

Mini review

Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines

C Peters¹ and CG Steward² on behalf of the NMDP, IBMTR, and the Working Party on Inborn Errors of the EBMT

¹Division of Hematology/Oncology, Blood and Bone Marrow Transplantation, Department of Pediatrics, University of Minnesota School of Medicine, Minneapolis, MN, 55455, USA; and ²Bone Marrow Transplant Unit, Royal Hospital for Children, Upper Maudlin Street, Bristol, BS2 8BJ, UK

Summary:

For the past two decades, hematopoietic cell transplantation (HCT) has been used as effective therapy for selected inherited metabolic diseases (IMD) including Hurler (MPS IH) and Maroteaux–Lamy (MPS VI) syndromes, childhood-onset cerebral X-linked adrenoleukodystrophy (X-ALD), globoid-cell leukodystrophy (GLD), metachromatic leukodystrophy (MLD), α -mannosidosis, osteopetrosis, and others. Careful pre-HCT evaluation is critical and coordinated, multidisciplinary follow-up is essential in this field of transplantation. The primary goals of HCT for these disorders have been to promote long-term survival with donor-derived engraftment and to optimize the quality of life. Guidelines for HCT and monitoring are provided; a brief overview of long-term results is also presented.

Bone Marrow Transplantation (2003) 31, 229–239.
doi:10.1038/sj.bmt.1703839

Keywords: inherited metabolic storage disease; mucopolysaccharidosis; Hurler syndrome; leukodystrophy; osteopetrosis; hematopoietic cell transplantation

In 1968, Fratantoni and Neufeld laid the foundation for our understanding of transferable lysosomal enzymes by demonstrating cross-correction of defects in cocultures of fibroblasts from Hurler and Hunter syndrome patients.¹ This observation and the later demonstration of correction by lymphocyte extracts or serum^{2,3} led Hobbs⁴ to trial hematopoietic cell transplantation (HCT) as a permanent source of enzyme in a Hurler patient. The dramatic improvement effected in the disease phenotype has resulted in two decades of HCT for many other inherited metabolic diseases (IMD).^{5–7}

There have been many surprises along the way. From the impressive results in Hurler syndrome,^{8,9} it was expected that all mucopolysaccharide (MPS) disorders could be alleviated by HCT. Sadly, among these other MPS subtypes, benefit from HCT only appears to be significant for MPS VI (Maroteaux–Lamy)^{10,11} and VII (Sly),¹² although the reasons for this remain unclear. However, promising results have been obtained in various other disorders. In some, these could be anticipated (eg, metachromatic⁷ and globoid-cell leukodystrophies⁵ because of their lysosomal enzyme basis) but in others (eg, X-linked adrenoleukodystrophy⁶), the mechanism underlying the success of timely HCT remains enigmatic even as our understanding of the disease pathogenesis evolves.

Evaluation of the true long-term value of HCT has been difficult for a variety of reasons: (a) Most diseases have a wide spectrum of clinical phenotype, which can be difficult to predict at diagnosis. (b) Benefit varies between organ systems. Reticuloendothelial organs such as liver and spleen often shrink quickly as engorged macrophages take up enzyme; however, CNS improvement is slower because of turnover of microglia and their replacement by donor-derived cells.¹³ The latter may explain the typical ‘incubation period’ of 6–12 months post-HCT before CNS deterioration is stabilized.⁶ Unfortunately, there is little impact of HCT on bone disease,¹⁴ presumably because of poor enzyme penetration into chondrocytes and the failure to correct or replace osteocytes. (c) Numerous aspects of the transplant affect outcome, for example, donor enzyme level, degree and persistence of donor chimerism, post-transplant complications, especially GVHD,^{8,9} and occasionally antibody formation against the novel protein to which the patient does not have tolerance.

Only now, with the benefit of years of follow-up and sufficient patients of each disease and phenotype transplanted, is it possible to draw conclusions for the commoner diseases transplanted. In this mini review, we summarize the impact of HCT on these candidate diseases, outlining recommended indications and contraindications. These must be seen in the context of emerging technology and may evolve as either transplantation techniques improve or alternative therapies emerge. For example, we have highlighted approaches such as enzyme replacement therapy (ERT) and mesenchymal stem cell infusion where

Correspondence: Dr Peters, Division of Hematology/Oncology, Blood and Bone Marrow Transplantation, Department of Pediatrics, University of Minnesota, Mayo Mail Code 477, Rm D-580 Mayo Building, 420 Delaware St SE, Minneapolis, MN 55455, USA
Received 0 January 2002; accepted 12 January 2002

these are under trial or development. We would stress that the following comments are only guidelines. In such complex diseases a decision to transplant can only be taken after extensive assessment, discussion, and counseling between metabolic and transplant experts and patients and their families.

Mucopolysaccharidosis (MPS)

The MPS disorders are a family of inherited disorders caused by deficiency of lysosomal enzymes needed to degrade glycosaminoglycans (GAGs) and are classified as types I–VII.¹⁵ MPS I has a spectrum of subtypes ranging from mild (Scheie, MPS IS), though moderate (Hurler–Scheie, MPS IHS) to severe (Hurler, MPS IH).¹⁵

Hurler syndrome (MPS IH)

MPS IH is characterized by progressive mental retardation and hydrocephalus, frequent ear infections and auditory impairment, corneal clouding, sleep apnea, cardiopulmonary disease (including thickened valves, coronary artery narrowing, pulmonary hypertension, and congestive heart failure), hepatosplenomegaly, and severe skeletal abnormalities (termed dysostosis multiplex). These result in substantial morbidity and early death, typically occurring between 5 and 15 years of age.¹⁵

Engraftment after HCT in Hurler patients leads to rapid reduction in GAG substrate in liver, tonsils, conjunctiva, CSF, and urine.^{4,16–18} As a consequence, obstructive airway symptoms are dramatically reduced^{19,20} together with hepatosplenomegaly^{4,21} and corneal clouding¹⁶, hydrocephalus is either prevented or stabilized^{22,23}, hearing improves in many children²⁴ and heart failure and tachyarrhythmias are eliminated by 1 year after successful HCT.^{25,26} Myocardial muscle function is stabilized or improved and coronary artery patency has been documented as long as 14 years after HCT.²⁷ However, some disease features show much poorer response because of poor penetration of α -L-iduronidase into the relevant tissue. Principal among these is the dysostosis multiplex,¹⁴ and successfully transplanted children often require major orthopedic surgery for genu valgum, acetabular hip dysplasia, kyphoscoliosis, carpal tunnel syndrome, and trigger digits.^{28–31} These problems need careful monitoring and appropriate intervention, although the optimal timing of the latter is still debated. Further intellectual and developmental deterioration may occur, especially in the first year post transplant (possibly aggravated where donor enzyme levels are low as in heterozygotes). Cardiac valvular deformities persist and can progress.³²

The positive changes mostly occur rapidly in the early years after HCT and greatly improve the quality of life. However, the orthopedic and CNS problems may have major adverse impact from the age of 5 years. These factors must be taken into account alongside a relatively high incidence of primary and secondary graft failure.^{4,8,9,33–36} The etiology of graft failure is unclear although aberrant processing of busulfan does not appear to be responsible.³⁷ This increases the transplant-related mortality and means

that many children require repeat procedures.³⁶ A decision to transplant in MPS IH therefore requires extremely careful patient assessment and family counseling especially where alternative donors are to be used. It is critical to perform the transplant as early as possible, ideally before 18 months of age, while intellectual function is relatively well preserved.^{8,9} Also, ongoing intensive physical, occupational, and speech therapy are essential to optimizing development before, during, and after HCT

Hurler/Scheie and Scheie syndromes (MPS IHS and MPS IS)

The indication for HCT is less clear in these phenotypes of MPS I because of the much slower disease course.¹⁵ In MPS IH/S, the central nervous system deterioration can be insidious; for MPS IS life expectancy can extend into the fourth and fifth decades. It seems likely that enzyme replacement therapy³⁸ will become the mainstay of therapy for these children since lack of CNS penetration of administered enzyme is less crucial than in MPS IH. However, this may change if transplantation technology improves substantially, especially with the use of less intensive conditioning regimens.

