Neurodevelopmental Outcome after Hematopoietic Cell Transplantation in Inborn Errors of Metabolism: Current Considerations and Future Perspectives

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Abstract

Inborn errors of metabolism (IEM) comprise an assorted group of inherited diseases, some of which are due to disordered lysosomal or peroxisomal function and some of which might be improved following hematopoietic cell transplantation (HCT). In these disorders the onset in infancy or early childhood is typically accompanied by rapid deterioration, resulting in early death in the more severe phenotypes. Timely diagnosis and immediate referral to an IEM specialist are essential steps in optimal management. Treatment recommendations are based on the diagnosis, its phenotype, rate of progression, prior extent of disease, family values, and expectations, and the risks and benefits associated with available therapies, including HCT. International collaborative efforts are of utmost importance in determining outcomes of therapy for these rare diseases, and have improved those outcomes significantly over the last decades. In this review, we will focus on the neurodevelopmental outcomes after HCT in IEM, providing an international perspective on progress, limitations, and future directions.

Keywords

- hematopoietic cell transplantation
- neurodevelopment
- indications
- gene therapy

Introduction

Inborn errors of metabolism (IEM) are a heterogeneous group of diseases caused by genetic defects in a wide array of metabolic pathways, including deficiencies in the production of lysosomal enzymes (lysosomal storage disease, LSDs) and abnormalities of peroxisomal function. Lysosomal enzymes are hydrolytic and catalyze the degradation of specific substrates within the acidic environment of lysosomes. Peroxisomes are subcellular organelles primarily involved in the metabolism of complex lipids (such as bile acids). The consequences of these diseases are multisystemic, affecting bone integrity, growth and development, cardiopulmonary status, the airway, hearing and vision, neurological and cognitive function, and often result in premature death. Allogeneic-hematopoietic cell transplantation (HCT) has shown to be a treatment option for a selected group of patients with an IEM. Timely diagnosis and immediate referral to a "specialist in IEM," followed by a thorough evaluation by a multidisciplinary team, discussion with a multidisciplinary team including a transplant-physician, are essential steps. Treatment recommendations are based on: the disorder; its phenotype, including age at onset, rate of progression,

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severity of clinical signs and symptoms; family values and expectations; and the risks and benefits associated with available therapies such as HCT.

To evaluate the efficacy of the various treatment modalities in these rare diseases, international collaborative efforts are critical. The collaborations started in late 1980s and have intensified over the past decade. Collaborative studies must distinguish early outcomes (transplant outcomes) from disease-specific outcomes in the longer term. Transplant outcomes are easier to study and identification of predictors that lead to engraftment failure or transplant mortality has resulted in really significant improvements. Assessment of long-term outcome is more difficult. The ability of HCT and the variables associated with HCT, for example, graft-type and age at transplant to affect disease manifestations is more difficult. Although difficult, it is a key achievement of the HCT and IEM communities that such studies are now taking place. These studies are of utmost importance as the very purpose of HCT is to improve disease manifestations and improve quality and length of life.

This review will focus on neurodevelopmental outcome of HCT for lysosomal storage diseases and peroxisomal disorders as IEM. We will also discuss which diseases to transplant, when to transplant, and how to follow-up.

Allogeneic HCT in IEM: What Is the Rationale and How Did We Get Here?

In 1968 Fratantoni et al first established that substrate accumulation in the cells of patients with lysosomal enzyme deficiencies could be dramatically reduced by coculturing these cells with cells producing the missing enzyme.[1] The ensuing principle of "cross-correction" was subsequently used to explore both exogenous enzyme replacement therapy and allogeneic HCT in numerous lysosomal diseases. As HCT also enables engraftment of donor-derived microglial cells in the brain—serving as local enzyme production units—this treatment, contrary to enzyme replacement therapies (ERT), has the potential to treat central nervous system (CNS) manifestations. This strategy has been tested in various disorders, including mucopolysaccharidosis type-1, Hurler phenotype (MPS-1H) and several leukodystrophies, in particular metachromatic leukodystrophy (MLD), X-linked adrenoleukodystrophy (X-ALD), and globoid cell leukodystrophy (GLD; or Krabbe disease). HCT has since become the standard of care in a selected group of disorders (e.g., MPS-1H, early X-ALD) and since the first HCT in an MPS-1H patient,[2] over 2,000 patients with an IEM have been transplanted (►**Fig. 1**).[9] Treatment recommendations may vary significantly, even within a particular diagnosis. These recommendations reflect the type of disorder, its predicted phenotype, the extent of disease progression, family values, and expectations and aim to balance the cumulative risks and benefits associated with available therapies.

