

# Trends in haematopoietic cell transplantation for inborn errors of metabolism

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**Summary** For the last 25 years, haematopoietic cell transplantation (HCT) has been used as effective therapy for selected inborn errors of metabolism (IEMs), mainly lysosomal storage diseases and peroxisomal disorders. The main rationale for HCT in IEMs is based on the provision of correcting enzymes by donor cells within and outside the blood compartment. The ultimate goal of HCT is to achieve a normal or near-normal life and normal neurodevelopment. HCT has been performed for more than 20 diseases. Only for Hurler syndrome, X-ALD and infantile Krabbe disease, are detailed studies available suggesting that HCT is indicated for carefully selected cases. Improvement of transplantation techniques and alternative therapies may change the recommended (contra-)indications for IEM. A recent example of emerging transplantation techniques is the fast availability of unrelated cord blood (UCB). UCB makes HCT feasible in patients with rapidly progressive neurological diseases. Because of the fast availability of UCB and therefore the ability to transplant shortly after diagnosis, there is no indication for patients in a moderate/good clinical condition to receive enzyme replacement therapy (ERT; in Hurler syndrome) prior to or during HCT and can ERT only be considered in patients with poor clinical condition. Mesenchymal stem cell infusions with HCT is an emerging technique, and might be interesting in halting the remaining defects after successful

HCT. Improvement in HCT techniques and novel stem cell sources will significantly impact the safety and efficacy of this therapy as well as expand the list of candidate disorders. A good functioning worldwide registry would be necessary to measure the effects of the procedures performed in more detail.

## Introduction

For the past two decades, haematopoietic cell transplantation (HCT) has been used as an effective therapy for selected inborn errors of metabolism (IEMs). Fratantoni and Neufeld laid the foundation for our understanding of transferable lysosomal enzymes by demonstrating cross-correction of metabolic defects in co-cultures of fibroblasts from Hurler and Hunter syndrome patients (Fratantoni et al 1969). Some years later, correction of the deficient enzyme was demonstrated with lymphocyte extracts or serum (Di Ferrante et al 1971; Knudson et al 1971). These results were the rationale for Hobbs to trial HCT in a Hurler patient in the early 1980s (Hobbs et al 1981). Dramatic improvement in the clinical phenotype of this first patient, and subsequently of others transplanted for selected lysosomal storage diseases (LSDs) and peroxisomal disorders, resulted subsequently in approximately 900–950 HCTs worldwide (for more than 20 diseases or disorders) (Rovelli and Steward 2005).

The main rationale for HCT in IEM is still based on the provision of correcting enzymes by donor cells within and outside the blood compartment. Correction outside the blood compartment is provided mainly by repopulating donor macrophages (e.g. Kupffer cells and microglial cells) in various tissues (Krivit et al 1995b). Secretion and delivery of the enzyme by donor cells leads to arrest of further progression of disease – neurodegeneration, and also the tissue storage

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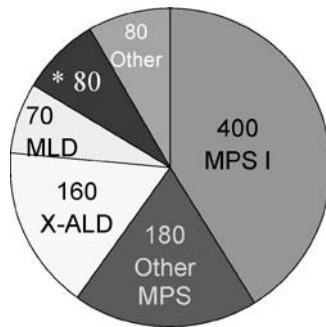
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**Fig. 1** Estimated frequencies of HCT for the various IEMs since 1980 worldwide. \*Other leukodystrophies/white-matter diseases (e.g. Pelizaeus–Merzbacher, Zellweger syndrome, vanishing white-matter disease)

(e.g. liver, heart, lungs) leading to dysfunction and interfering with normal daily life. The ultimate goal of HCT is to achieve a normal or near-normal life and normal neurodevelopment. However, the exact mechanisms for therapeutic benefit of HCT are not completely understood and may differ between the various diseases. For instance, in X-linked adrenoleukodystrophy (X-ALD) the mechanism may be related to halting the central nervous system (CNS) inflammatory process associated with myelin injury.

