type II	SCR		Yes
Multiple enzyme deficiency				
	Galactosialidosis			
	Mucolipidosis type II	SCR		
	Other mucolipidoses			
Lysosomal transport defects				
	Cystinosis			
	Sialic acid storage disease			
	Salla disease			
Peroxisomal storage disorders (PSD)				
	Adrenoleukodystrophy	Refs.[2,8]	Refs.[12,14]	
	Adrenomyeloneuropathy			

Abbreviations: BMT = bone marrow transplantation; ERT = enzyme replacement therapy; SCR = single or small case reports; UCBT = umbilical cord blood transplants.
Most BMT are from related donors while UCBT are from unrelated donors.

donors, screened for genetic diseases, tested for infectious diseases markers, HLA typed and available for transplantation. These units are frozen in many repositories all over the world. Many are linked to computerized search registries such as the National Marrow Donor Program, Netcord and the WMDA. In some cases, individual banks manage and distribute their units through local, non-networked registries (for example, the Placental Blood Program). To date, almost 10 000 URD UCBT have been performed worldwide. UCB grafts can be transplanted without full HLA matching. Generally, intermediate-resolution DNA results are used for matching at HLA class I A and B loci and high-resolution DNA results are used for matching at HLA class II, DRB1. Matching at HLA C, DP and/or DQ have not been utilized. Donors matching at $\geqslant 4/6$ loci are considered adequate. It is also critical to deliver an adequate cell dose with the UCB graft. Generally, doses $\geqslant 2.5 \times 10^7$ nucleated cells per kg (based on the precryopreservation cell count) are considered adequate, but doses above 5×10^7/kg yield superior results and can be achieved in most pediatric patients.

The first prospective, multi-institutional trial of UCBT for IMD was performed as a part of the cord blood transplantation (COBLT) study sponsored by NIH's National Heart, Lung, and Blood Institute.[12] Figure 1 shows the survival data from that study. Subsequent data from the European Blood and Marrow Transplantation (EBMT) registry and disease-specific reports from single centers suggest that UCBT is an appropriate and viable option for HSCT for infants and children with IMD.[11,14,15,17] Advantages of UCBT include its ready availability, quick search and procurement process, less

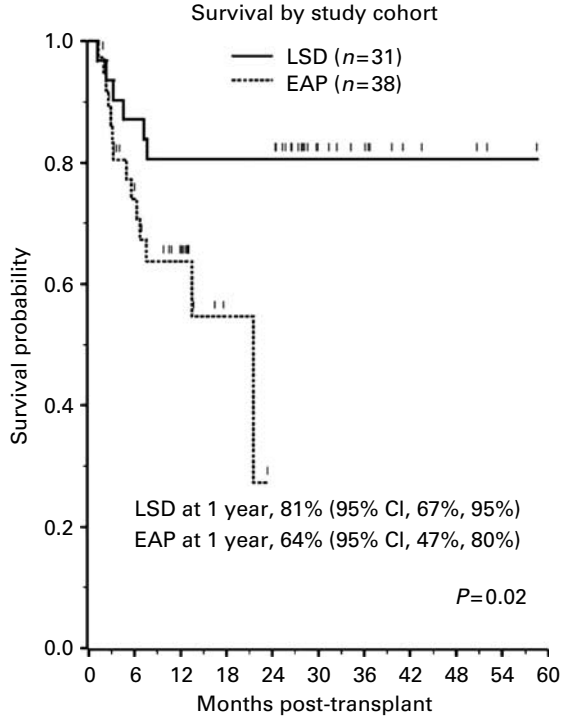

Figure 1 Survival of patients with lysosomal diseases on cord blood transplantation (COBLT) study by study cohort—original lysosomal storage disorders (LSD) stratum versus expanded access protocol (EAP) stratum (Figure 1c from Martin *et al.*[12]). Patients on the EAP stratum had significantly worse survival than those on LSD stratum ($P=0.024$). One-year survival was 81% (95% confidence interval (CI) 67–95%) for LSD stratum patients but only 64% (95% CI 47–80%) for EAP patients. The explanation seems to be related to the lower performance status of patients on the EAP stratum.

