Bone marrow transplantation for lysosomal storage disorders

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Bone marrow transplantation for lysosomal storage disorders has been used for the past 25 years. The early allure of a promising new therapy has given way to more realistic expectations, as it has become clear that bone marrow transplantation is not a cure, but merely ameliorates the clinical phenotype. The results in some disorders are more acceptable than in others. Significant challenges have emerged, particularly the poor mesenchymal and neurological responses. Important recent advances in lysosomal biology, both in health and disease, have helped us to better understand the results of bone marrow transplantation, and to rationalize its role in the treatment of lysosomal storage disorders alongside newer therapies. At the same time, they have helped researchers to explore new therapeutic applications of bone marrow cells, such as gene and stem cell therapy.

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Bone marrow transplantation (BMT) has been used to treat a wide variety of disorders. Over the last 25 years or more, this has come to include several lysosomal storage disorders (LSDs). Over 40 such disorders have been described. They tend to be multisystemic and are always progressive, although the rate of progression may vary. Recent advances in the cell biology of the LSDs have helped in understanding the mechanism of action of BMT.

The results of BMT can be used as a yardstick by which to judge the effects of newer treatments, such as enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). It is therefore an opportune time to review the role of BMT in the management of these disorders.

The emergence of alternative sources of progenitor cells, such as peripheral blood [1] and umbilical cord blood [2], mean that the term hematopoeitic stem cell transplantation (HSCT) is probably more accurate. However, for the purpose of this review the term BMT will be used.

Lysosomal biology

A detailed description of lysosomal biology is beyond the scope of this review. However, it is important to mention some aspects that are of relevance to therapy.

Lysosomes are part of the endosomal–lysosomal pathway. This is a series of intracellular organelles, connected functionally, not structurally. The lysosome is the final compartment of this pathway. It was discovered by De Duve in 1955 [3]. Lysosomal enzymes are glycoproteins that are formed in the rough endoplasmic reticulum (RER) and make their way, through a series of steps, to the lysosome. The lysosome possesses an acid intracellular pH, which is critical to lysosomal enzyme function. The majority of LSDs result from defective lysosomal acid hydrolysis of endogenous macromolecules and their consequent accumulation.

In order to be active, lysosomal enzymes must acquire a mannose-6-phosphate (M6P) marker. This takes place in the Golgi apparatus [4–6]. It is important to understand these two steps because failure of acquisition of this marker results in mistargeting of lysosomal enzymes; they will not enter the lysosome and substrate breakdown will not occur.

Secretion–recapture hypothesis

A significant proportion of newly synthesized enzyme is not bound to the M6P receptor in the Golgi but, instead, is secreted and then endocytosed into neighbouring cells via M6P

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receptors on the plasma membrane [7]. The concept of M6P-based secretion and recapture is of considerable importance when considering therapy. However, there is now evidence that, for some lysosomal enzymes at least, M6P-independent secretion–recapture may operate [8].

Lysosomal function in the CNS

The CNS is involved in nearly all LSDs, so an understanding of CNS lysosomal biology is important. The main classes of cells in the CNS are nerve cells (neurons) and glial cells. Glial cells are divided into two major classes: macroglia (astrocytes and oligodentrocytes) and microglia. Neural and macroglial cells derive from the ectodermal embryonic layer. Microglia represent approximately 5–20% of glial cells. Microglia of bone marrow origin secrete enzyme that is taken up by neurons [9]. There was initially indirect evidence of this from BMT for feline α-mannosidosis [10]. More recently there has been direct proof of neuronal uptake of enzyme from an implanted, genetically corrected fibroblast graft [11]. Therefore, the secretion–recapture mechanism seems to operate in the CNS. However, other mechanisms, such as axonal transport, are also thought to play an important role in enzyme transfer [12].

Blood–brain barrier

The blood–brain barrier (BBB) is created by the endothelial cells of the brain capillaries. These cells are linked by tight junctions that form an effective physical, electrical and chemical barrier [13–15]. However, circulating monocytes are able to cross the BBB, probably transcellularly [16].