The great majority of the transplants have been performed for patients with Hurler syndrome, followed by other mucopolysaccharidoses (MPSs) (e.g. Hunter syndrome, Sanfilippo syndrome, Maroteaux–Lamy syndrome), X-linked adrenoleukodystrophy, metachromatic leukodystrophy, globoid-cell leukodystrophy (including Krabbe disease) and various miscellaneous disorders (Fig. 1). Unfortunately, for unknown reasons, not all LSDs benefit from HCT; careful evaluation of the effect of HCT is therefore important to establish clear guidelines for indications for HCT (Peters and Steward 2003). On the basis of all available literature, consisting mostly of retrospective studies, case reports and personal communications, Peters and Steward published a practical guideline outlining recommended current indications and contraindications (Peters and Steward 2003). However, evaluation of the true long-term effects of HCT is difficult for various reasons: (1) There is a wide spectrum of phenotype and disease stage before HCT. (2) Benefit varies between organs: reticuloendothelial organs such as liver and spleen often benefit more and faster than the CNS, in case of the latter probably because of the slower turnover of microglia and their replacement by donor cells. In addition, little impact of HCT on bone defects has been described. (3) Transplantation related morbidity (GvHD, viral infections) and mixed chimerism (and graft failure) can influence the outcome. (4) The absence of a good functioning (worldwide) registry is a hindrance.

In this mini-review the outcome/effect of HCT on Hurler syndrome, X-ALD and infantile Krabbe disease will be

described, these being the diseases with the best detailed studies. In addition, new trends in HCT will be discussed for IEMs: (1) unrelated cord blood as an emerging stem cell source, (2) enzyme replacement therapy (ERT) in combination with HCT and (3) mesenchymal stem cell transplantation.

## Outcome/effect of HCT in IEMs

### Hurler syndrome

The number of Hurler patients who have undergone HCT is estimated to be more than 400, and the results for Hurler syndrome are the most extensively studied (Boelens et al 2005a; Kurtzberg and Krivit 2004; Peters et al 1996, 1998a; Souillet et al 2003; Staba et al 2004). Donor engraftment after HCT in Hurler patients leads to a rapid reduction of obstructive airway symptoms, hepatosplenomegaly and corneal clouding. Hydrocephalus is either prevented or stabilized and hearing impairment improves in many children (Boelens et al 2005a; Peters et al 1996; Peters et al 1998a, b; Souillet et al 2003; Staba et al 2004). In addition, successful HCT averts death from cardiac dysfunction (Braunlin et al 2001; Vinallonga et al 1992), improves growth (near to normal growth velocity) and psychomotor development, and prolongs survival (Krivit et al 1995a; Peters et al 1996; Peters et al 1998a, b; Shapiro et al 1995; Souillet et al 2003; Staba et al 2004; Summers et al 1989). The remaining problems after successful HCT are mainly orthopaedic problems (odontoid dysplasia, thoracolumbal gibbus, carpal tunnel syndrome), for which additional interventions are sometimes needed (Krivit et al 1995a; Souillet et al 2003; Staba et al 2004). In comparison, untreated Hurler syndrome children have severe growth failure by the age of 2 years, achieving a maximal height of 110 cm (in case of longer survival) (Neufeld and Muenzer 2001), and might have more orthopaedic interventions. Longer follow-up is needed for evaluation of the effect of successful HCT on skeletal manifestations. Untreated patients die young severely retarded, by the median age of 7 (range 1–15 years). In addition to the results from studies cited above, a European retrospective study was performed recently on behalf of the EBMT (European Blood and Marrow Transplantation) working committee. Factors influencing the engraftment and long-term follow-up were analysed (Boelens et al 2005a) in 146 patients transplanted for Hurler syndrome between 1994 and 2004, this being the largest number of case histories reported so far. Patients, extracted from the EBMT database, were analysed on the basis of completed questionnaires (transplantation-associated questions as well as some long-term follow-up data). Sixty-two patients were more than 36 months post HCT with a functioning graft. The acquired data (Table 1) confirm the data published earlier