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. In published reports overall 'alive and engrafted' rates following UCBT range from 72 to 100%. In the COBLT study of 69 patients with MPS, Krabbe disease, ALD, MLD, mucolipidoses and Tay-Sachs disease were transplanted with UCBT after myeloablative chemotherapy with busulfan, cyclophosphamide and anti-thymocyte globulin (ATG). The GVHD prophylaxis was methylprednisone and cyclosporine. The median nucleated cell dose from the precryopreservation count and the administered post-graft thawing were 8.7×10^7/kg and 7.1×10^7/kg, respectively. A total of 90% of the patients received 4/6 or 5/6 matched units by low-resolution HLA-A and -B and high-resolution HLA-DRB1 typing. The donor units were selected from public cord blood banks and screened for the enzyme deficiency where possible. Durable donor cell engraftment was achieved in 84% of patients with no secondary graft failures. The incidence of grade III–IV and grade II acute GVHD was 9 and 27%, respectively. The probability of OS was 68% with a median follow-up of 24.5 months. The study demonstrated that UCBT is a therapeutic option for infants and children with IMD lacking matched related donors. Despite significant donor–recipient HLA mismatching, the incidence of acute and chronic GVHD was acceptable. On an average, it took only 15 days to identify a suitable CBU (including enzyme testing where applicable) from the onset of a search. This study reported traditional transplant end points but did not assess neurofunctional outcomes.

Suitability of UBCT for patients with IMD with assessment of neurocognitive and function outcomes is further supported by reports of UCBT in 20 Hurler[17] and 25 infantile Krabbe disease[15] patients. In the first of these reports of 20 consecutive patients with severe phenotype MPS I (Hurler syndrome) transplanted with UCBT after myeloablative chemotherapy (busulfan (BU)/cyclophosphamide (CY)/ATG) from our center, 85% of patients were alive with full donor cell engraftment and normal peripheral blood α-L-iduronidase levels at a median follow-up of 29.8 months. Figure 2 shows the engraftment and survival probabilities. All patients continue to do well with an additional 3 years of follow-up. The median age of these patients was 11 months at diagnosis and 16 months at transplant. Moderate–severe (grades II–IV) acute GVHD was seen in 25% of patients who received methylprednisolone and cyclosporine for prophylaxis against GVHD despite the fact that all but one patient had received UCB grafts mismatched at 1–3 HLA loci. With additional follow-up, extensive chronic GVHD has occurred in 2 of 17 evaluable patients. The functional and neurocognitive gains of these patients are dramatic and are discussed in the next section and shown in Figure 3. A report of UCBT in patients with early and late onset infantile Krabbe disease transplanted after myeloablative (BU/CY/ATG) chemotherapy before ($n=11$) or after ($n=14$) the onset of clinical symptoms showed dramatic efficacy if the patient was transplanted early in the course of the disease (Figure 4). All 11 patients diagnosed prenatally or neonatally because of a family history of an affected sibling, who were transplanted in the first month of life, are alive and well with a median follow-up of 71 months. All have full donor chimerism, normal peripheral blood galactocerebrosidase levels and have outlived their affected siblings who had not been transplanted. Two of 11 patients remain on immunosuppressive therapy for chronic GVHD 2–4 years post transplant. The neurodevelopmental outcomes in these patients were positive and are discussed below. In contrast, in the 14 patients transplanted as infants but after the onset of clinical symptoms, survival was lower at 45% and while disease stabilized, there were no appreciable gains in neurologic development beyond the time of transplantation.

A retrospective EBMT study of 146 patients with Hurler syndrome undergoing HSCT revealed better transplant and neurofunctional outcomes if the transplant was performed early in the disease when children had good Lansky scores.[11] The 'alive and engrafted' rate in 24 patients who received UBCT was 72% after a median follow-up of 36 months. Full donor chimerism was seen in 94% of UCBT compared to only 63% of BM/PBSC recipients.