Pathogenesis of lysosomal storage disorders

There have been significant advances in our understanding of the pathogenesis of LSDs in recent years. A detailed discussion is beyond the scope of this review. However, for the purposes of understanding the effects of therapy, it is useful to discuss these under two headings: primary and secondary events.

Primary events

These are enzyme deficiency and the resulting accumulation of its substrate. The latter results in lysosomal distension and organ enlargement. However, it is now known that while substrate accumulation is fundamental to pathology, it is not solely responsible for it.

Secondary events

Several secondary phenomena have been reported. They include accumulation of lysosphingolipids in sphingolipid disorders (lyso- forms lack the acyl group) [17–20], abnormal intracellular calcium flux [21–23], extralysosomal, as well as intralysosomal, accumulation of substrate [24], and macrophage activation. Of these, macrophage activation deserves special mention.

Macrophage activation and/or cytokine release has been demonstrated to cause pathology in *ex vivo* models of lysosomal storage [25]. Evidence of macrophage activation has been reported in Gaucher disease [26,27]. Importantly, preclinical evidence of macrophage activation in the brain [28], resulting in neuronal apoptosis, has been reported [29]. There is the intriguing possibility that the presence of activated macrophages could compromise the integrity of the BBB, as is seen in HIV dementia [30].

It is important to realize that different types of secondary events may operate in different LSDs. It is also not surprising that more than one secondary event may operate in a particular disease [31]. Whatever the progression of events from primary to secondary, it is important to note that once secondary events are set in motion, they may not respond to enzyme delivery via BMT.

Secondary structural changes in neurons

As with cells elsewhere, neurons in storage disorders display storage of primary substrate. However, they also display a variety of other structural changes. This abnormal morphology was clearly delineated by Purpura and Suzuki in 1976 [32]. Two types of morphological changes have now been described: meganeurites and axonal spheroids. Meganeurites are enlargements of the axon hillock and are of two types: spiny, and non-spiny or smooth, depending upon their appearance. They always contain the specic storage bodies found in the neurons. The spiny appearance is conferred by the presence of new dendritic membrane. This process is known as ectopic dendritogenesis. It was first reported in a patient with gangliosidosis and, indeed, it results from accumulation of ganglioside, predominantly GM2. However, it is seen in other LSDs as well and is confined to neurons in which primary storage occurs. The precise relationship between ectopic dendritogenesis and the secondary events referred to above is not clear. However, it is interesting that dendritic morphology is disease-specific and this might be another reason for a differential response to BMT. For a more detailed review, see Walkley 2004 [33].

Clinical features of lysosomal storage disorders

Nearly every eukaryotic cell, with the exception of the erythrocyte, contains lysosomes. Furthermore, many lysosomal substrates have key roles in cellular structure and function. Consequently, the effects of lysosomal malfunction are widespread. BOX 1 lists the known lysosomal storage disorders. However, it is useful to separate the various disorders according to the predominant cell type involved, as this has the most important implications for therapy.

Neurological involvement

Most LSDs have neurological involvement and can be further divided into two groups, those in which all patients have neurological involvement, and those in which only the most severely involved patients have it. It is important to make this distinction, as additional mechanisms are probably responsible for the neurological disease in the latter group, particularly as the distinction is usually fairly clear cut (e.g., mucopolysaccharidoses [MPS] I-Hurler [H] from the milder MPS I-Hurler-Scheie [HS] or MPS I-Scheie [S], or types II and III Gaucher disease from type I).

Box 1. Known lysosomal storage disorders.

Mucopolysaccharidoses (MPS)
MPS I
MPS II
MPS IIIA-D
MPS IVA
MPS IVB
MPS VI
MPS VII
MPS IX
Defects in lysosomal enzyme targeting
Mucolipidoses II and III
Glycoproteinoses
Aspartylglucosaminuria
Fucosidosis
α-mannosidosis
β-mannosidosis
Mucolipidosis I
Schindler disease
Sphingolipidoses
Fabry disease
Farber disease
Gaucher disease
GM1 gangliosidosis
GM2 gangliosidosis
Krabbe disease
Metachromatic leukodystrophy
Sphingomyelinase deficiency (Niemann–Pick A and B)
Other lipidoses
Niemann–Pick C
Wolman disease
Neuronal ceroid lipofuscinoses I and II
Glycogen storage disease
Type II
Multiple enzyme deficiency
Multiple sulphatase deficiency
Galactosialidosis
Transport defects
Cystinosis
Sialic acid storage disorders (Salla disease and infantile sialic acid storage disease)
Lysosomal membrane protein defects
LAMP-2 deficiency (Danon disease)
Channelopathies
Mucolipidosis IV
Cl-C7 causing ostepetrosis