**Table 1** Long-term follow-up of 62 Hurler patients more than 36 months post HCT

	Missing	
Lansky score	4	Median 90 (70–100)
Thoracolumbal gibbus	15	Progressive in 15%
Length	15	Median SDS – 1 (23% < SDS – 2)
Mental development	20	70% DQ/IQ > 90%
Airway obstruction	2	Improved > 95%

in smaller series: high Lansky scores (a rough parameter for play activity: scale ranges from 10 (moribund) to 100 (normal activity); Lansky et al 1987), dramatic improvement of the airway obstructions, and normal mental development. A study analysing all ‘alive and engrafted’ patients in the European series using the same tests performed by the same ‘specially trained’ doctors would be the most precise way to analyse the long-term outcome in this historical group. Of course, prospective studies evaluating the outcome of HCT for IEMs are the most valuable.

After the impressive results of HCT in Hurler syndrome (Hobbs et al 1981), it was expected that all MPS disorders could be alleviated by HCT. Unfortunately, of the other MPS disorders, benefit from HCT appears to be significant only for MPS VI (Maroteaux–Lamy) (Krivit et al 1984) and MPS VII (Sly) (Yamada et al 1998). It is unclear whether it will remain an indication for MPS VI if and when ERT becomes available.

#### Krabbe disease and globoid-cell leukodystrophy

In globoid-cell leukodystrophy (GLD), a disease characterized by periventricular demyelination, resulting in overwhelming spasticity and mental retardation/deterioration, two major phenotypes can be distinguished: (1) an early-onset form also known as Krabbe disease and (2) late-onset disease (juvenile and adult forms) (Wenger et al 2001). For the late-onset forms it was demonstrated that, with appropriate timing of HCT, disease progression can be aborted (Krivit et al 1998). It was demonstrated also for the early-onset form that disease progress can be ameliorated when HCT is performed in the early neonatal period (Escolar et al 2005). This was recently confirmed in a large series of patients. Escolar and colleagues (2005) reported 25 patients transplanted for infantile Krabbe disease. Eleven of the babies were asymptomatic and 14 were symptomatic cases at the time. The study reports that the probability of overall survival and donor cell engraftment among asymptomatic patients is 100%, in comparison to less than 40% in the symptomatic group and the untreated control group. Cause of death in the symptomatic group was mainly due to disease progression, even after donor engraftment. In addition, it was shown that the neurological and neurodevelopmental function was significantly better in the transplanted asymptomatic group than in

the symptomatic patients; after a median of 3 years’ follow-up, asymptomatic patients showed normal vision and hearing and normal cognitive development. Moreover, cerebral MRI scanning showed normal myelination with age-appropriate changes in signal intensity at various white-matter sites. Only the gross motor development was found to be compromised in all asymptomatic patients. This probably due to pre-existing irreversible damage acquired prenatally or within the first weeks of life, preceding the HCT. In comparison, all surviving patients in the nontreated and symptomatic group were severely affected with overwhelming spasticity, blindness and a developmental level equivalent to that of a 1-month-old. On the basis of the encouraging data from this study, HCT is an accepted indication for asymptomatic patients, whereas it is no longer advised for the symptomatic ones. For the late-onset form of GLD also there seems to be an indication, when timed appropriately, although the number of patients transplanted for this form of GLD is low. It remains important to follow all GLD patients up for the rest of their lives to determine the real long-term effect.

#### X-linked adrenoleukodystrophy

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder involving defective  $\beta$ -oxidation of very long-chain fatty acids (VLCFAs). Six clinical phenotypes are described, ranging in severity from the ‘Addison-only’ phenotype without CNS involvement to the rapidly progressive ‘childhood-onset cerebral form’ as the most severe form (Moser 1997, 2001). Although compliant use of ‘Lorenzo’s oil’ in boys may reduce, but not eliminate, the risk for development of the childhood cerebral X-ALD (Moser et al 2003), HCT is assumed to be the only effective treatment for childhood cerebral X-ALD. A first HCT was performed as early as 1982, but the first successful case was reported many years later in 1991 by Aubourg and colleagues (1990). Recently, Peters analysed 94 patients, of the 126 patients transplanted worldwide between 1982 and 1999, including only 5 patients reported before 1990 (Peters et al 2004). All patients showed either clinical symptoms (neurological deficits) or MRI changes suggestive for early cerebral X-ALD according to the Loes criteria (Loes et al 1994a, b). The survival in this group was 53/94 (56%). With a transplantation-related mortality of 14%, disease progression was by far the main