Analyses of the outcomes of UCBT following chemotherapy-based myeloablative conditioning and the factors that may predict the outcome were performed in a cohort

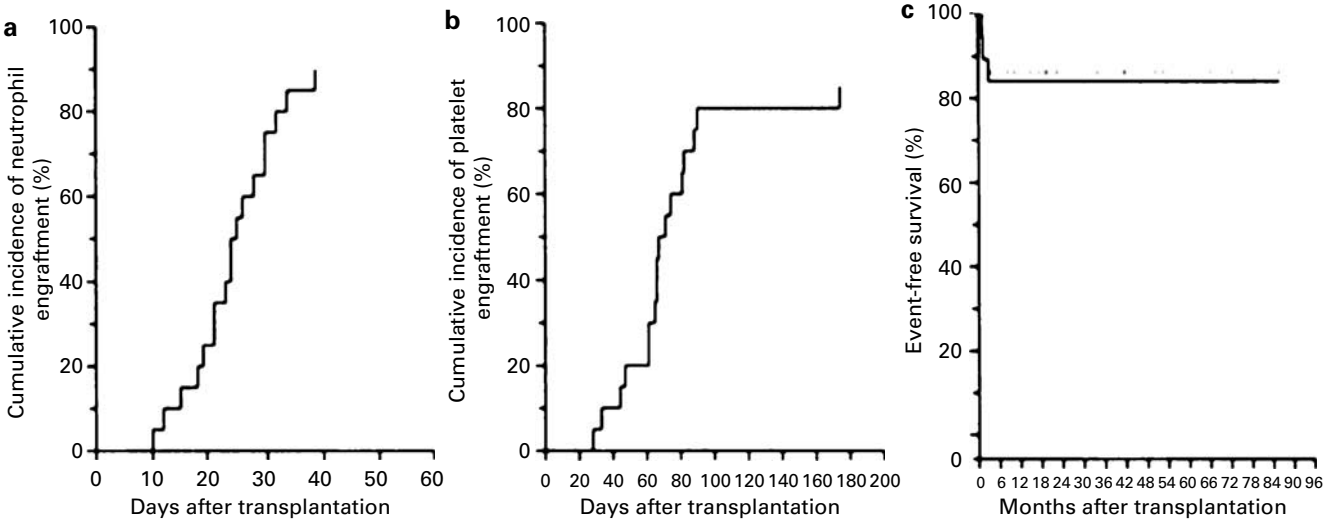

Figure 2 Cumulative incidence of neutrophil (**a**) and platelet (**b**) engraftment after cord blood transplantation and Kaplan–Meier estimates of the probability of event-free survival (**c**) (Figure 1 from Staba *et al*.[17]). In (**a**), myeloid engraftment is defined by an absolute neutrophil count of at least 500 per cubic millimeter on 3 consecutive days. In (**b**), platelet engraftment is defined by a platelet count of at least 50 000 per cubic millimeter without the need for transfusion for at least 7 consecutive days. In (**c**), event-free survival is defined by survival with full (greater than 99%) donor chimerism. Tick marks indicate the most recent follow-up visit for each patient.