Initially, HCT was associated with significant mortality due to high rates of graft-failure and transplantation-related mortality. International collaborations have identified predictor for these mortalities, resulting in engrafted survival

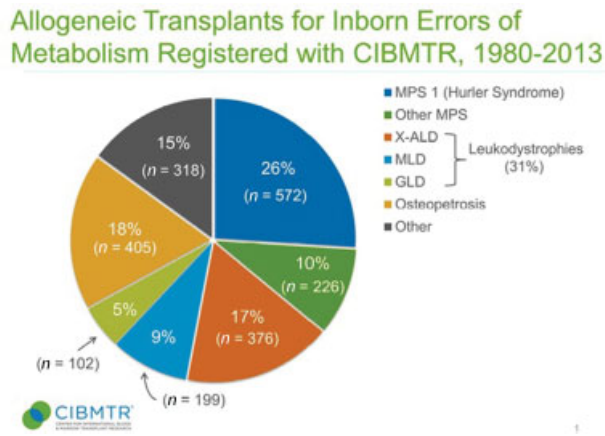

Fig. 1 Since early 1980s over 2,000 HCT in IEM have been performed. Here, the distribution of the various diseases/disease-groups is shown (CIBMTR database 2013). HCT, hematopoietic cell transplantation; IEM, inborn errors of metabolism. (Adapted from Boelens JJ, Orchard PJ, Wynn RF. Transplantation in inborn errors of metabolism: current considerations and future perspectives. Br J Haematol 2014;167(3):293–303).[9]

rates of over 90% nowadays.[3–5] HCT for IEM is performed using donor-derived hematopoietic stem cells obtained from bone marrow (BM), growth factor mobilized peripheral blood (PB), and the last decade predominantly from umbilical cord blood (CB). Allogeneic HCT has become much safer due to the availability of better-matched cords, enhanced techniques for HLA matching and increased inventory, individualized conditioning regimens and supportive care. Currently, for patients with nonmalignant disease such as IEM, the rate of HCT-related complications such as infections and "graft-versus-host disease" (GvHD), are relatively low, especially chronic-GvHD ($< 10\%$).[3,6]

Which Patients to Transplant?

Although HCT has proven to influence the natural course of a variety of IEM significantly not all diseases and disease phenotypes benefit from HCT. The currently accepted IEM indications (including optional or investigational diagnoses) for HCT are described in ►**Table 1**.

Transplant decisions require balancing potential risks and benefits. Patients with a milder phenotype and/or in those patients that are earlier in the course of their disease are more likely to benefit. Early recognition is therefore of utmost importance as much of the morbidity associated with the disease itself is not reversed by HCT. Treatment of the CNS with HCT is primarily mediated by the engraftment of donor-derived microglial cells in the brain. As it takes several months to replace sufficient microglia with those originating from the donor, there may be a delay in benefits of transplant to the CNS. As a consequence, diseases affecting the brain that are rapidly progressive (e.g., infantile GLD) are much more difficult to treat with HCT. HCT may only offer clinical benefit in these diseases if established presymptomatically, for example, in families with affected siblings. As short-term results of HCT improve (higher engrafted survival rates) and its overall risk is thereby reduced, it is now