cause of death in transplanted patients. However, looking at the long-term follow-up data, based on neurological deficit score and X-ALD disability rating scale (Peters et al 2004), it appears that many patients were already severely affected at the time of HCT; only 34/94 patients (36%) had an X-ALD disability rating scale value of 0 or 1 before HCT (values indicating that there are no or few problems not requiring support/intervention in daily life). After HCT only 17/94 (18%) had a disability rating scale value of 0 or 1. This number includes 2/36 patients (5.5%) having a disability rating scale of 2. Of the other surviving patients, 8/94 (9%) had moderate difficulties and required support or interventions in some areas of daily life. The remaining 30% are alive but severely incapacitated. This leads to the conclusion that despite successful (donor engraftment) HCT in the less affected group, disease progress occurs in more than 40% of the patients. It is also shown that the more neurological deficits present before HCT, the more likely the disease will progress post HCT (Peters et al 2004). These results as well as the results from Shapiro and colleagues (2000) suggest that HCT is indicated only for carefully selected cases. The absence of any correlation between the clinical phenotype and the ALD-gene mutation or the biochemical defect, and the effectiveness of HCT only at an early stage of disease, leads to the recommendation of careful planning and frequent observation of all boys biochemically identified as having X-ALD with normal brain MRI (Shapiro et al 2000). Thus, careful and continuous MRI (and magnetic resonance spectroscopy) examinations (Eichler et al 2002) and neuropsychological tests are the only tools allowing the identification of patients who will benefit from HCT (having MRI changes according to the Loes criteria) (Loes et al 1994a, b). Even then patients and parents should be aware that the disease may progress despite successful (donor cell engraftment) HCT.

For the other X-ALD phenotypes there does not appear to be a role for HCT, as for adrenomyeloneuropathy (AMN) (Moser 1997, 2001). This phenotype will develop during the third or fourth decades of life with or without cerebral involvement. But if a successfully transplanted patient with childhood cerebral X-ALD does not develop AMN later, this would suggest that HCT may also prevent the onset of this form of disease, since all untreated cerebral X-ALD patients develop AMN when they are older than 25 years of age.

### Other LSDs

For all other LSDs and peroxisomal disorders, only limited data are available. The recommended indications and contraindications summarized by Peters and Steward are mainly based on some smaller series, single case reports and personal communications (Peters and Steward 2003). For some indications however, despite low numbers of transplanted

patients, there is some evidence that HCT dramatically ameliorates the natural course of disease (e.g.  $\alpha$ -mannosidosis, MLD). No large series are available for MLD, but the general opinion is that HCT is recommended in presymptomatic patients, on the basis of preservation of neuropsychological functions after successful HCT (Malm et al 1996; Peters 2003). In contrast, for some others, available data suggests that successful HCT failed to ameliorate disease progression (e.g. Hunter–Sanfilippo syndrome and symptomatic MLD) and is therefore not an appropriate indication for HCT (Klein et al 1995; Vellodi et al 1992; Wall et al 1998). This again indicates that the exact mechanism of effective HCT for IEMs is not clear. Perhaps the site of primary involvement of the diseases might be important for the outcome. For instance, in Sanfilippo the CNS is primarily and mostly compromised, with relatively few somatic manifestations. At the time of diagnosis for most patients, neurodevelopment is already retarded. We have learned from all the HCT procedures performed for IEMs that damage to the CNS is irreversible, as demonstrated by X-ALD and GLD, and is therefore a contraindication for HCT (Escolar et al 2005; Peters et al 2004). This might be applicable to all IEMs. Presymptomatic HCT offers hope that it might influence the course of the disease in disorders affecting the CNS. To detect these cases, a prenatal diagnosis or prompt postnatal selective screening is required. It should be stressed that for such cases undergoing HCT, it is very important to report the results. Even after more than 20 years of HCT for IEMs it is still not clear for some diseases whether patients might benefit from HCT. A good registry might give answers earlier and could result in more firmly based guidelines. The best way to achieve this goal would be a registry for all patients transplanted worldwide.