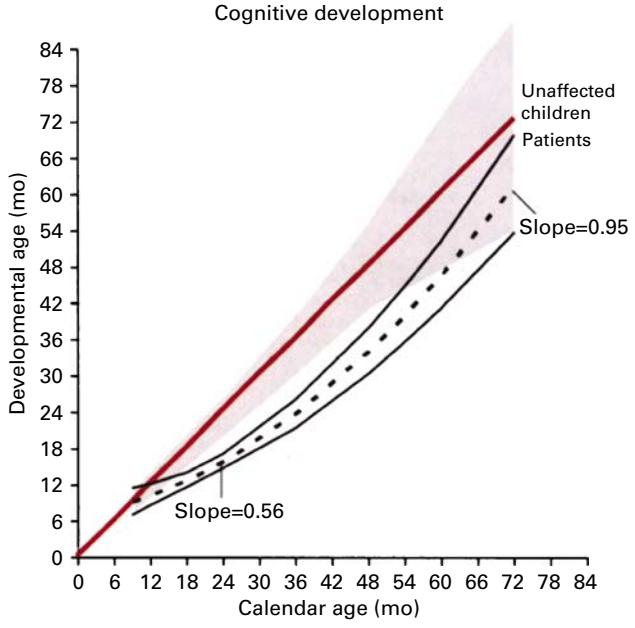

Figure 3 Neurocognitive performance of children with Hurler syndrome after cord blood transplantation. We used age-equivalent scores for comparisons and to monitor the children's developmental progress (Figure 3b from Staba *et al*.[17]). The picture shows the mean cognitive growth curve for all surviving patients plotted against the mean typical cognitive growth curve for unaffected children. The two thin black lines indicate the 95% confidence interval for the patients. The shaded area indicates the variability (± 2 s.d.) in typical cognitive development. Only two of the patients (three observations) had data recorded before 6 months of age, and these observations were not included in the final analysis, because they could have overly influenced the estimates.

of 12 young boys with X-ALD.[14] The patients had received a median of 6.98×10^7 nucleated cells per kg from UCB units that were discordant for up to 2 of 6 HLA markers. All units had normal level of very long chain fatty acids. Variables including neurophysiologic, neuroimaging, neurodevelopmental status, state of disease progression, and other routine graft and host characteristics were evaluated. Neutrophil engraftment occurred at a median of 22.9 days after transplantation. Three patients had grade II–IV acute GVHD; two had extensive chronic GVHD. Despite HLA mismatching, the transplant procedure yielded similar outcomes to those previously reported after HLA-matched BMT.[8,27] With a median follow-up of 3.3 years the probability of OS was 71.9% with the three younger children, demonstrating a survival of 100%. Similar to the experience in BMT recipients, UCBT in symptomatic patients resulted in lower survival and rapid neurologic deterioration. This study included three patients transplanted at a very young age (2.6–3.5 years) before the onset of clinical symptoms who continue to develop at a normal rate for 3–5 years post transplant. Baseline Loes scores in the magnetic resonance imaging (MRI) correlated with cognitive and motor outcome but neurophysiologic studies failed to show statistically significant impact on transplant outcomes.

Functional and neurologic outcomes

The overarching goal of any therapy, in particular one that is as intense and complex as HSCT with potential for significant morbidity and some treatment-related mortality, must be improvement in the quality of life, preservation of functional abilities and potential for neurocognitive gains and not merely the prolongation of life. This requires analysis of functional outcomes in nonhematopoietic organ systems and the expertise of nontransplant health care professionals. Functional outcomes can be assessed with neurocognitive testing, with adaptation of tests requiring