Table 1 Inborn errors of metabolism for which HCT may be indicated

Disorder	Enzyme/protein	Indication	Comments
Mucopolysaccharidosis			
Hurler (MPS-1H)	α-L-iduronidase	Standard	
Hurler/Scheie (MPS-1H/S)	α-L-iduronidase	Option	ERT first-line therapy
Scheie (MPS-1S)	α-L-iduronidase	Option	ERT first-line therapy
Hunter: Severe (MPS-2A)	Iduronate-2-sulfatase	Investigational	Only early or asymptomatic
Hunter: Attenuated (MPS-2B)	Iduronate-2-sulfatase	Option	ERT first-line therapy
Maroteaux–Lamy (MPS-6)	Arylsulfatase B	Option	ERT first-line therapy
Sly (MPS-7)	β-glucuronidase	Option	
Leukodystrophies			
X-ALD, cerebral	ALD protein	Standard	Not for advanced disease
MLD: Early infantile	Arylsulfatase A	No	
MLD: Late-infantile/juvenile	Arylsulfatase A	Option/standard	Gene-therapy trial open (Milan)
MLD: Adult onset	Arylsulfatase A	Standard	Only early or asymptomatic
GLD: Early onset	Galactocerebrosidase	Standard	Neonate, screening diagnosis, or second case in known family; not for advanced disease
GLD: Late onset	Galactocerebrosidase	Option	
Glycoprotein metabolic and miscellaneous disorders			
Fucosidosis	Fucosidase	Option	
α-mannosidosis	α-Mannosidase	Option	
Aspartylglucosaminuria	Aspartylglucosaminidase	Option	
Farber	Ceraminidase	Option	
Tay–Sachs: Early onset	Hexosaminidase A	No	
Tay–Sachs: Juvenile	Hexosaminidase A	Option	In known family
Sandhoff: Early onset	Hexosaminidase A and B	No	Neonate, screening diagnosis, or second case
Sandhoff: Juvenile	Hexosaminidase A and B	Option	
Gaucher I (nonneuronopathic)	Glucocerebrosidase	Unknown	ERT first-line therapy
Gaucher II (acute neuronopathic)	Glucocerebrosidase	Option	
Gaucher III (subacute neuronopathic)	Glucocerebrosidase	Unknown	Limited benefit of ERT
Pompe	Glucosidase	Unknown	ERT available
Niemann–Pick: Type A	Acid sphingomyelinase	Investigational	
Niemann–Pick: Type B	Acid sphingomyelinase	Unknown	ERT first-line therapy
Niemann–Pick: Type C	Cholesterol trafficking	Option	Only early or asymptomatic
Wolman syndrome	Acid lipase	Option	May be viewed as standard
Multiple sulfatase deficiency	Sulfatases	Investigational	Not in advanced disease
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	Thymidine phosphorylase	Option	

Abbreviations: ERT, enzyme replacement therapies; HCT, hematopoietic cell transplantation.
Notes: Table does not include diseases where HCT is not indicated/contraindicated.
Standard: HCT applied routinely. Considerable published research evidence from registries and institutions demonstrates efficacy. Delayed diagnosis and/or advanced disease may preclude transplant for individual patients.
Option: HCT is effective but other therapy is increasingly considered first choice. Insufficient published evidence for HCT to be considered standard.
Investigational: Possible a priori reason for HCT. Further published evidence needed to support the use of HCT in clinical practice.

appropriate to consider whether diseases of milder phenotype might be considered for HCT, as the alternative is weekly 4 to 6-hour infusions of enzyme, and data suggest better metabolic correction after unrelated HCT compared with intravenous enzymes.[7] This might include milder LSD currently managed with ERT, such as Hurler–Scheie, MPS-6 but also (attenuated) MPS-2.

Much of the literature describing outcomes with HCT in any particular disease is outdated: for example, it is said that HCT is ineffective in MPS-2 (Hunter), but such a statement is derived from HCT experience in symptomatic children using sibling donor grafts (which may often be carriers). The outcomes may be different in those same patients had it been performed earlier and using an unrelated cord blood donor, where enzyme delivery would have been optimized as shown in some recent studies.[3,4] Thus, some of these HCT questions must be re-evaluated in this modern era. Also, here collaboration between centers for these re-evaluations is of importance since these diseases are rare and sometimes even ultrarare.