Hunter syndrome (MPS II)

MPS II also comes in a range of phenotypes, some being relatively mild.¹⁵ Unfortunately, severity is difficult to predict accurately at diagnosis. This may explain the presence of several case reports (all with relatively short follow-up), suggesting a beneficial effect from HCT.^{39–41} However, there have also been many extremely disappointing outcomes from transplants.^{23,42,43} It is the firm belief of the authors, and of many metabolic physicians experienced in following such children, that MPS II is not an appropriate indication for HCT. The reasons for the poor CNS responses (as in MPS III) remain unclear.

Sanfilippo syndrome (MPS III)

MPS III patients have progressive neurodevelopmental delay but with relatively few somatic manifestations.¹⁵ Successful HCT performed early in the MPS III disease course does not seem to ameliorate neuropsychological deterioration significantly.^{44–46}

Morquio syndrome (MPS IV)

Patients with MPS IV exhibit severe dysostosis multiplex, but typically have preserved intellectual function.¹⁵ At this time, there is no role for HCT since skeletal deformities can not be helped to any appreciable extent.²³

Maroteaux-Lamy syndrome (MPS VI)

MPS VI is characterized by the onset of hydrocephalus and subsequent mental decline, cardiopulmonary dysfunction, hepatosplenomegaly and dysostosis multiplex;¹⁵ the disease has mild and severe phenotypes. Reported benefits of HCT in MPS VI include enzymatic and biochemical correction,

resolution of hepatosplenomegaly, stabilization of cardiopulmonary function, and improvement of visual acuity and joint mobility.^{10,11,40} All phenotypes of MPS VI are associated with reduced life expectancy and should therefore be considered candidates for HCT or ERT.

Sly syndrome (MPS VII)

MPS VII, in certain circumstances, can be ameliorated by HCT provided that the neuropsychological and clinical status of the patient is good at the time of transplant.¹²

Leukodystrophies and other white matter diseases

Cerebral x-linked adrenoleukodystrophy (X-ALD)

X-ALD^{47,48} is a peroxisomal disorder involving defective β -oxidation of very long-chain fatty acids (VLCFA). Phenotypes vary in severity from pure Addisonian presentations without obvious CNS involvement,⁴⁹ through the insidious adult-onset form (adrenomyeloneuropathy (AMN)), adolescent and adult onset cerebral X-ALD to the rapidly demencing and fatal childhood onset cerebral form at most severe. Approximately 40% of boys with X-ALD will develop childhood cerebral disease.⁴⁷ The remaining boys are likely to develop AMN during the third or fourth decades with or without cerebral involvement. There does not appear to be a role for HCT in AMN alone based upon the nature of the disease (an axonopathy) and limited HCT experience in several cases.

HCT must be reserved for boys/men who have early yet definite evidence of cerebral disease as determined by brain magnetic resonance imaging⁵⁰ (MRI). In the near future, it is anticipated that magnetic resonance spectroscopy (MRS) will supplant MRI for the earliest detection of cerebral disease.^{51–54} A timely diagnosis is unlikely to occur in males identified from disease signs and symptoms because of the rapidly progressive character of cerebral X-ALD,⁴⁷ the expected delays in performing medical evaluations and confirming the diagnosis. However, boys less than 15 years of age diagnosed with X-ALD because of positive family history yet still symptom free can and should be monitored serially for the earliest evidence of demyelination.⁵⁵ These monitoring tests include gadolinium-enhanced brain MRI scans^{50,56} at intervals of 6 months or less to evaluate for cerebral demyelination on T2-weighted images, neuropsychological measures, and endocrinologic tests to evaluate for adrenal insufficiency (ie, Addison's disease). It appears that an MRI severity score as low as 2–3 and/or gadolinium enhancement⁵⁰ in a boy less than 10 years of age with X-ALD, is highly predictive (approaching 90%) of subsequent progressive cerebral demyelination. It is strongly suggested that such boys undergo HCT as soon as possible. Conversely, boys without evidence of abnormality on brain MRI should be monitored and not transplanted given the likelihood of not developing childhood cerebral form of X-ALD⁴⁷ (*vide supra*).

The 5 to 10-year follow-up of 12 boys with childhood-onset cerebral X-ALD shows the long-term beneficial effect of HCT when the transplant is done at an early stage of

disease.^{6,57,58} Outcome measures included neuroradiologic assessment of demyelination, neurologic examination, and neurocognitive testing including verbal intelligence and performance (nonverbal) abilities. Unfortunately, the typical boy with parietal–occipital demyelination who is diagnosed due to clinical symptomatology (ie, not at an early stage of disease) has relatively spared verbal intelligence, visual processing difficulties, neurologic impairments in one or more of the following areas – vision, hearing, speech, and gait; and an MRI severity score always >7 and usually ≥ 11 . The HCT and disease-specific outcomes in these boys have been very discouraging with many dying of progressive ALD.^{50,55,56} For survivors, there are permanent, severe neurologic, and neuropsychologic sequelae; quality of life is compromised. Clearly, as currently practiced, HCT has not been successful for these patients.

Globoid-cell leukodystrophy (GLD)

GLD is characterized by periventricular demyelination and has two major phenotypes: (1) early onset also known as Krabbe disease and (2) late onset – juvenile and adult forms.⁵⁹ With appropriate timing and use of HCT, GLD can be effectively treated in late onset cases with normalization of CSF protein, stabilization of the neurologic examination, neuropsychologic function, and the extent of demyelination on MRI.⁵ However, to date, Krabbe disease, if diagnosed antenatally, can only be ameliorated if HCT is performed in the neonatal period.^{5,60}

Metachromatic leukodystrophy (MLD)

MLD, definitively diagnosed based upon both leukocyte arylsulfatase A deficiency and increased urinary sulfatides (in order to exclude patients with pseudodeficiency of arylsulfatase A),⁶¹ cannot be treated effectively by HCT if neuropsychologic and/or neurologic signs are advanced or in late-infantile disease.^{62–65} HCT is recommended in presymptomatic patients or while neuropsychologic function and independence in activities of daily living remain good.^{63–66} Late infantile MLD may be helped if HCT occurs early in the first year of life following early post-natal or pre-natal diagnosis.⁶⁷ Koc *et al*⁶⁸ are investigating the role of mesenchymal stem cell infusion for MLD (See the Clinical care guidelines and future directions section).