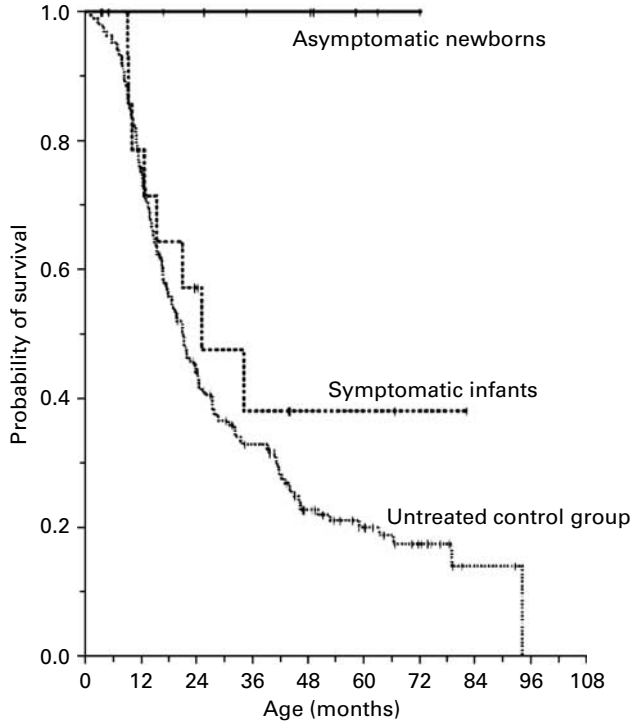

Figure 4 Kaplan–Meier estimates of the probability of overall survival among patients with Krabbe disease (Figure 1 Escolar *et al.*[15]). Shown are Kaplan–Meier estimates of survival among all 11 asymptomatic newborns with Krabbe disease who underwent transplantation of umbilical cord blood from unrelated donors, as compared with 6 of 14 infants who underwent transplantation after the development of clinical symptoms ($P=0.01$) and 190 untreated affected babies ($P=0.001$). $P=0.28$ for the comparison between the symptomatic infants and the control group. The tick marks indicate the most recent follow-up for each patient.

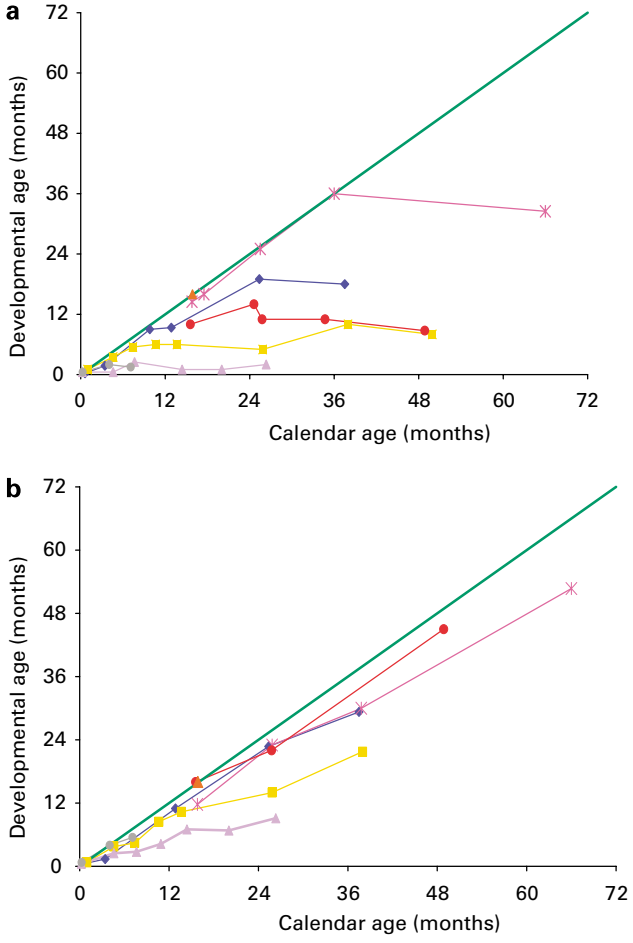

Figure 5 (**a**, **b**) Neurodevelopmental outcomes of children with infantile Krabbe disease who received unrelated umbilical cord blood transplantation as neonates (Figures 3a and b from Escolar *et al.*[15]). A unique line represents each patient's development. The green diagonal line represents typical development of unaffected children. Eight of the eleven newborns were assessed in all developmental domains before transplantation, and six of the eight were followed up in all domains after transplantation (the other two were too young to be scheduled). They were followed up in a predefined schedule every 3 months during the first year, every 6 months during the second year and once a year thereafter. The remaining three patients had less comprehensive evaluations because their hospitals did not have a dedicated multidisciplinary team. Gross motor skill (**a**) refers to proximal large-muscle groups used in locomotion and balance. Cognitive development (**b**) refers to the child's ability to solve problems verbally and nonverbally. Six patients have scores for cognitive development at less than 1 month of age. Four of these subjects have additional cognitive measures at older ages.

motor skills to assess performance on the test. In addition, neurophysiologic (electroencephalogram (EEG), brainstem auditory evoked potential, visual evoked potential (VEP), nerve conduction) and neuroradiologic (MRI, spectroscopy, fractional anisotrophy, fiber tract analysis) testing is paramount.