The role of HCT in a selected group of LSD and cerebral-ALD (C-ALD) is well established and is discussed in more detail below especially focusing on the neurodevelopmental outcomes. The role of HCT in other metabolic disease is less clear.

What Are the Neurodevopmental Outcomes of HCT in IEM?

Here, we describe the outcomes of the most frequently transplanted diseases-groups: Leukodystrophies (31%) and MPS-1H (27%, ►**Fig. 1**).

Leukodystrophies

GLD or Krabbe disease (incidence, 1:100,000), is a recessive disorder caused by defects in the galactocerebrosidase. Over 80% of cases of GLD present in infancy, with irritability, poor feeding, and progressive loss of motor function; the majority of these patients expire before 2 years of age. It is generally accepted that there is no role for HCT in symptomatic patients with the classic infantile phenotype. In patients identified and treated very early in life, either due to a positive family history or through newborn screening, HCT alters the course of the disease.[8] In these patients, cognitive function is relatively spared, but significant loss of gross motor function is still being observed post-HCT (although less clear in attenuated phenotypes). The relative contribution of peripheral demyelination to motor-related dysfunction is difficult to assess, but it is clear that nerve conduction abnormalities are present in GLD post-HCT. The later onset forms of GLD progress less quickly, providing an opportunity longer time window for HCT. Later onset forms of GLD may not only be stabilized, but can potentially improve following HCT (reviewed recently[9]).

MLD, also recessive in inheritance (1 in 40,000) is caused by a defect in the arylsulfatase A (*ARSA*) gene. In this disorder, sulfatides accumulate in myelin-producing cells, resulting in both central and peripheral demyelination. ARSA testing is important in establishing the diagnosis, however, pseudodeficiency states exist in which measured ARSA levels are low. Urinary sulfatide excretion is only elevated if ARSA is really deficient, urine sulfatide testing is therefore, necessary to confirm the diagnosis of MLD. MLD is categorized based on age at onset of clinical manifestations: late-infantile (younger than 2 years), juvenile (3–16 years), and adult forms. Late-infantile MLD is the most common form and is characterized by progressive motor dysfunction resulting in a gradual loss of the ability to walk, stand and sit, dysarthria, swallowing difficulties, an inability to handle secretions, and early death ($<$ 4 years of age). There is no role for HCT in symptomatic late-infantile MLD.[8] Patients with late-infantile disease that proceeded to HCT presymptomatically achieved some stabilization of disease, but eventually severe motor difficulties were observed in most, if not all, primarily due to peripheral nerve dysfunction.[10] The asymptomatic late-infantile group is also the target of recent gene-therapy initiatives and has the capacity to deliver more enzyme than standard allogenic-HCT. First clinical evidence of efficacy has been shown recently.[11] In attenuated forms of the disease a greater opportunity exists to impact the disease process with HCT. It has been reported that patients with juvenile disease transplanted while still asymptomatic attain much better outcomes.[10] Patients with adult form of MLD (20% of cases), which can become apparent as late as the sixth or seventh decade, have less motor findings, but may be emotionally labile and have difficulties in executive function, progressive dementia, psychosis, and drug abuse. Although limited data available there appears to be a role for allogeneic HCT for adult-onset disease (reviewed recently[9]).