Other leukodystrophies: Pelizaeus-Merzbacher, Zellweger syndrome, Vanishing white matter disease, etc

To date, there has been neither experience nor a rationale developed for the use of HCT for any of the following leukodystrophies: Pelizaeus–Merzbacher,⁶⁹ Zellweger syndrome,^{70,71} and vanishing white matter disease.^{72,73}

Glycoprotein metabolic disorders

Fucosidosis

The extremely limited HCT experience in fucosidosis (ie, probably less than 10 HCT cases in the world) precludes

any definitive statement about the outcomes. HCT performed early in the disease course may be beneficial.^{74–76}

Gaucher disease types I, II, III

HCT is effective in alleviating most disease manifestations of Gaucher including arresting further neuropsychological deterioration in type III (Norbottnian) disease^{77–81} and greatly reducing skeletal problems in severe early onset type I disease.^{34,82–84} HCT is not currently regarded as first-line treatment because of the low morbidity of ERT.^{85,86} This approach may change in type III disease as ERT results are closely scrutinized and if HCT techniques improve.⁸⁷ The only experimental indication for HCT at present is in type III children who deteriorate neurologically and/or have pulmonary compromise while on ERT.^{87,88}

α -mannosidosis

At this time, fewer than 20 cases have been transplanted in the world. Pulmonary complications may be increased during the first several months after HCT. Early and later follow-up (ie, at ≥ 4 years) in several cases suggests that neurocognitive and cardiopulmonary function have been preserved, implying that HCT has had a favorable impact on the natural history of α -mannosidosis.^{75,89}

Aspartylglucosaminuria (AGU)

Four Finnish patients with AGU received HCT;⁹⁰ recent longer-term follow-up raises questions about the degree of benefit from HCT.⁹¹

Miscellaneous disorders

Neuronal ceroid lipofuscinosis (NCL)

Two forms of NCL (ie, NCL 1 and 2) are recognized as true lysosomal enzyme storage disorders (see Table 1), suggesting that HCT could be successful.⁹² However, this has not been borne out by the only presymptomatic HCT performed in NCL 2 or by animal model transplant studies.^{93–96} Additional data are needed.

Niemann–Pick (NP, types A, B, and C)

NP type A is not amenable to effective treatment with HCT because of its rapid progression;^{97,98} there is limited experience suggesting that HCT ameliorates NP type B.⁹⁹ It should be noted that ERT clinical trials are planned for NP type B. The case report describing a patient with NP type C treated with HCT is not encouraging.¹⁰⁰

Mucopolipidosis, type II (I-cell disease)

Historical experience with HCT for I-cell disease¹⁰¹ was initially only in patients with end-stage cardiopulmonary disease.^{40,102,103} Over the past 5 years, three patients (0.3–1.7 years of age at HCT) have been transplanted at the University of Minnesota.¹⁰⁴ The early follow-up has shown good cardiopulmonary function in two patients

while one has developed pulmonary hypertension. All children remain mildly to moderately neurodevelopmentally delayed and are receiving appropriate additional educational resources.

Gangliosidoses

The G_{M2} gangliosidoses include Tay–Sachs disease, Sandhoff disease, and G_{M2} activator deficiency and demonstrate widely varying clinical phenotypes. Infantile onset, rapidly progressive neurodegenerative disease leads to death by 4 years (classic Tay–Sachs, Sandhoff and G_{M2} activator deficiency), while later onset subacute or chronic forms show more slowly progressive neurologic conditions compatible with survival into late childhood, adolescence, or even long-term survival. HCT does not appear to successfully treat these disorders. However, future therapy that combines direct CNS intervention with HCT may ultimately prove beneficial.^{23,105}

G_{M1} gangliosidosis typically presents in infancy; however, later onset forms are also recognized (ie, type 2 disease).¹⁰⁶ HCT may be beneficial in type 2 patients with suitable neurologic and neuropsychologic function, though not in type 1 infants.¹⁰⁷

Malignant infantile osteopetrosis (MIOP)

Absence or defective function of osteoclasts causes this disease of bone sclerosis.¹⁰⁸ There are many animal models, both spontaneously occurring and created by gene knock-outs, although few seem to have overlap with human disease.^{109–111} It is becoming apparent that there are also multiple causes in humans.^{110,112,113} The commonest is mutation of a gene encoding a vacuolar proton pump, which is responsible for approximately 50% of human cases.^{113,114} All of the described genetic causes of osteopetrosis are defects in acidification and are not abnormalities of osteoclast differentiation. However, the phenotypic variation of the disease suggests that additional gene defects will be defined.

Some other forms of MIOP are metabolic diseases with a neurological component. These include carbonic anhydrase II deficiency¹¹⁵ (renal tubular acidosis and cerebral calcification) and a severe disease characterized by early onset of spasticity and death with eosinophilic inclusion bodies seen on CNS pathological examination (here termed ‘neuronopathic’ osteopetrosis since it mimics neuronal ceroid lipofuscinosis).^{116,117} In both diseases HCT abolishes bone sclerosis. However, it has no impact on neurodegenerative disease in the latter form^{116,118} and CNS amelioration in CAII deficiency seems unlikely.^{115,119} Therefore, these issues must be considered as transplantation is discussed in affected children.

Distinguishing children with neuronopathic osteopetrosis from those with the conventional disease is difficult, especially since these children are often irritable. This can be because of occult hypocalcemia in the first two months,¹²⁰ multiple fractures, hydrocephalus, or raised intracranial venous pressure (because of bony encroachment on the jugular foramen). There should be strong suspicion of primary neurological disease if irritability does not respond to correction of hypocalcemia and analgesia.

Table 1

<i>Disorder</i>	<i>Genetics</i>	<i>Enzyme/Protein</i>	<i>HCT</i>	<i>Other treatments</i>
<i>(A) MPS</i>				
MPS I Hurler (MPS IH) Hurler/Scheie (MPS IH/S) Scheie (MPS IS)	AR	α -L-iduronidase	Yes Yes No	ERT – clinical trials ERT – clinical trials
Hunter (MPS II) MPS II A MPS II B	X-linked	Iduronate-2-sulfatase	No No	ERT – clinical trials
Sanfilippo (MPS III) MPS III A MPS III B MPS III C MPS III D	AR	Heparan- <i>N</i> -sulfatase <i>N</i> -acetylglucosaminidase AcetylCaA: <i>N</i> -acetyltransferase <i>N</i> -acetylglucosamine 6-sulfatase	No No No No	
Morquio (MPS IV) MPS IV A MPS IV B	AR	Galactose 6-sulfatase β -galactosidase	No No	
Maroteaux–Lamy (MPS VI) MPS VI Mild MPS VI Severe	AR	Arylsulfatase B	No Yes	ERT – clinical trials
Sly (MPS VII)	AR	β -glucuronidase	Yes	
<i>(B) Leukodystrophies and other white matter diseases</i>				
X-ALD Childhood and adolescent onset <i>cerebral X-ALD</i> X-ALD without cerebral changes Adult onset cerebral X-ALD with or without AMN	X-linked	ALD protein (increased fasting plasma VLCFA)	Yes No DEV	Lorenzo's oil
Globoid-cell leukodystrophy Early onset Late onset	AR	Galactocerebrosidase	Yes ^a Yes	
Metachromatic leukodystrophy Early onset Late onset	AR	Arylsulfatase A	No Yes	
Alexander disease			No	
Pelizaeus Merzbacher	X-linked	Proteolipid protein (PLP)	No	
Vanishing white matter disease		Mutations in translation initiation factor eIF2B, and possibly others	No	
Zellweger syndrome		Several including accumulation of VLCFA, and marked deficiency of plasmalogens	No	
<i>(C) Glycoprotein metabolic and miscellaneous disorders</i>				
Fucosidosis	AR	Fucosidase	DEV	
α -Mannosidosis	AR	Mannosidase	Yes	
AGU	AR	Aspartylglucosaminidase	DEV	
Cerebrotendinous xanthomatosis	AR	27-Hydroxylase	No	
Fabry	X-linked	Galactosidase A	No	ERT – clinical practice
Farber lipogranulomatous	AR	Ceramidase	DEV	
Gangliosidoses GM1 GM2 Tay Sachs Sandhoff	AR	Galactosidase GM2-activator deficiency Hexosaminidase A Hexosaminidase A & B	DEV No No No	
Gaucher Type I	AR	Glucocerebrosidase	Yes	ERT – clinical practice

Table 1 (continued)

Disorder	Genetics	Enzyme/Protein	HCT	Other treatments
Type II			No	
Type III			DEV	ERT – limited benefit
Glycogen storage disease II (Pompe)	AR	Glucosidase	No	ERT – clinical trial
Mucopolidosis II (I-cell disease)	AR	Phosphotransferase	DEV	
Neuronal ceroid lipofuscinosis	AR			
CLN1 (Batten)		Palmitoyl protein thioesterase	DEV	
CLN2 (Batten)		Tripeptidyl peptidase I	DEV	
Niemann-Pick	AR			
Type A		Acid sphingomyelinase	No	
Type B		Acid sphingomyelinase	Yes	ERT – planned
Type C		Cholesterol trafficking	Probably not	
Osteopetrosis (OP)		Mutation analysis of OC116 and CLN7		
Malignant infantile OP		genes recommended in children	Yes	
Neurodegenerative OP		who do not have CAD	No	
Carbonic anhydrase II deficiency (CAD)			DEV	

^aDuring the neonatal period

AR: autosomal recessive; Yes: routine use in selected patients; DEV: developmental or pilot studies are being undertaken in highly specialized HCT units; No: contraindicated based upon current experience and understanding.