LSD and PSD exhibit a wide spectrum of clinical manifestations with varying severity and pace of disease progression. In most diseases, we lack adequate information to correlate genotype with clinical phenotype. Furthermore, the lack of natural history studies in all of these diseases limits critical evaluations of specific treatment interventions. The fact that these diseases are extremely rare and that newborn screening or other population studies are lacking create additional barriers. The decision about the use of HSCT in patients with other, related and similar, rare disorders often has to be made using extrapolation of HSCT outcomes data from more common and similar diseases that have been transplanted.

The benefits of HSCT in Hurler syndrome include improvement of neurocognitive functioning (Figure 3), joint integrity, motor development, linear growth, hydrocephalus, corneal clouding, cardiac function, hepatosplenomegaly, obstructive airway symptoms, hearing, visual and auditory processing, and OS. These benefits have been described in many reports of BMT and some UCBT from many centers.[7,11,17,28–30] The orthopedic benefits, particularly after BMT, are less apparent than those in other organ systems with many MPS I patients requiring corrective hip, back, knee and carpal tunnel surgeries during later childhood after otherwise 'successful' HSCT. Some benefit in odontoid dysplasia has been described. All Hurler patients showed either stabilization or improvement of neurocognitive function and continued to gain new skills after UCBT that was performed at a median age of 16 months. There was also an improvement in the somatic features, linear growth and bone disease in these patients.

Krabbe disease, a form of globoid cell leukodystrophy can manifest as a severe, early onset, infantile form that is fatal in infancy or milder forms either as juvenile or adult types that start later in life and exhibit a slower course. BMT has been shown to arrest progression of the disease 3–6 months post transplant. The data following UCBT in early onset Krabbe disease are significant for a number of reasons.[15] When transplanted in the asymptomatic stage, the survival is high (>90%), and the babies demonstrate gains in neurocognitive function (Figures 5a and b) with normal vision and hearing. Studies of fractional anisotrophy demonstrate normal to near-normal myelination for age (Figure 6) on brain MRI.[31,32] Peripheral nerve conduction studies stabilize and, in some patients, improve. However, ~80% of patients do not walk without assistance after 2 years of age, demonstrating varying degrees of spasticity of the lower extremities. In contrast, patients with the early infantile form of Krabbe disease transplanted with active symptoms have lower survival and a much poorer functional status after HSCT. Importantly, older patients with juvenile forms of Krabbe disease benefit from HSCT even after symptoms develop.

In 12 X-ALD undergoing UCBT, the pre-transplant MRI Loes score strongly correlated with the post transplant neurocognitive functioning similar to the experience in BMT patients.[8,27] In addition, baseline nonverbal/spatial scores and overall cognitive scores strongly influenced outcome. Brainstem auditory evoked responses and nerve conduction studies were not always predictive of progressive neurologic deterioration and became abnormal later in the disease process. However, the VEP and EEG became abnormal earlier in the disease process. Most patients with pre-transplant EEG abnormalities developed clinical seizures post transplant and had poor outcome. However, this finding was not statistically significant. Most of the children in our sample were <10 years. Age and pattern of demyelination in brain MRI may also be predictive of progression. The youngest patients with normal performance status had the best outcomes. In a large registry and questionnaire-based study of BMT, the patients with performance intelligence quotient (IQ) <80 (also referred as nonverbal IQ) at baseline were significantly more impaired post transplant and those with parietal-occipital pattern demonstrate greater mean loss in their performance IQ.[8]