ALD: In 1976 it was demonstrated that very long chain fatty acids (VLCFAs) accumulate in the brain and adrenal tissue of patients with ALD.[12,13] The inability to degrade VLCFA is due to mutations in the *ABCD1* gene, encoding a peroxisomal membrane protein.[14,15] ALD is an X-linked in inheritance (1 in 17,000) and clinical manifestations of the disease are highly variable. The most severe phenotype of ALD is the cerebral form (C-ALD), which is found in 35 to 40% of individuals with ALD by age 20. Cerebral ALD is an acute, inflammatory, demyelinating condition. In almost all (95%) cases, C-ALD is associated with progressive neurological deterioration and ultimately death within several years. C-ALD is rare before 4 years of age, the median age in which cerebral manifestations occur is at 7 years. Since the first report by Aubourg et al on a beneficial effect of HCT in a boy with early-stage C-ALD in 1990[16] additional experience has established allogeneic HCT as the standard of care for early C-ALD. Until now the exact mechanism of action remains unclear, but it is thought that chemotherapy and immune suppression associated with HCT controls neuroinflammation. Presumably, donor microglial cells provide support to the ALD oligodendrocyte. The Loes magnetic resonance imaging (MRI) scoring system, which provides a numeric score based on the number of areas of the brain with evidence of demyelination,[17,18] is a predictor of survival, with higher mortality rates in advanced patients: those with higher scores ($>$ 9) have worse outcomes.[6] Unfortunately, most patients are not diagnosed as having C-ALD until they develop clinically

evident neurological changes, thus are having already advanced disease when HCT is considered. Presently, these patients are no longer eligible for treatment with HCT as mortality rates associated with transplant are high and disease burden after transplant is very high. Novel strategies such as using a reduced intensity regimen and antioxidative therapy, may change this recommendation in the future.[6] An intriguing question regarding the role of HCT in ALD is whether HCT alters the natural history adrenomyeloneuropathy (AMN), a late-onset ALD disease complication. AMN affects the spinal cord, is noninflammatory and results in a slow progression of motor-related limitations beginning in the third decade of life.[15] Recently, early reported success of gene therapy (autologous gene-transduced HCT) has been published and a second trial recently has started.[19] Important will be the comparison between patients receiving allogenic-HCT and gene-transduced autologous HCT, not only for the short (transplant)-term outcomes, but more importantly on the long-term outcomes.

Hurler Syndrome, MPS-1H

Hurler syndrome (MPS-1H), the most severe phenotype of α-L-iduronidase deficiency, is an autosomal recessive disorder characterized by progressive accumulation of glycosaminoglycans (GAGs). Hurler and other phenotypes of MPS-1-Scheie (attenuated) and Hurler–Scheie (MPS-1H/S, intermediate) represent a continuous clinical spectrum. Accumulation of GAGs results in progressive, multi-system dysfunction associated with premature death. Over 600 HCTs have been performed worldwide for children with MPS-1H since 1980 (European Society for Blood and Marrow Transplantation/Center for International Blood and Marrow Transplantation Research (EBMT/CIBMTR) registry), making it the most commonly transplanted IEM (►**Fig. 1**).

HCT for children with MPS-1H has been shown to increase life expectancy and improve the clinical manifestations of disease.[4,20] HCT must be performed early in the disease course as any disease-related complications, particularly neurocognitive dysfunction, are irreversible. Donor-cell engraftment after HCT has resulted in the rapid reduction of obstructive airway symptoms and hepatosplenomegaly.[20] Hearing, vision, and linear growth, improve in most cases. Hydrocephalus is either prevented or stabilized and the otherwise expected cardiovascular pathology is altered beneficially after HCT. Although cerebral damage already present before HCT appears to be irreversible, successful HCT is able to prevent progressive psychomotor deterioration and permit continued neurodevelopment.[4,21]

International collaborative studies identified predictors for graft-failure associated with poor "event-free survival" rates; T-cell depleted grafts and reduced intensity conditioning, while busulfan with therapeutic drug monitoring (targeting to a myeloablative exposure) appeared to be a predictor for higher "event-free survival" in comparison to prior experiences.[3,22] These data have led to an EBMT transplant protocol/guideline (EBMT/European Hematology Association (EHA) handbook 2008 and 2012).[23] These guidelines included a standardized busulfan/cyclophosphamide conditioning regimen and the use of CB as a preferred graft-source, second only to noncarrier-matched sibling BM. This transplant protocol with well-matched grafts resulted in a significantly improved engrafted survival rate of over 90% in larger experienced HCT-centers specialized in transplanting MPS patients, who also have standardized long-term follow-up programs.[5] Recently, the conditioning was modified to busulfan with pharmacokinetic monitoring: targeting to myeloablative busulfan exposure) + fludarabine (EBMT/EHA handbook 2012). Recent conditioning comparisons (BuCy vs. FluBu) suggest similar HCT outcomes, but with reduced toxicity.[5,24]