Mesenchymal involvement

This group comprises essentially all the MPS, in whom mesenchymal involvement is universal; it is responsible for the dysostosis multiplex and spinal cord involvement that is characteristic of this group.

Reticuloendothelial involvement

This group comprises many of the sphingolipidoses (e.g., Gaucher disease, Fabry disease and Niemann–Pick disease [NPD]). Reticuloendothelial cells are usually far more accessible to therapy than mesenchymal cells and neurons. Hence, this group of disorders tend to respond best to therapy, especially in those disorders in which the CNS is not involved.

Relationship of clinical severity to residual enzyme activity

Clinical heterogeneity is a feature of every LSD. One of the most important factors responsible is residual enzyme activity. Conzelmann and Sandhoff proposed that there was a critical threshold of enzyme activity above which storage did not occur. A small change in residual enzyme activity can have a profound effect on rate of accumulation of substrate [34]. This has two important implications for therapy. First, the lower the residual activity, the earlier the age of onset and the more severe the disease. Therefore, residual enzyme activity is of critical importance in determining response to treatment. The lower the residual activity, the less satisfactory the response. Second, it is probably not necessary to replace 100% of activity to achieve a satisfactory clinical response.

Mechanism of correction of lysosomal storage disorders by bone marrow transplantation

Monocytes form resident populations of macrophages in different organs. These nests of macrophages are, in terms of lysosomal enzyme function, the critical effector cells, capable of secreting enzyme that is taken up by surrounding cells (secretion–recapture mechanism). Following engraftment, monocytes of donor origin enter tissues and engraft. Importantly, cells of donor origin have been demonstrated in the brain following human BMT [35]. Therefore, these resident macrophages are now capable of providing endogenous enzyme. Transfer of enzyme to surrounding cells takes place and clears accumulated substrate. Studies in mice revealed that 30% of microglial cells are of donor origin by 12 months following BMT [36]. In fact, it is possible that egress across the BBB is increased following BMT, as activated T cells have been shown to enter the CNS more easily [37].

However, enzyme transfer and uptake is probably not the only mechanism of action of BMT. Macrophage activation can be reversed by BMT [29].

Preclinical studies

A number of LSDs have been identified in animals. These models have been very useful in studying the effects of BMT at cellular and organ levels. TABLE 1 lists the studies carried out to

Table 1. Animal models of lysosomal storage disorders treated by bone marrow transplantation.

Disease	Animal	Ref.
α-mannosidosis	Cat	[10]
Aspartylglucosaminuria	Mouse	[118]
Fucosidosis	Dog	[113]
Gm1 gangliosidosis	Dog	[157]
GM2 gangliosidosis	Mouse	[29]
Globoid cell	Mouse	[158,159]
Leukodystrophy Fabry disease	Mouse	[160]
Mucopolysaccharidosis I	Dog	[161,162]
Mucopolysaccharidosis VI	Rat, cat	[25,163–166]
Mucopolysaccharidosis VII	Mouse, dog	[167–172]
Sphingomyelinase deficiency	Mouse	[173]
Ceroid lipofuscinosis	Dog	[174]

date. In summary, animal studies have established the following general points:

- Enzyme-producing cells of donor origin make their way to affected organs. Importantly, donor-derived cells are seen in the CNS post-BMT
- These cells are capable of transferring enzyme to surrounding neurons
- Clearance of storage occurs
- There is clinical benefit
- The younger the age at transplant, the greater the benefit is likely to be
- Nearly all organs respond, although some better than others

These results have provided proof of principle that BMT is capable of delivering enzyme to tissues where it is deficient and that storage can be cleared.