Finding cerebral atrophy on CT scan, retinopathy (as distinct from optic atrophy) may provide other clues on ophthalmic examination and abnormal EEG. Mutation analysis of the OC116 and CLCN7 genes should be considered in children who do not have CA II deficiency.¹¹³

Successful allogeneic HCT is currently the only therapy capable of producing long-term benefit in children.^{121–125} This results in bone remodeling, restoration of growth, and reconstitution of normal hematopoiesis and neutrophil function. Early HCT offers the best possibility for limiting neurosensory defects and impaired growth. Serious risks include high frequencies of graft rejection, veno-occlusive disease, and the newly recognized problem of severe pulmonary hypertension. The latter is easy to mistake for pneumonitis but affects up to 25% of transplanted patients (CG Steward *et al*, submitted for publication). Results using alternative donors have typically yielded poor results but megadose stem cell transplants from family donors matching at least one haplotype are now giving more promising results.¹²⁶

Wolman disease

Deficiency of acid lipase in Wolman disease leads to massive accumulation of cholesteryl esters and triglycerides in most body tissues. HCT has been performed in a small number of patients.¹²⁷ One engrafted surviving patient has been reported.¹²⁸

Clinical care guidelines and future directions

Comprehensive, multidisciplinary care

The best outcomes have occurred following an expeditious and timely referral to a transplant center.^{6,8,9,43,58,64,75}

Comprehensive, multidisciplinary specialist care coordinated through this center, with significant experience in the peri- and post-HCT management of these complex diseases is essential. Specific members of such a team might include a transplant physician who interacts directly with neurologists, geneticists, neuropsychologists, neuroradiologists, ophthalmologists, audiologists, otolaryngologists, pulmonologists, cardiologists, hand and orthopedic surgeons, pediatric surgeons, endocrinologists, anesthesiologists, radiation therapists, pharmacologists, and infectious disease specialists prior to transplant and during annual or every 2-year follow-up evaluations.

Donor and stem cell selection

The source of stem cells could be bone marrow, umbilical cord blood, or peripheral blood. Identification of optimal graft characteristics for these various stem cell sources is ongoing. Specifically, the role of bone marrow graft engineering (T-cell depletion), cell dose (ie, nucleated cells, CD34+ cells), HLA-matching, timing of transplant, and availability are all under study. Selection of the donor will initially focus on the availability of an HLA-matched sibling. If one is not available, alternative donors would include a closely matched unrelated graft or perhaps a graft from a haploidentical relative. There is increasing interest in and use of umbilical or peripheral blood as a source of stem cells. The experience is too limited at this time to draw any conclusions regarding engraftment, incidence or severity of graft-versus-host disease (GVHD), or disease-specific outcomes using these sources of stem cells in IMD patients. However, consideration should be given to their use under appropriate circumstances. It is highly recommended that the relevant leukocyte enzyme activity be determined in the donor. Questions persist regarding the use of a heterozygous (ie, carrier) donor. No definitive

comparison of outcomes has been performed, although higher enzyme levels achieved in the recipient have correlated with better outcomes in Hurler patients.^{9,129}

Preparative regimen

A variety of preparative regimens have been used for these disorders.^{8,9,58,130} No clear preferred regimen has been identified. However, transplanters must be aware of the patient's medical condition and the potential for significant regimen-related toxicity because of disease-specific organ system problems, as well as the propensity for disease progression, particularly in the CNS.^{8,9,36,58} Less intensive conditioning regimens are being explored and may play a role in the treatment of selected patients and diseases.

Alternative stem cells

Koc *et al*⁶⁸ have investigated bone marrow-derived mesenchymal stem cells (MSCs) in 13 patients (Hurler: 5; MLD: 3; X-ALD: 2; Gaucher, MPS VI, GLD: 1 each) from 1 to 14 years after allogeneic HCT and found that MSCs isolated from recipients are not of donor genotype and have persistent phenotypic defects despite successful donor-type hematopoietic engraftment. Whether culture-expanded normal MSCs can be successfully transplanted into patients with IMD and provide therapeutic benefit was unclear. Koc *et al*³¹ have recently reported on allogeneic MSC infusion for treatment of 11 patients (MLD: 6, Hurler: 5). There was no MSC infusion-related toxicity, delayed toxicity, or GVHD at a median clinical follow-up of 2 years. The percentage of MSCs observed to be of donor origin was low (ie, 0.4–2.0%). Although there was no clinically apparent change in patients' overall health and no objective change in mental and physical development after MSC infusion, in four of six MLD patients, nerve conduction velocity was faster after MSC infusion. Bone mineral density was either maintained or slightly improved in all patients. They concluded that donor allogeneic MSC infusion was safe and may be associated with amelioration of disease pathophysiology in some tissues. Growth of other specialized cells including osteoblasts, chondroblasts, neurons, oligodendrocytes, and astrocytes is under study. It can be anticipated that there would be the potential for infusion or direct introduction of such cells to correct existing defects.

Enzyme replacement therapy

Enzyme replacement therapy (ERT) is currently available for a number of IMD and is in development for many others. The role of pre-HCT ERT is yet to be explored but may serve to decrease the incidence and/or severity of transplant- and disease-related complications during the peritransplant period. There may also be a role for the use of ERT after HCT.

Gene therapy

With time, gene therapy could obviously become an adjunct to or even replace HCT. However, pitfalls in the areas of transducing stem cells, achieving high levels of

gene expression, assuring appropriate localization of the gene product as well as sustained gene expression must be addressed.

Conclusions

Transplant therapy can be effective for selected inherited metabolic diseases including MPS syndromes (ie, Hurler, Maroteaux–Lamy, and Sly syndromes), leukodystrophies (ie, childhood and adolescent cerebral X-ALD, GLD, and MLD), fucosidosis, α -mannosidosis, Gaucher disease, Niemann–Pick type B, and malignant infantile osteopetrosis. To increase the likelihood of a good outcome, complex, multidisciplinary decision-making regarding whether to recommend HCT, when to do so, and how to provide optimal peri- and post-HCT care is essential. Transplant has led to favorable outcomes for many but not for all of these disorders. Improvements in HCT techniques and the development of novel stem cells will significantly impact the safety and efficacy of therapy as well as expand the list of candidate diseases.

Acknowledgements

The authors acknowledge the pioneering work of Professors John Hobbs of the Westminster Children's Hospital and William Krivit of the University of Minnesota and the assistance of Drs Paul Orchard and Satkiran Grewal in the preparation of this mini review. The authors also recognize the Working Party on Inborn Errors of the European Bone Marrow Transplant Group, National Marrow Donor Program, International Bone Marrow Transplant Registry, International Storage Disease Collaborative Study Group, and the Correction of Genetic Diseases by Transplantation (COGENT) Society for their roles in promoting international dialogue, collaboration, and co-operation.