### Stem cell source: unrelated cord blood (UCB) as an emerging stem cell source

Although longer-term follow-up data of successfully transplanted children are very encouraging for some diseases, graft failure and transplantation-related mortality are a limiting factor for success. For Hurler syndrome/disease, for instance, ‘alive and engrafted’ rates vary between 25% and 85% (Table 2) (Boelens et al 2005a; Kurtzberg and Krivit 2004; Peters et al 1996, 1998a; Souillet et al 2003; Staba et al 2004). In addition to graft failure, the availability of an unrelated donor is a limiting factor. Many children lack a matched family donor, and recruitment of an unrelated adult donor sometimes takes months, too long for the treatment of a (rapidly) progressive disorder. Banked umbilical-cord blood from unrelated donors is readily available because of prospective HLA-typing (Rubinstein et al 1993, 1995). Within a month from diagnosis, HCT can be performed using UCB as a stem cell source (Chao et al 2004; Escolar

**Table 2** Overview of ‘alive and engrafted’ rates for Hurler syndrome after first HCT

	<i>n</i>	Median age at treatment (months)	Donor source	Median follow-up (months)	Alive and engrafted (%)	Note
Peters et al (1996)	40	18	BM	36	43 <sup>a</sup> 25 <sup>a</sup>	High BM dose Low BM dose
Peters et al (1998a)	54	18	BM	100	75 <sup>a</sup> 33 <sup>a</sup>	SIB HIR (14/26 TCD)
Souillet et al (2003)	27	25	BM	72	70 <sup>a</sup>	
Staba et al (2004)	35	16	Cord	36	87	All full donor chimerism
Boelens et al (2005a)	146	18	Various	38	57 <sup>a</sup>	

BM, bone marrow  
<sup>a</sup>30–40% mixed chimerism

et al 2005; Staba et al 2004). In addition, better engraftment rates are reported (Staba et al 2004) for UCB in comparison to other stem cell sources (Table 2). Thus, in theory, optimizing the transplantation techniques to result in fewer graft failures and faster availability of unrelated donors can greatly improve the outcome of patients with IEM.

Regarding the better engraftment rates reported for UCB in IEMs, it is not clear whether cord blood is an independent factor for better engraftment. The risk factors for graft failure were assessed in the European retrospective study (*n* = 146: 1994–2004) mentioned above for Hurler syndrome. Using a multivariate analysis (with possible confounders sex, age, conditioning, graft source, T-cell depletion, HLA-disparity, (un)related donor, busulfan-targeting, and heterozygous donor regarding gene defect), T-cell depletion (RR 5.7: 2–28) and reduced intensity conditioning (RR 13.4: 3–67) were found to be risk factors for nonengraftment (Boelens et al 2005a). No difference was found between stem cell sources (peripheral blood stem cells (PBSC), bone marrow (BM) and cord blood), but significantly more patients receiving a cord blood (16/17: 94%) had a full donor chimerism in comparison with patients receiving PBSC/BM (42/66: 63%). Reviewing the literature, the ‘alive and engrafted’ rates after umbilical cord blood were encouraging (Table 3) (Boelens et al 2005a, b; Escolar et al 2005; Staba et al 2004). Rates vary from 72% up to 100%, with only one patient having mixed chimerism (Table 3). In addition to the better engraftment, lower rates of acute graft-versus-host disease