The disadvantages of animal models are:

- There is not as much heterogeneity, as a single mutation is always responsible
- Where several clinical subgroups exist, as, for example, in MPS I, it is not always clear which subgroup the animal model corresponds to
- The tool for assessing neurological response in animals gives little or no insight into cognitive function
- There are no quality-of-life tools in animals

Clinical results

At least 18 of the known LSDs have been treated by BMT. TABLE 2 gives a list of these and the key references.

Mucopolysaccharidoses

The greatest experience has been gained with the MPS disorders. They are caused by deficiencies of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAGs).

Mucopolysaccharidosis I

MPS I results from the deficiency of α-L-iduronidase. Patients with MPS I are classified into three clinical syndromes: MPS I-H, MPS I-HS and MPS I-S. MPS I-H is the most severe clinical phenotype. Death usually occurs by age 10 years with a median of 5.19 years.

The first transplant for a LSD was in 1980 for MPS I-H by Hobbs and colleagues [38]. Several centers have now reported long-term follow-up [39–42]. The rate of rejection is very high [43]; the reasons for this remain unclear. The first patients to be transplanted are now in their early 20s. It is clear that BMT ameliorates the most severe complications (i.e., upper airway obstruction and cardiomyopathy) [44]. Not surprisingly, the life expectancy of these patients has been considerably prolonged. There has been only one reported death in long-term follow-up; this was secondary to pulmonary infection and abnormal lung function may have been a factor [45]. With

Table 2. Lysosomal storage disorders treated by bone marrow transplantation.

Disease	Ref.
α-mannosidosis	[112,175]
Aspartylglucosaminuria	[116]
Fucosidosis	[114,115]
MPS I	[39–41,43]
MPS II	[59–64]
MPS III	[66,67]
MPS IV	[UNPUBLISHED]
MPS VI	[73,176–178]
MPS VII	[75]
Mucolipidosis II	[76]
Metachromatic leukodystrophy	[91,92,95,81,83–87,89,179–186]
Globoid cell leukodystrophy	[93–97]
Gaucher disease	[99–102,187–189]
GM1 gangliosidosis	[103]
Niemann–Pick A	[104]
Niemann–Pick B	[105,106]
Niemann–Pick C	[110]
Wolman disease	[120]
Farber disease	[121,122]

MPS: Mucopolysaccharidosis.

improved survival, it has become clear that different aspects of the disease respond differently. There is a striking improvement in the physical appearance, especially the facial features, and skin texture improves. The hepatosplenomegaly resolves. Chronic hydrocephalus is arrested in most cases once engraftment has occurred [41]. There is, however, a slow but definite progression of the dysostosis multiplex [46]. Significant orthopedic problems develop, particularly of the hips, knees and spine. This results in a variety of physical and neurological disabilities. The significant spinal deformity may affect lung function, although this has not been studied systematically. Carpal tunnel syndrome is a peculiar feature of the MPS disorders and is not prevented by BMT. It appears to be closely associated with trigger finger. The association can best be explained by accumulation of GAGs in the flexor tendon sheaths. The corneal clouding improves, although usually not completely and corneal transplantation may be required. The reason for this may be related to mechanical ultrastructual changes that are not reversed by BMT [47]. Retinal disease seems to be universal and progressive [48]. It has been shown experimentally that the accumulation of sulphated GAGs in retinal cells is toxic [49]. Cardiac valvular disease, especially that of the aortic and mitral valves, progresses [50]. However, coronary artery involvement is relatively mild [45] and no patients have developed symptoms of coronary artery disease.

Cognitive outcome varies considerably. It is probably most closely related to the age at transplant. In general, BMT over the age of 2 years is associated with a poor outcome, although there is no guarantee that younger patients will achieve a better result. A Mental Developmental Index (MDI) of less than 70 appears to correlate with a poor outcome [51]. It is felt by some that cognitive outcome following BMT from a heterozygous donor is not as good as that from a donor with normal enzyme levels [40,52]. However, this has not been substantiated by other groups; Conway and colleagues recently reported good outcome in a patient with very low levels of chimerism [53]. In an effort to try and improve morbidity and graft rejection, many centers are now treating patients with ERT for a few weeks pre- and post-BMT [54]. It is too early to determine how useful this is likely to be.