References

- 1 Fratantoni JC, Hall CW, Neufeld EF. The defect in Hurler and Hunter syndromes. II. Deficiency of specific factors involved in mucopolysaccharide degradation. *Proc Natl Acad Sci USA* 1969; **64**: 360–366.
- 2 Di Ferrante N, Nichols BL, Donnelly PV *et al*. Induced degradation of glycosaminoglycans in Hurler's and Hunter's syndromes by plasma infusion. *Proc Natl Acad Sci USA* 1971; **68**: 303–307.
- 3 Knudson Jr AG, Di Ferrante N, Curtis JE. Effect of leukocyte transfusion in a child with type II mucopolysaccharidosis. *Proc Natl Acad Sci USA* 1971; **68**: 1738–1741.
- 4 Hobbs JR, Hugh-Jones K, Barrett AJ *et al*. Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation. *Lancet* 1981; **2**: 709–712.
- 5 Krivit W, Shapiro EG, Peters C *et al*. Hematopoietic stem-cell transplantation in globoid-cell leukodystrophy. *N Engl J Med* 1998; **338**: 1119–1126.
- 6 Shapiro E, Krivit W, Lockman L *et al*. Long-term effect of bone-marrow transplantation for childhood-onset cerebral X-linked adrenoleukodystrophy. *Lancet* 2000; **356**: 713–718.

- 7 Stillman AE, Krivit W, Shapiro E *et al.* Serial MR after bone marrow transplantation in two patients with metachromatic leukodystrophy. *Am J Neuroradiol* 1994; **15**: 1929–1932.
- 8 Peters C, Balthazor M, Shapiro EG *et al.* Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. *Blood* 1996; **87**: 4894–4902.
- 9 Peters C, Shapiro EG, Anderson J *et al.* Hurler syndrome: II. Outcome of HLA-genotypically identical sibling and HLA-haploidentical related donor bone marrow transplantation in fifty-four children. The Storage Disease Collaborative Study Group. *Blood* 1998; **91**: 2601–2608.
- 10 Krivit W, Pierpont ME, Ayaz K *et al.* Bone-marrow transplantation in the Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI). Biochemical and clinical status 24 months after transplantation. *N Engl J Med* 1984; **311**: 1606–1611.
- 11 Krivit W. Maroteaux-Lamy syndrome (Mucopolysaccharidosis type VI): treatment by allogeneic bone marrow transplantation in 6 patients and potential for autotransplantation bone marrow gene insertion. *Int Pediatr* 1992; **7**: 47.
- 12 Yamada Y, Kato K, Sukegawa K *et al.* Treatment of MPS VII (Sly disease) by allogeneic BMT in a female with homozygous A619V mutation. *Bone Marrow Transplant* 1998; **21**: 629–634.
- 13 Krivit W, Sung JH, Shapiro EG *et al.* Microglia: the effector cell for reconstitution of the central nervous system following bone marrow transplantation for lysosomal and peroxisomal storage diseases. *Cell Transplant* 1995; **4**: 385–392.
- 14 Field RE, Buchanan JA, Copplemans MG *et al.* Bone-marrow transplantation in Hurler's syndrome. Effect on skeletal development. *J Bone Jt Surg Br* 1994; **76**: 975–981.
- 15 Neufeld E, Muenzer J. The Mucopolysaccharidoses. In: Schriver CR, Beaudet AL, Sly WS, Walle W (eds). *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. McGraw-Hill: New York, 2001, pp 3421–3452.
- 16 Summers CG, Purple RL, Krivit W *et al.* Ocular changes in the mucopolysaccharidoses after bone marrow transplantation A preliminary report. *Ophthalmology* 1989; **96**: 977–984. Discussion 984–985.
- 17 Resnick JM, Krivit W, Snover DC *et al.* Pathology of the liver in mucopolysaccharidosis: light and electron microscopic assessment before and after bone marrow transplantation. *Bone Marrow Transplant* 1992; **10**: 273–280.
- 18 Resnick JM, Whitley CB, Leonard AS *et al.* Light and electron microscopic features of the liver in mucopolysaccharidosis. *Hum Pathol* 1994; **25**: 276–286.
- 19 Whitley CB, Ramsay NK, Kersey JH *et al.* Bone marrow transplantation for Hurler syndrome: assessment of metabolic correction. *Birth Defects Orig Artic Ser* 1986; **22**: 7–24.
- 20 Malone BN, Whitley CB, Duvall AJ *et al.* Resolution of obstructive sleep apnea in Hurler syndrome after bone marrow transplantation. *Int J Pediatr Otorh* 1988; **15**: 23–31.
- 21 Hugh-Jones K, Hobbs JR, Vellodi A *et al.* Long-term follow-up of children with Hurler's disease treated with bone marrow transplantation. In: Hobbs JR (ed.). *Correction of Certain Genetic Diseases by Transplantation* 1989. Headstart Printing: London, 1989, pp. 103–111.
- 22 Whitley CB, Belani KG, Chang PN *et al.* Long-term outcome of Hurler syndrome following bone marrow transplantation. *Am J Med Genet* 1993; **46**: 209–218.
- 23 Krivit W, Sung JH, Lockman L *et al.* Bone marrow transplantation for the treatment of lysosomal and peroxisomal diseases: focus on central nervous system reconstitution. In: Rich RR, Fleisher TA, Schwartz BD (eds). *Principles of Clinical Immunology*. Mosby: St. Louis, 1995, pp. 1852.
- 24 Krivit W, Lockman LA, Watkins PA *et al.* The future for treatment by bone marrow transplantation for adrenoleukodystrophy, metachromatic leukodystrophy, globoid cell leukodystrophy and Hurler syndrome. *J Inherit Metab Dis* 1995; **18**: 398–412.
- 25 Braunlin EA, Hunter DW, Krivit W *et al.* Evaluation of coronary artery disease in the Hurler syndrome by angiography. *Am J Cardiol* 1992; **69**: 1487–1489.
- 26 du Cret RP, Weinberg EJ, Jackson CA *et al.* Resting Tl-201 scintigraphy in the evaluation of coronary artery disease in children with Hurler syndrome. *Clin Nucl Med* 1994; **19**: 975–978.
- 27 Braunlin EA, Rose AG, Hopwood JJ *et al.* Coronary artery patency following long-term successful engraftment 14 years after bone marrow transplantation in the Hurler syndrome. *Am J Cardiol* 2001; **88**: 1075–1077.
- 28 Masterson EL, Murphy PG, O'Meara A *et al.* Hip dysplasia in Hurler's syndrome: orthopaedic management after bone marrow transplantation (see comments). *J Pediatr Orthop* 1996; **16**: 731–733.
- 29 Odunusi E, Peters C, Krivit W *et al.* Genu valgum deformity in Hurler syndrome after hematopoietic stem cell transplantation: correction by surgical intervention. *J Pediatr Orthop* 1999; **19**: 270–274.
- 30 Van Heest AE, House J, Krivit W *et al.* Surgical treatment of carpal tunnel syndrome and trigger digits in children with mucopolysaccharide storage disorders. *J Hand Surg (Am)* 1998; **23**: 236–243.
- 31 Krivit W, Shapiro EG, Balthazor M *et al.* Hurler syndrome: outcomes and planning following bone marrow transplantation. In: Stewards C, Hobbs JR (eds). *Correction of Genetic Diseases by Transplantation III*. Oxbridge Press Ltd: London, 1995, pp. 25–40.
- 32 Stauffer NR, Braunlin E, Whitley CB *et al.* Echocardiographic follow-up of Hurler syndrome after bone marrow transplantation. *Circulation* 1991; vol 84 (suppl II):462a.
- 33 Guffon N, Souillet G, Maire I *et al.* Follow-up of nine patients with Hurler syndrome after bone marrow transplantation (see comments). *J Pediatr* 1998; **133**: 119–125.
- 34 Hoogerbrugge PM, Brouwer OF, Bordigoni P *et al.* Allogeneic bone marrow transplantation for lysosomal storage diseases. The European Group for Bone Marrow Transplantation. *Lancet* 1995; **345**: 1398–1402.
- 35 Vellodi A, Young EP, Cooper A *et al.* Bone marrow transplantation for mucopolysaccharidosis type I: experience of two British centres. *Arch Dis Child* 1997; **76**: 92–99.
- 36 Grewal SS, Krivit W, Defor TE *et al.* Outcome of second hematopoietic cell transplantation in Hurler syndrome. *Bone Marrow Transplant* 2002; **29**: 491–496.
- 37 Jacobson P, Park JJ, DeFor TE *et al.* Oral busulfan pharmacokinetics and engraftment in children with Hurler syndrome and other inherited metabolic storage diseases undergoing hematopoietic cell transplantation. *Bone Marrow Transplant* 2001; **27**: 855–861.
- 38 Kakkis ED, Muenzer J, Tiller GE *et al.* Enzyme-replacement therapy in mucopolysaccharidosis I. *N Engl J Med* 2001; **344**: 182–188.
- 39 Vellodi A, Young E, Cooper A *et al.* Long-term follow-up following bone marrow transplantation for Hunter disease. *J Inherit Metab Dis* 1999; **22**: 638–648.
- 40 Imaizumi M, Gushi K, Kurobane I *et al.* Long-term effects of bone marrow transplantation for inborn errors of metabolism: a study of four patients with lysosomal storage diseases. *Acta Paediatr Jpn* 1994; **36**: 30–36.
- 41 Bergstrom SK, Quinn JJ, Greenstein R *et al.* Long-term follow-up of a patient transplanted for Hunter's disease type IIB: a case report and literature review. *Bone Marrow Transplant* 1994; **14**: 653–658.