(GvHD: 15–20% ≥ grade II for UCB versus 30–55% for BM and PBSC) and no cases of extensive chronic GvHD were reported (Boelens et al 2005a, b; Kurtzberg and Krivit 2004; Peters et al 1996, 1998a). Lower GvHD rates were also reported using UCB for other diseases (Ballen 2005; Chao et al 2004; Gluckman et al 2004; Wagner et al 2001). No clear guidelines have yet been defined regarding HLA disparities allowed in HCT using UCB. One or two mismatched UCBs (according to the Rubinstein criteria) are mostly used (Escolar et al 2005; Gluckman et al 2004; Staba et al 2004), which is in general a higher mismatch compared to the molecularly (high-resolution: HR) typed unrelated donors. Despite the higher number of HLA disparities, the outcome seems to be comparable with mismatched unrelated donors (with a lower number of HLA disparities) (Laughlin et al 2005; Rocha et al 2005). In addition, a recent paper showed that further HR-typing of UCB does not improve long-term clinical outcome, despite the fact that this analysis showed that the mismatching was even higher than expected (up to a mismatch of 8/10) (Kogler et al 2005). The cell dose of the UCB, on the other hand, does seem to influence the outcome: higher cell doses of the UCB are associated with higher engraftment rates (Gluckman et al 2004). Nevertheless, more studies are needed. With future studies (retrospective/prospective), clear guidelines for HLA disparity and cell dose might improve donor selection and outcome of HCT using UCB.

As summarized above, the advantages of banked umbilical cord blood are (1) rapid availability, associated with (2) a

**Table 3** ‘Alive and engrafted’ rate after first UCB HCT in IMD: a literature review

	<i>n</i>	Median age at treatment (months)	Disease	Median follow-up (months)	Alive and engrafted (%)
Escolar (2005)	11	0.5	Krabbe	36	100
Kurtzberg and Krivit (2004)	35	18	Hurler	36	87
European study	24	18	Hurler	36	72
last 5 years	16	17		15	82
ERT data (2005)	10	18	Hurler	10	80
Utrecht (2005)	9	14	Various	8	78

lower incidence of GvHD (therefore less stringent criteria for HLA-matching), (3) reduced likelihood of transmitting infection (viral), (4) less graft-failure reported for IEM, and finally (5) suggestions of capability for transdifferentiation (to osteoblasts and astrocytes, for instance) because of a more primitive stem cell population.

Based on these results, new EBMT guidelines were defined for HCT in IEMs. T-cell depletion and reduced intensity conditioning are risk factors for graft failure and should therefore be avoided. If no identical sibling donor is available, second in the hierarchy is either a matched UCB donor (according to the Rubinstein criteria; Rubinstein et al 1993, 1995) or a matched (molecularly) unrelated donor. When no identical donor is available or prompt availability is required, the next choice is mismatched cord blood – 5 out of 6 or 4 out of 6, according to the Rubinstein criteria (Rubinstein et al 1993, 1995). This gives UCB a higher place in the stem cell hierarchy in HCT for IEMs.

### ERT in combination with HCT

In recent years, ERT has become available or will soon be available for various lysosomal disorders (e.g. Gaucher disease, MPS I, II, VI, Niemann–Pick A/B, Fabry disease, Pompe disease). Unfortunately, for the ‘neuronopathic’ forms of these diseases, HCT will still be needed because the ‘blood–brain barrier’ prevents passage of the ERT. Despite this drawback of ERT, it was postulated that ERT could probably influence the mortality and morbidity rates by bringing the patient into a better clinical condition before HCT, and positively influence the engraftment rates. Recently, a review of the data of 21 Hurler patients who underwent HCT in combination with ERT in Europe between December 2003 and April 2005 were analysed to assess the ‘alive and engrafted’ rate and transplantation-related morbidity/mortality (Boelens et al 2005b). The weekly ERT dose was 100 U/kg from diagnosis until approximately 7 weeks (range 0–20 weeks) after successful HCT. Except for one patient, clinical condition was moderate/good before the start of ERT. Before HCT, clinical condition was good for all patients. The ‘alive and engrafted’ rate after first transplantation and the overall ‘alive and engrafted’ rate after one to three HCT procedures was 12/21 (57%) and 18/21 (86%), respectively. The median follow-up was 8 months (3–17 months). Two patients died: one after the second HCT and one after the third HCT. In a multivariate analysis (probable confounders: age, sex, heterozygote donor, (un)related donor, stem cell source, HLA disparity, conditioning regimen, T-cell depletion, ERT and busulfan targeting) with the historical control group (described earlier:  $n = 146$ ), ERT did not significantly influence the primary endpoint of ‘alive and engrafted’ (RR

0.54: 0.15–2) (Boelens et al 2005b). In addition, morbidity and mortality rates similar to those for the historical group. ERT infusion-related toxicity was limited to mild reactions.