An increasing number of patients are now surviving into adulthood; most of them have significant disability. There have been no long-term studies of psychosexual function in these survivors and, therefore, this needs to be carried out urgently.

BMT is currently reserved for patients with the severe form of MPS I (i.e., MPS I-H). It is important to ensure that the patient does not have a milder variant. At present, the distinction is mainly clinical. Genotyping may help but only if the genotype clearly correlates with a severe phenotype [55]. Fuller and colleagues measured oligosaccharides derived from dermatan and heparan sulphate in fibroblasts using electrospray–ionization tandem mass spectrometry [56]. A total of 15 oligosaccharides were measured, of which two seemed to predict a severe phenotype. The discrimination was even clearer when the ratio of α-L-iduronidase activity to these trisaccharides was measured.

MPS II (Hunter)

There have been several reports of BMT for MPS II [57–64]. In general, the results have been disappointing, with little or no change in the neurological progression. It is possible that this may be due, in part at least, to poor patient selection. The long-term outcome in MPS II is closely related to CNS involvement [65]. Clinical trials of ERT for MPS II are in progress and this is likely to become the treatment of choice in patients without CNS involvement. In patients with CNS involvement, neither ERT nor BMT is likely to be useful. It is not clear why the CNS involvement in this condition does not respond to BMT in the same way as it does in MPS I-H. The relatively advanced age of patients at transplant may be a factor, as may the presence of heparan sulphate, which is the predominant GAG, as it is in MPS III.

Mucopolysaccharidosis III (Sanfilippo)

The results of BMT in MPS III have been uniformly poor. The clinical course, even in transplanted presymptomatic children, has remained unchanged [66,67]. It is not clear why these patients respond so poorly. Heparan sulphate, the predominant GAG in this condition, plays a key role in early CNS development [68–70] and its accumulation in the MPS III-B mouse model has been shown to inhibit neuroplasticity [71].

Morquio Mucopolysaccharidosis IV A

There are no formal published data. However, from personal experience of two cases, there is no doubt that there is a complete lack of response of the skeletal manifestations and that BMT should not be offered to these patients.

Mucopolysaccharidosis VI (Maroteaux–Lamy)

Cardiomyopathy and upper airway obstruction dominate this condition. Although neuronal storage has been demonstrated in the feline model [72], clinically, CNS involvement is minimal or absent. Following BMT, there is a significant soft tissue response, but the bony changes progress [73]. The responses in the upper airway and heart are similar to those seen in MPS I. Clinical trials of ERT have demonstrated efficacy [74] and this is likely to become the treatment of choice in this condition.

Mucopolysaccharidosis VII

Only one report of BMT for MPS VII exists: that of a 12-year-old girl homozygous for the A619V mutation. Over 31 months, there was significant improvement in mobility, upper airway obstruction and upper respiratory infections [75]. Given the rarity of this condition, it is unlikely that ERT will become available and so BMT may remain the only therapeutic option for the foreseeable future.

Mucolipidosis type II (I cell disease)

Severe physical and neurodisability with early death (< 10 years) is characteristic of this condition. There is no convincing evidence that BMT has any useful effect. Neurodevelopmental improvement was reported in one patient but it was very slow [76].

Effects of BMT on the skeleton in mucopolysaccharidoses disorders

The uniformly poor response of the dysostosis multiplex in this group of disorders deserves special consideration. The dysostosis is largely the result of defects in articular cartilage and endochondral ossification. Articular cartilage is mesenchymal in origin and, therefore, any improvement following BMT would have to rely on mesenchymal stem cell (MSC) engraftment. Unfortunately, MSC engraftment following BMT tends to be predominantly host derived [77,78]. However, this is unlikely to be the only explanation, as chondrocytes possess a M6P uptake mechanism [79]. Access may be a problem; growth plates in younger patients may be more accessible as evidenced by skeletal response to neonatal adenoviral gene transfer in MPS VII mice [80]. However, secondary events triggered by storage may also play an important role. Simonaro and colleagues showed that chondrocytes from MPS VI cats undergo apoptosis, that the apoptosis is caused by the release of nitric oxide (NO) and cytokines and that this in turn is secondary to the accumulation of dermatan sulphate [25].