Over the past decade, unrelated CB has been used with increasing frequency as a graft source for HCT in children with an IEM. CB offers several advantages over BM or PB including reduced time to HCT, greater tolerance for HLA-mismatch, lower incidence, and severity of GvHD, and reduced likelihood of transmitting viral infections. Recent collaborative studies suggest that highest event-free survival (EFS) rates are achieved in patients receiving an identical matched sibling donor or an identical (6/6) unrelated cord blood, followed by 5/6 matched CB (or a 4/6 matched CB donor with high-cell dose) or 10/10 matched unrelated donor. Interestingly, almost all CB recipients had full-donor chimerism associated with normal enzyme levels, while mixed-chimerism was more frequently seen in matched sibling and matched unrelated donor (MUD) donors.[3] It is also important to recognize that most matched sibling donors are carriers, influencing posttransplant enzyme levels. Lower enzyme levels appear to be important for long-term outcomes, including neurocognitive outcomes: patients with normal enzymes (in leukocytes according to local reference range) have much better outcomes: better growth, less orthopedic interventions less/no respiratory support.[4,20]

Survival of MPS-1H patients has significantly improved last decade; however, the major limitation is substantial morbidity due to "residual disease burden"; primarily musculoskeletal features that often require orthopedic surgical interventions.[4,20,21] Use of improved and reduced toxicity HCT techniques at an earlier age and the achievement of full donor-chimerism with normalization of enzyme activity may enhance outcomes. Newborn screening may prove a major step forward in early identification of individuals with MPS-1H.

When to Transplant?

It is clear that in IEM the outcomes (both transplant outcomes and late outcomes) are superior in patients in whom transplant is performed early. This has thus far been demonstrated for several diseases, including MPS-1H (Hurler disease), MLD, C-ALD, and Krabbe disease.[3,6,8,10] It will likely hold true for other (ultrarare) IEM for which HCT has a role.

Newborn screening is emerging as an option for these disorders; previously the median age at transplant for Hurler was ~16 months of age,[3] as most children are diagnosed based on clinical signs and symptoms. The age at transplant will likely be significantly reduced as neonatal screening is

implemented (which is agreed upon in several countries; including the Netherlands). The test(s) need to be specific, cost-effective, be able to identify disease-causing mutations and be able to offer a reliable prediction of the phenotype to minimizing anxiety and uncertainty in families. Of course the introduction of such screening should be prospectively evaluated in a standardized manner to evaluate the benefits of intervention.

In C-ALD, as discussed above, intervention with HCT is only offered when demyelination is documented based on MRI changes. Neonatal screening for ALD has already begun in New York, and will likely expand in the near future (including the Netherlands). This will allow boys to be identified early, providing them the best chance for performing HCT quickly as cerebral disease is identified and allowing detection of adrenal failure so that life-saving hormone replacement therapy can be given. Currently, HCT is not performed in boys without documented MRI changes because of the risk of HCT, and due to our inability to identify those who will ultimately develop cerebral disease. This paradigm is likely to change when evidence proves that HCT alters the course of AMN, as discussed above.

How to Transplant a Patient with an IEM?

Engraftment has been shown to require myeloablative conditioning (which means maximal intensity to make space in the bone marrow) most commonly utilizing full-dose targeted busulfan.[3,22,25] In dedicated, experience centers, transplanting patients with IEM, the engrafted survival rates are above 90 to 95% using busulfan-based myeloablative conditioning.[5] If in upcoming years protocols can be developed with even further reduction of the toxicity associated with equivalent engraftment as the current myeloablative conditioning protocols this will be advantageous, especially when this will give benefits in regards to fertility and normal endocrine function after HCT. Agents, such as, treosulfan are considered to be less toxic (but is proven to be less ablative and systematic pharmacokinetic (PK) and pharacodynamic (PD) studies are lacking), there are data that clearly suggest that busulfan may provide superior microglial engraftment (essential for earlier and higher delivery of the missing enzyme in the brain). The replacement of cyclophosphamide for fludarabine combined with exposure-targeted busulfan has proven to be as effective (including absence of mixed chimerism, which is also more frequently seen in treosulfan-based regimens) but significantly less toxic.[24] Based on current literature the recommended conditioning regimen and cell source hierarchy is described in ►**Table 2**.