- 42 McKinnis EJ, Sulzbacher S, Rutledge JC *et al.* Bone marrow transplantation in Hunter syndrome. *J Pediatr* 1996; **129**: 145–148.
- 43 Shapiro EG, Lockman LA, Balthazor M *et al.* Neuropsychological outcomes of several storage diseases with and without bone marrow transplantation. *J Inherit Metab Dis* 1995; **18**: 413–429.
- 44 Klein KA, Krivit W, Whitley CB. Poor cognitive outcome of eleven children with Sanfilippo syndrome after bone marrow transplantation and successful engraftment. *Bone Marrow Transplant* 1995; **15**: S176.
- 45 Vellodi A, Young E, New M *et al.* Bone marrow transplantation for Sanfilippo disease type B. *J Inherit Metab Dis* 1992; **15**: 911–918.
- 46 Bordigoni P, Vidailhet M, Lena M *et al.* Bone marrow transplantation for Sanfilippo syndrome. In: Hobbs JR (ed.), *Correction of Certain Genetic Diseases by Transplantation 1989*, Headstart Printing: London, 1989, pp. 114–119.
- 47 Moser HW, Smith KD, Watkins PA *et al.* X-Linked adrenoleukodystrophy. In: Schriver CR, Beaudet AL, Sly WS, Valle D (eds). *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. McGraw-Hill, New York, 2001, pp. 3257–3302.
- 48 Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. *Brain* 1997; **120**(8): 1485–1508.
- 49 Ronghe MD, Barton J, Jardine PE *et al.* The importance of testing for adrenoleukodystrophy in males with idiopathic Addison's disease. *Arch Dis Child* 2002; **86**: 185–189.
- 50 Loes DJ, Hite S, Moser H *et al.* Adrenoleukodystrophy: a scoring method for brain MR observations. *Am J Neuroradiol* 1994; **15**: 1761–1766.
- 51 Eichler FS, Barker PB, Cox C *et al.* Proton MR spectroscopic imaging predicts lesion progression on MRI in X-linked adrenoleukodystrophy. *Neurology* 2002; **58**: 901–907.
- 52 Izquierdo M, Adamsbaum C, Benosman A *et al.* MR spectroscopic imaging of normal-appearing white matter in adrenoleukodystrophy. *Pediatr Radiol* 2000; **30**: 621–629.
- 53 Pouwels PJ, Kruse B, Korenke GC *et al.* Quantitative proton magnetic resonance spectroscopy of childhood adrenoleukodystrophy. *Neuropediatrics* 1998; **29**: 254–264.
- 54 Rajanayagam V, Balthazor M, Shapiro EG *et al.* Proton MR spectroscopy and neuropsychological testing in adrenoleukodystrophy. *Am J Neuroradiol* 1997; **18**: 1909–1914.
- 55 Shapiro E, Lockman L, Balthazor M. Neuropsychological and neurological function and quality-of-life before and after bone marrow transplantation for adrenoleukodystrophy. In: Ringden O, Hobbs JR, Stewards C (eds). *Correction of Genetic Diseases by Transplantation IV*. The COGENT Press: Middlesex, 1997, pp. 52–62.
- 56 Loes DJ, Stillman AE, Hite S *et al.* Childhood cerebral form of adrenoleukodystrophy: short-term effect of bone marrow transplantation on brain MR observations. *Am J Neuroradiol* 1994; **15**: 1767–1771.
- 57 Aubourg P, Blanche S, Jambaque I *et al.* Reversal of early neurologic and neuroradiologic manifestations of X-linked adrenoleukodystrophy by bone marrow transplantation. *N Engl J Med* 1990; **322**: 1860–1866.
- 58 Peters C, Abel S, Defor TE *et al.* The worldwide hematopoietic cell transplant experience for childhood onset cerebral X-linked adrenoleukodystrophy (COCALD). *Blood* 2000; **96**: 842 (Abstr. 3638).
- 59 Wenger DA, Suzuki K, Suzuki Y *et al.* Galactosylceramide lipidoses: globoid cell leukodystrophy (Krabbe disease). In: Schriver CR, Beaudet AL, Sly WS, Valle D (eds). *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. McGraw-Hill: New York; 2001, pp. 3669–3694.
- 60 Kurtzberg J, Richards K, Wenger D *et al.* Correction of Krabbe disease with neonatal hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2002; **8**: 97 (Abstr. 130).
- 61 von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. In: Schriver CR, Beaudet AL, Sly WS, Valle D (eds). *The Metabolic and Molecular Bases of Inherited Disease*. 8th edn. New York; McGraw-Hill; 2001, pp. 3695–3724.
- 62 Peters C. Hematopoietic cell transplantation for storage diseases. In: Forman S, Blume K, Appelbaum F (eds). *Thomas' Hematopoietic Cell Transplantation*. Blackwell Scientific: London, 2003.
- 63 Fasth A, Oskarsdottir S, Tulinius M *et al.* Bone marrow transplantation in metachromatic leukodystrophy (MLD): disease progress in a boy despite transplantation two years before expected onset of symptoms. In: Ringden O, Hobbs JR, Stewards C (eds). *Correction of Genetic Diseases by Transplantation IV*. The COGENT Press: Middlesex, 1997, pp. 24–27.
- 64 Peters C, Wayne JS, Vellodi A. Hematopoietic stem cell transplantation for metachromatic leukodystrophy prior to onset of clinical signs and symptoms. In: Ringden O, Hobbs JR, Stewards C (eds). *Correction of Genetic Diseases by Transplantation IV*. The COGENT Press: Middlesex, 1997, pp. 34–48.
- 65 Solders G, Celsing G, Hagenfeldt L. Bone marrow transplantation for adult metachromatic leukodystrophy. In: Ringden O, Hobbs JR, Stewards C (eds). *Correction of Genetic Diseases by Transplantation IV*. The COGENT Press: Middlesex, 1997, pp. 32–33.
- 66 Malm G, Ringden O, Winiarski J *et al.* Clinical outcome in four children with metachromatic leukodystrophy treated by bone marrow transplantation. *Bone Marrow Transplant* 1996; **17**: 1003–1008.
- 67 Krivit W, Shapiro E, Kennedy W *et al.* Treatment of late infantile metachromatic leukodystrophy by bone marrow transplantation. *N Engl J Med* 1990; **322**: 28–32.
- 68 Koc ON, Peters C, Aubourg P *et al.* Bone marrow-derived mesenchymal stem cells remain host-derived despite successful hematopoietic engraftment after allogeneic transplantation in patients with lysosomal and peroxisomal storage diseases. *Exp Hematol* 1999; **27**: 1675–1681.
- 69 Seitelberger F. Pelizaeus-Merzbacher disease. In: Vinken PJ, Bruyn GW (eds). *Handbook of Clinical Neurology, Leucodystrophies and Poliodystrophies*. North-Holland: Amsterdam, 1970, p 150.
- 70 Wilson GN, Holmes RG, Custer J *et al.* Zellweger syndrome: diagnostic assays, syndrome delineation, and potential therapy. *Am J Med Genet* 1986; **24**: 69–82.
- 71 Goldfischer S, Moore CL, Johnson AB *et al.* Peroxisomal and mitochondrial defects in the cerebro-hepato-renal syndrome. *Science* 1973; **182**: 62–64.
- 72 Leegwater PA, Vermeulen G, Konst AA *et al.* Subunits of the translation initiation factor eIF2B are mutant in leukoencephalopathy with vanishing white matter. *Nat Genet* 2001; **29**: 383–388.
- 73 van der Knaap MS, Barth PG, Gabreels FJ *et al.* A new leukoencephalopathy with vanishing white matter. *Neurology* 1997; **48**: 845–855.
- 74 Miano M, Lanino E, Gatti R *et al.* Four year follow-up of a case of fucosidosis treated with unrelated donor bone marrow transplantation. *Bone Marrow Transplant* 2001; **27**: 747–751.
- 75 Krivit W, Peters C, Shapiro EG. Bone marrow transplantation as effective treatment of central nervous system disease in globoid cell leukodystrophy, metachromatic leukodystrophy, adrenoleukodystrophy, mannosidosis, fucosidosis, aspartylglucosaminuria, Hurler, Maroteaux-Lamy, and Sly syndromes,