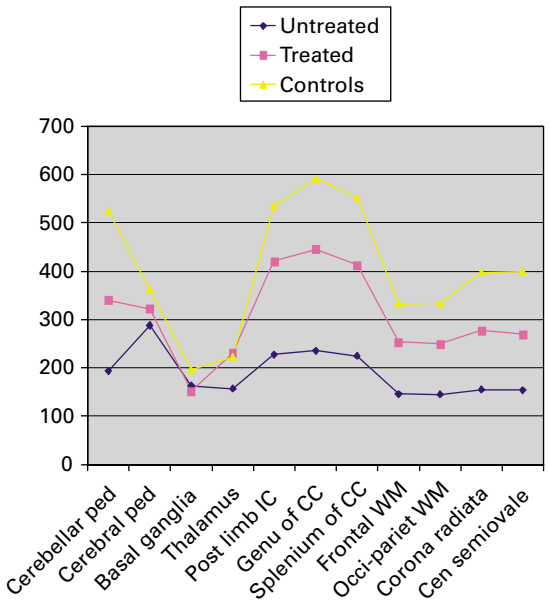

Figure 6 Graph of mean anisotropy indices for the three patients treated with hematopoietic stem cell transplantation, three untreated patients and three control subjects (Figure 4 from Guo *et al.*[32]). The abscissa is labeled with each region of interest (ROI). The ordinate is labeled with the anisotropy index scale. The anisotropy indices of treated patients are approximately halfway between those of untreated patients and control subjects. CC, corpus callosum; Cen, centrum; IC, internal capsule; Occi-pariet, occipitoparietal; Ped, peduncle; Post, posterior; WM, white matter.

Future directions and controversies

While HSCT is a highly effective treatment for pediatric patients with some inherited metabolic diseases, the procedure carries a significant risk of morbidity and mortality, largely due to early and late effects of preparative regimens necessary to facilitate engraftment of donor cells in the recipient. As the longest follow-up is about two decades in a limited number of patients, the late effects of administration of chemotherapy at an early age and also the 'natural history' of disease in transplanted patients are not known. Registry and natural history studies of transplanted and untreated patients must be conducted to answer these questions. As alternative therapies are discovered (for example, ERT, gene therapy, substrate inhibition therapy and so on), their effects must be compared to outcomes with transplantation therapy and to the natural history of the disease without any treatment. Approaches that combine HSCT with one or more of these alternative interventions may also be feasible.

Development of strategies to reduce early and late toxicities of transplantation therapy will decrease morbidity and mortality. Current approaches under investigation include reduced-intensity cytoreduction, targeted cellular therapies and fetal transplantation to induce donor cell tolerance. Other approaches are likely to emerge in the next decade. Graft engineering methodologies to increase the pace and rate of engraftment will also decrease transplant-related toxicities.

Implementation of newborn screening for IMDs is essential to identify and treat patients at risk before irreversible organ damage occurs. A pilot program was initiated in New York State in August 2006 allowing for screening of all newborns for Krabbe, Gaucher, Fabry and Pompe diseases. Similar and expanded programs (MPS, ALD, MLD, inherited immunodeficiency syndromes and others) should be implemented.

There are anecdotal reports of pre-implantation genetic testing and selection of embryos negative for the genetic defect responsible for the IMD in question. However, the procedure is not always successful. In addition, there are reports of implantation of HLA-matched embryos to be used as a source of HSCT graft for the affected sibling. There are significant ethical and practical issues related to this approach.

The optimal graft source for correction of IMDs through HSCT remains an open question. It is possible that UCB contains a greater dose of nonhematopoietic progenitor cells as compared to adult HSTs derived from BM or mobilized peripheral blood. If true, correction or prevention of nonhematopoietic organ damage may be optimized with a UCBT graft. The use of sibling donors who are carriers of the disease and thus deliver approximately 50% of the 'dose' of enzyme may yield inferior results as compared to noncarrier donors. These and other questions remain unanswered at the present time.

In summary, HSCT is a promising and effective therapy for patients with IMDs. However, the procedure is associated with significant risks related to the preparative regimen. Patient performance status at the time of transplant is the best predictor of the likelihood of benefit and best clinical outcomes. Responses of these patients to HSCT may provide insights into the potential of cellular therapies for tissue regeneration and repair in more common diseases for development of future innovative approaches.

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