The enzyme dose delivered by HCT is important in patient's "late outcomes" after HCT. Children that are fully engrafted from unrelated donors or noncarrier-related donors have typically high enzyme levels and need less orthopedic surgery and grow better.[4] Several lines of evidence suggest that autologous cells that are gene-modified to express the deficient enzyme may further improve outcomes compared with the wild type donor.[3,11] Furthermore, gene therapy has the capacity to enhance enzyme secretion not only by increasing the gene copy number but also by re-regulating gene expression so that it occurs in monocytic and other mature blood cells. As the enzyme level has shown to be a predictor of long-term outcomes (e.g., skeletal disease)[4] higher enzymes achieved by gene-therapy may influence the long-term outcomes positively in the future. Comparing the gene-therapy outcomes with current practice (HCT) is of course important to prove possible superiority.

What Are Alternative Treatment Options for Patients with an IEM?

In addition to supportive care of disease manifestations and HCT alternative therapies are increasingly available for these conditions. The success of Cerezyme (imiglucerase, genzyme) for the treatment of Gaucher disease has led to the development of similar therapies for other LSDs. Fabry disease, MPS I, II, VI, and Pompe disease all have ERT and many more enzymes are in various stages of clinical development. This approach however has several limitations; not all patients are suitable for treatment, some organs or tissues (e.g., lung, liver, spleen) are more amenable to correction than others (e.g., skeletal, CNS). In addition, there are problems gauging efficacy in this group of highly variable disorders. Furthermore, there is a burden of weekly (or even more frequent) infusions, development of (neutralizing) antibodies to the recombinant proteins and ERT will not penetrate of the CNS which makes ERT not an effective treatment option for patients with CNS disease.

Other alternative therapies are being developed such as oral small molecules acting as either inhibitors of substrate accumulation or as chaperones to misfolded proteins. With this approach, or combined strategies it is hoped that there is some or better effect on CNS disease, but all are too early to change decision making.

As already discussed above, gene therapy approaches have translated from the laboratory to the clinic; the first trials are accruing patients in C-ALD and MLD.[11,19] In the very near future also trials in other LSDs will start: for example, MPS-3, MPS-1.

How to Follow-Up and Provide Care to Patients Enouncing Residual Disease Burden

Structured multidisciplinary follow after HCT is an essential element of any transplant program as it provides robust feedback on the decisions made during the process. Given the rarity of these disorders and the heterogeneity within each disorder (age at transplant, disease severity, etc.) the risks and benefits may be unclear at the time of transplant. It is increasingly recognized that residual disease burden may be substantial despite HCT.[4] The residual disease burden is multifaceted, often involving several organ systems, and structured and multidisciplinary follow-up ensures that the various aspects are recognized and treated at an early stage. Also, it allows recognition of previously unsuspected long-term morbidity, which may be amenable to treatment.[26] In