- and Gaucher disease type III. *Curr Opin Neurol* 1999; **12**: 167–176.
- 76 Vellodi A, Cragg H, Winchester B *et al.* Allogeneic bone marrow transplantation for fucosidosis. *Bone Marrow Transplant* 1995; **15**: 153–158.
- 77 Erikson A, Groth CG, Mansson JE *et al.* Clinical and biochemical outcome of marrow transplantation for Gaucher disease of the Norrbottnian type. *Acta Paediatr Scand* 1990; **79**: 680–685.
- 78 Ringden O, Groth CG, Erikson A *et al.* Long-term follow-up of the first successful bone marrow transplantation in Gaucher disease. *Transplantation* 1988; **46**: 66–70.
- 79 Ringden O, Groth CG, Erikson A *et al.* Ten years' experience of bone marrow transplantation for Gaucher disease. *Transplantation* 1995; **59**: 864–870.
- 80 Svennerholm L, Erikson A, Groth CG *et al.* Norrbottnian type of Gaucher disease – clinical, biochemical and molecular biology aspects: successful treatment with bone marrow transplantation. *Dev Neurosci* 1991; **13**: 345–351.
- 81 Tsai P, Lipton JM, Sahdev I *et al.* Allogenic bone marrow transplantation in severe Gaucher disease. *Pediatr Res* 1992; **31**: 503–507.
- 82 Rapoport JM, Ginns EI. Bone-marrow transplantation in severe Gaucher's disease. *N Engl J Med* 1984; **311**: 84–88.
- 83 Hobbs JR, Jones KH, Shaw PJ *et al.* Beneficial effect of pre-transplant splenectomy on displacement bone marrow transplantation for Gaucher's syndrome. *Lancet* 1987; **1**: 1111–1115.
- 84 Starer F, Sargent JD, Hobbs JR. Regression of the radiological changes of Gaucher's disease following bone marrow transplantation. *Br J Radiol* 1987; **60**: 1189–1195.
- 85 Barton NW, Brady RO, Dambrosia JM *et al.* Replacement therapy for inherited enzyme deficiency–macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med* 1991; **324**: 1464–1470.
- 86 Figueroa ML, Rosenbloom BE, Kay AC *et al.* A less costly regimen of alglucerase to treat Gaucher's disease. *N Engl J Med* 1992; **327**: 1632–1636.
- 87 Schiffmann R, Heyes MP, Aerts JM *et al.* Prospective study of neurological responses to treatment with macrophage-targeted glucocerebrosidase in patients with type 3 Gaucher's disease. *Ann Neurol* 1997; **42**: 613–621.
- 88 Brady RO. Gaucher disease. In: Moser HW (ed.). *Handbook of Clinical Neurology: Neurodystrophies and Neurolipidoses*. Elsevier Science: Amsterdam, 1996, pp. 123–132.
- 89 Wall DA, Grange DK, Goulding P *et al.* Bone marrow transplantation for the treatment of alpha-mannosidosis. *J Pediatr* 1998; **133**: 282–285.
- 90 Autti T, Santavuori P, Raininko R *et al.* Bone marrow transplantation in aspartylglucosaminuria: MRI of brain suggests normalizing myelination. In: Ringden O, Hobbs JR, Stewards C (eds). *Correction of Genetic Diseases by Transplantation IV*. The COGENT Press: Middlesex, 1997, p. 92.
- 91 Arvio M, Sauna-Aho O, Peippo M. Bone marrow transplantation for aspartylglucosaminuria: follow-up study of transplanted and non-transplanted patients. *J Pediatr* 2001; **138**: 288–290.
- 92 Santavuori P, Lauronen L, Kirveskari E *et al.* Neuronal ceroid lipofuscinoses in childhood. *Neurol Sci* 2000; **21**: S35–S41.
- 93 Lake BD, Steward CG, Oakhill A *et al.* Bone marrow transplantation in late infantile Batten disease and juvenile Batten disease. *Neuropediatrics* 1997; **28**: 80–81.
- 94 Lipman RD, Donohue LR, Hoppe P *et al.* Evidence that lysosomal storage of proteolipids is a cell autonomous process in the motor neuron degeneration (mnd) mouse, a model of neuronal ceroid lipofuscinosis. *Neurosci Lett* 1996; **219**: 111–114.
- 95 Westlake VJ, Jolly RD, Jones BR *et al.* Hematopoietic cell transplantation in fetal lambs with ceroid-lipofuscinosis. *Am J Med Genet* 1995; **57**: 365–368.
- 96 Deeg HJ, Shulman HM, Albrechtsen D *et al.* Batten's disease: failure of allogeneic bone marrow transplantation to arrest disease progression in a canine model. *Clin Genet* 1990; **37**: 264–270.
- 97 Krivit W, Whitley CB, Chang PN. Lysosomal storage diseases treated by bone marrow transplantation: Review of 21 patients. In: Johnson FL, Pochedly C (eds). *Bone Marrow Transplantation in Children*. Raven Press: New York, 1990. pp. 261–287.
- 98 Bayever E, August CS, Kamani N *et al.* Allogeneic bone marrow transplantation for Niemann–Pick disease (type IA). *Bone Marrow Transplant* 1992; **10**: 85–86.
- 99 Vellodi A, Hobbs JR, O'Donnell NM *et al.* Treatment of Niemann–Pick disease type B by allogeneic bone marrow transplantation. *Br Med J (Clin Res Ed)* 1987; **295**: 1375–1376.
- 100 Hsu YS, Hwu WL, Huang SF *et al.* Niemann–Pick disease type C (a cellular cholesterol lipidosis) treated by bone marrow transplantation. *Bone Marrow Transplant* 1999; **24**: 103–107.
- 101 Kornfeld S, Sly WS. I-cell disease and pseudo-Hurler polydystrophy: disorders of lysosomal enzyme phosphorylation and localization. In: Schriver CR, Beaudet AL, Sly WS, Valle D (eds). *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. McGraw-Hill: New-York, 2001, pp. 3469–3482.
- 102 Kurobane I, Inoue S, Gotoh Y *et al.* Biochemical improvement after treatment by bone marrow transplantation in I-cell disease. *Tohoku J Exp Med* 1986; **150**: 63–68.
- 103 Yamaguchi K, Hayasaka S, Hara S *et al.* Improvement of tear lysosomal enzyme levels after treatment with bone marrow transplantation in a patient with I-cell disease. *Ophthalmic Res* 1989; **21**: 226–229.
- 104 Grewal SS, Orchard PJ, Krivit W *et al.* Hematopoietic cell transplantation in I-cell disease. *Third Scientific Lysosomal Storage Disorders Congress and Seventh International Symposium on Mucopolysaccharide and Related Diseases*, 2002.
- 105 Gravel RA, Kaback MM, Proia RL *et al.* The G_{M2} gangliosidoses. In: Schriver CR, Beaudet AL, Valle D, Sly WS (eds). *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. McGraw-Hill: New York, 2001, pp. 3827–3876.
- 106 Suzuki Y, Oshima A, Nanba E. b-Galactosidase deficiency (b-galactosidosis): G_{M1} gangliosidosis and marquo B disease. In: Schriver CR, Beaudet AL, Valle D, Sly WS (eds). *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. McGraw-Hill: New-York, 2001, pp. 3775–3810.
- 107 O'Brien JS, Storb R, Raff RF *et al.* Bone marrow transplantation in canine GM1 gangliosidosis. *Clin Genet* 1990; **38**: 274–280.
- 108 Coccia PF. Cells that resorb bone. *N Engl J Med* 1984; **310**: 456–458.
- 109 Popoff SN, Marks Jr SC. The heterogeneity of the osteopetroses reflects the diversity of cellular influences during skeletal development. *Bone* 1995; **17**: 437–445.
- 110 Felix R, Hofstetter W, Cecchini MG. Recent developments in the understanding of the pathophysiology of osteopetrosis. *Eur J Endocrinol* 1996; **134**: 143–156.
- 111 Seifert MF, Popoff SN, Jackson ME *et al.* Experimental studies of osteopetrosis in laboratory animals. *Clin Orthop* 1993; 23–33.
- 112 Kornak U, Kasper D, Bosl MR *et al.* Loss of the ClC-7 chloride channel leads to osteopetrosis in mice and man. *Cell* 2001; **104**: 205–215.