In summary, in patients with Hurler syndrome, ERT in combination with HCT was well tolerated but had no effect (either positive or negative) on the engraftment in this group. No differences in morbidity and mortality rates were found in comparison to the historical group (EBMT data) (Boelens et al 2005a, b). Only in selected patients in poor clinical condition prior to HCT might ERT be of advantage. For patients in good clinical condition, there appears to be no advantage of ERT, especially because HCT can be performed within 1–2 months of diagnosis owing to the availability of banked umbilical cord blood.

### Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are pluripotential stem cells with the potential to differentiate into various cells of mesenchymal origin: osteoblasts, chondrocytes, adipocytes and astrocytes. For most IEMs, HCT does not resolve all the symptoms and defects remain after successful HCT, such as neurological defects (polyneuropathy) in metachromatic leukodystrophy (MLD) and Krabbe disease and musculoskeletal defects in most MPS disorders. It was therefore hypothesized that residual defects could be corrected by supplemental cell therapy in the form of mesenchymal cells. This was investigated by Koc and colleagues (Koc et al 1999, 2002). Twelve successfully transplanted MLD and Hurler patients received *ex vivo*-expanded MSCs from their initial identical donor years after HCT. Although no clinically apparent changes in the patient’s overall health and mental and physical development were noted, changes in ‘bone mineral density’ and ‘nerve conduction velocity’ were interesting observations. No side-effects were reported, indicating that MSC infusion was a safe procedure in the patients. Although no clear clinical effect was found in this study, MSCs remain an interesting cell population because of their capability for transdifferentiation. MSCs therefore represent an expanding area, not only in IEMs but also for other indications (e.g. tissue repair, acute GvHD) (Le Blanc et al 2004; Nauta et al 2004). Although the field of MSC transplantation is ‘investigational’, multiple infusions of donor MSCs, co-infusion of donor MSCs at the time of HCT and targeted delivery of MSCs may result in improved outcome in storage diseases by halting musculoskeletal deformities or neurological disease before damage is present.

### Conclusions

Until there is effective and safe gene-therapy, HCT can be an effective procedure for selected IEMs (e.g. Hurler disease,

infantile Krabbe disease and X-ALD). For other disorders the effects/outcome of HCT are still difficult to assess because of the limited number of cases, the wide range of clinical heterogeneity and the absence of a good functioning registry for proper long-term follow-up. The indications and contraindication listed by Peters and Steward are good guidelines to start with (Peters and Steward 2003). Guidelines, however, should be interpreted in the context of emerging progress in transplantation. Improvement of transplantation techniques and alternative therapies may change the recommended (contra-) indications for IEMs.

A recent example of emerging transplantation techniques is the rapid availability of unrelated cord blood (UCB). UCB makes HCT feasible in patients with rapidly progressive neurological diseases (Escolar et al 2005; Staba et al 2004). In addition to the rapid availability of UCB (often within a month of diagnosis), less graft failure and GvHD are reported, resulting in better outcome. One implication of the use of UCB in asymptomatic patients might be antenatal or prompt postnatal screening in selected cases or even newborn screening for IEMs for which asymptomatic HCT has proved to be successful. Because of the rapid availability of UCB and therefore the ability to transplant shortly after diagnosis, there is no indication for patients in a moderate/good clinical condition to receive ERT (in Hurler syndrome) prior to or during HCT, and ERT need only be considered in patients with poor clinical condition. Finally, MSC infusion with HCT is an emerging technique, and might be interesting in halting the remaining defects after successful HCT.

Improvement in HCT techniques and novel stem cell sources will significantly impact the safety and efficacy of this therapy as well as expanding the list of candidate disorders. A good functioning worldwide registry would be necessary to measure the effects of the procedures performed in more detail.

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