Table 2 Donor hierarchy and conditioning

Stem cell source hierarchy in lysosomal storage diseases and peroxisomal disorders
Identical-SIB (not carriers)
UCB (6/6) = UD (10/10[a])
UCB (5/6)
UCB (4/6) = mismatched-UD (non-T-depleted)
UCB (3/6) = HAPLO (not recommended)
UD (10/10) may be bypassed depending on institutional preference or because of time
For UD: BM preferred cell source
Cell dose for UCB: > 5 × 10e7 NC/kg and/or > 2 × 10e5 CD34 + /kg. Matching according to intermediate resolution criteria (low resolution on A and B, high resolution on DR). If HR typing is available this is preferred
Unrelated donors are regarded as noncarriers of the mutation
Serotherapy:
id-SIB: no
UCB: ATG (thymoglobulin)[b] 4 × 2.5 mg/kg (day −9 to −6)
UD: either Campath-1H 3 × 0.3 mg (day −9 to −7)
or ATG (thymoglobulin)[b] 4 × 2.5 mg/kg (day −9 to −6)
Conditioning
SIB/UCB/UD: Busulfan weight-based dosing (IV: day −5 to −2) with therapeutic drug monitoring AUC 90 mg × h/L (range: 85–95) cumulative over 4 d (AUC in μM × min = 22, range: 20.5–23.5). Preferably in once daily dosing (in 3 h)
Fludarabine 160 mg/m^2 (day −5 to −2): 40 mg/m^2 in hour before busulfan
GvHD prophylaxis
SIB: CsA (+ MTX: 10 mg Msq; day +1, +3, and +6)
UD (BM)
with Campath-1H CsA
with ATG: CsA + MTX (10 mg Msq; day +1, +3, and +6)
UD (PBSC) UD/
Mismatched-UD (BM) CsA + MMF (30 mg/kg: stop day +28 in case no GvHD)
UCB: CsA + prednisone 1 mg/kg (until day +28, taper in 2 wks)
CsA-trough level: 200 μg/L
Tapering GvHD-prophylaxis
SIB/UD: CsA until day +50. Then taper 20%/wk
UCB: CsA until + 6 mo. Then taper in 3 mo

Abbreviations: ATG, anti-thymocyte globuline; AUC, area under the curve; Campath-1H, Alemtuzumab; CsA, ciclosporine-A; GvDH, graft-versus-host disease; HLA, human leukocyte antigen; MMF, mofitil-mycofenolaat; mo, month; Msq, meter square; MTX, methotrexate; NC, nucleated cells; HR, high resolution; PBSC, peripheral blood stem cells; UCB, unrelated cord blood; UD, unrelated donor; SIB, identical sibling donor; BM, bone marrow.
[a]10/10 HLA matched on high resolution typed.
[b]ATG dose for > 25 kg: 3 × 2.5 mg/kg and > 50 kg: 2 × 2.5 mg/kg (start day −9).

case of research/developmental indication for HCT, structured multidisciplinary follow-up will help determining whether the indication is proving valid.

Summary

HCT is an effective treatment option for a selected group of inborn errors of metabolism: for example, some LSDs, and peroxisomal disorders. The HCT outcomes as well as the long-term perspective have positively changed over the last decade. Intense international collaboration has resulted in these better outcomes due to the identification of predictors of outcomes. It however remains important to continue with these tight collaborations as novel therapies are being developed to further improve the outcomes. In summary:

- Full-intensity myeloablative conditioning has been required for sustained donor cell engraftment in patients with IEM. This is best achieved by exposure-targeted busulfan in combination with immune suppressive drugs

(fludarabine or cyclophosphamide) and serotherapy (e.g., antithymocyte globulin/Campath [ATG and Campath: Genzyme, Cambridge, Massachusetts, United States])
- Engrafted survival rates have significantly improved and in experienced centers might be expected to be over 90%
- Cord blood as a donor cell source gives better chimerism than bone marrow or peripheral blood after myeloablative conditioning
- Structured multidisciplinary follow-up after HSCT is an essential element in the care of these patients not only to optimize treatment of residual disease, but also to delineate efficacy and to identify clinical targets for improvement
- The primary goal of HCT is optimizing the functional outcomes of these patients, and their "quality of life." Variables that can be addressed to increase efficacy of therapy, including:
  - *Age at transplant*: The earlier the better
  - *Levels of enzyme delivered to recipient tissue* by engrafted donor leukocytes, which are currently best achieved after myeloablative cord blood transplantation. In the future, the use of gene-therapy protocols may result in supranormal enzyme levels, which may have an impact on the long-term outcomes of these patients
  - *Phenotype of disease*: The milder the more promising

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