- 113 Kornak U, Schulz A, Friedrich W *et al.* Mutations in the $\alpha 3$ subunit of the vacuolar H(+)-ATPase cause infantile malignant osteopetrosis. *Hum Mol Genet* 2000; **9**: 2059–2063.
- 114 Frattini A, Orchard PJ, Sobacchi C *et al.* Defects in TCIRG1 subunit of the vacuolar proton pump are responsible for a subset of human autosomal recessive osteopetrosis. *Nat Genet* 2000; **25**: 343–346.
- 115 Sly WS, Whyte MP, Sundaram V *et al.* Carbonic anhydrase II deficiency in 12 families with the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification. *N Engl J Med* 1985; **313**: 139–145.
- 116 Gerritsen EJ, Vossen JM, van Loo IH *et al.* Autosomal recessive osteopetrosis: variability of findings at diagnosis and during the natural course. *Pediatrics* 1994; **93**: 247–253.
- 117 Jagadha V, Halliday WC, Becker LE *et al.* The association of infantile osteopetrosis and neuronal storage disease in two brothers. *Acta Neuropathol (Berl)* 1988; **75**: 233–240.
- 118 Gerritsen EJ, Vossen JM, Fasth A *et al.* Bone marrow transplantation for autosomal recessive osteopetrosis. A report from the Working Party on Inborn Errors of the European Bone Marrow Transplantation Group. *J Pediatr* 1994; **125**: 896–902.
- 119 McMahon C, Will A, Hu P *et al.* Bone marrow transplantation corrects osteopetrosis in the carbonic anhydrase II deficiency syndrome. *Blood* 2001; **97**: 1947–1950.
- 120 Srinivasan M, Abinun M, Cant AJ *et al.* Malignant infantile osteopetrosis presenting with neonatal hypocalcaemia. *Arch Dis Child Fetal Neonatal Ed* 2000; **83**: F21–F23.
- 121 Eapen M, Davies SM, Ramsay NK *et al.* Hematopoietic stem cell transplantation for infantile osteopetrosis. *Bone Marrow Transplant* 1998; **22**: 941–946.
- 122 Sieff CA, Chessells JM, Levinsky RJ *et al.* Allogeneic bone-marrow transplantation in infantile malignant osteopetrosis. *Lancet* 1983; **1**: 437–441.
- 123 Fischer A, Griscelli C, Friedrich W *et al.* Bone-marrow transplantation for immunodeficiencies and osteopetrosis: European survey, 1968–1985. *Lancet* 1986; **2**: 1080–1084.
- 124 Coccia PF, Krivit W, Cervenka J *et al.* Successful bone-marrow transplantation for infantile malignant osteopetrosis. *N Engl J Med* 1980; **302**: 701–708.
- 125 Cheow HK, Steward CG, Grier DJ. Imaging of malignant infantile osteopetrosis before and after bone marrow transplantation. *Pediatr Radiol* 2001; **31**: 869–875.
- 126 Schulz AS, Classen CF, Mihatsch WA *et al.* HLA-haplo-identical blood progenitor cell transplantation in osteopetrosis. *Blood* 2002; **99**: 3458–3460.
- 127 Krivit W, Freese D, Chan KW *et al.* Wolman's disease: a review of treatment with bone marrow transplantation and considerations for the future. *Bone Marrow Transplant* 1992; **10**(Suppl 1): 97–101.
- 128 Krivit W, Peters C, Dusenbery K *et al.* Wolman disease successfully treated by bone marrow transplantation. *Bone Marrow Transplant* 2000; **26**: 567–570.
- 129 Peters C, Khanna W, Krivit W *et al.* A retrospective study of the factors affecting the developments of carpal tunnel syndrome (CTS) symptoms in Hurler patients after bone marrow transplant. *Third Scientific Lysosomal Storage Disorders Congress and seventh International Symposium on Mucopolysaccharide and Related Diseases*, Paris, 2002.
- 130 Peters C, Orchard PJ, Defor TE *et al.* Hematopoietic cell transplantation for Hurler syndrome: The University of Minnesota experience from 1983 to 2001. *Blood* 2001; **98**: 667 (Abstr. 2797).
- 131 Koc ON, Day J, Nieder M, Gerson SL, Lazarus HM, Krivit W. Allogeneic mesenchymal stem cell infusion for treatment of metachromatic leukodystrophy (MLD) and Hurler syndrome (MPS-1H). *Bone Marrow Transplant* 2002; **30**: 215–222.