Metachromatic leukodystrophy

Neurological involvement secondary to demyelination is the hallmark of this disorder. Central and peripheral nervous systems are affected and there is a wide phenotypic spectrum. Patients with varying degrees of neurological involvement have undergone BMT and this has made interpretation of the data very difficult [81–90]. Not surprisingly, in the childhood forms of MLD, there is no evidence of improvement in symptomatic patients. Although it is quite clear that early-onset disease does not respond, long-term stabilization has been reported in some juvenile patients. However, the longest period of follow-up reported has been 8 years. Given the evidence, it is difficult to draw firm conclusions; longer follow-up may yield more information. Adult-onset MLD may be a better candidate; improvement in all aspects of the disease has been reported in one patient [91]. It is also unclear whether or not the central and peripheral nervous system pathologies are equally accessible to donor-derived cells after BMT. Interestingly, a patient with saposin B deficiency was reported to show some response post-BMT [92]. Although the response was not sustained, it provides proof of principle for correction of saposin deficiencies by BMT.

Globoid cell leukodystrophy (Krabbe disease)

Krabbe disease is a demyelinating disorder caused by a deficiency of galactosylceramidase. The majority of cases are of infantile onset with rapid clinical course. A rare late-onset form with milder clinical symptoms also exists. While it seems that the infantile form does not respond to BMT, after onset of symptoms, it appears that BMT in presymptomatic infants may prevent symptoms [93,94]. Certainly, the milder forms do appear to respond at least partially [95–97]. However, no significant long-term follow-up has been reported so it is difficult to draw firm conclusions. Moreover, the peripheral nerves appear to be more resistant to BMT than the CNS [98]; long-term follow-up information about peripheral nerve function is lacking and is needed urgently.

Gaucher disease

There is no doubt that BMT is highly effective in treating the non-neuronopathic form (type I) and the visceral aspects of the chronic neuronopathic form (type III) [99–102]. However, its efficacy in treating the CNS involvement is less clear [100] and its role in type I has been completely superseded by that of ERT. The mechanism of action of BMT is also unclear, since β-glucosidase is tightly membrane-bound and not secreted, unlike most lysosomal enzymes.

GM1 gangliosidosis

Shield and colleagues recently reported the results of BMT in a presymptomatic patient with the juvenile onset form of this disorder. Despite achieving good enzyme levels, no clinical benefit was seen [103].

Sphingomyelinase deficiency (Niemann–Pick A & B)

There is a single case report of an unsuccessful BMT for NPD type A [104]; the rapid clinical progression clearly precludes BMT. Two patients with type B NPD have been reported. The first was a 3-year-old girl. Despite full donor engraftment, there was a gradual, progressive neurodisability, which is not typical for this condition. Hepatic cirrhosis continued to progress; hematemesis, secondary to portal hypertension, occurred at 17 years of age [105]. The patient eventually died aged 19. The second patient was a 4-year-old girl; 5 years following a second graft, she was well with no neurodisability [106]. Interestingly, in both cases, pulmonary infiltration regressed after BMT. The different responses of the liver and lungs to BMT suggest that the critical receptors in these organs are different. It is also important to realize that hepatic storage is predominantly in hepatocytes (unlike in Gaucher disease, where Kupffer cell storage predominates). These are important considerations for ERT for this condition [107].

Niemann–Pick C

Niemann–Pick type C disease results from mutations in the *NPC1* gene that encodes a protein involved in the net movement of unesterified cholesterol from the late endosomal/lysosomal compartment to the metabolically active pool of sterol in the cytosol. This results in accumulation of free intracellular cholesterol. In a small number of patients (approximately 5% of all NPC), another gene, *NPC2*, has been found to be defective [108]. This is a soluble lysosomal protein, unlike the NPC1 protein, which is predominantly located within the late endosomal membrane. It appears that NPCI and NPC2 work in concert to transport cholesterol but precisely how is not clear [109]. Although NPC does not result from a lysosomal enzyme deficiency, it is widely recognized as a lysosomal storage disorder. Liver disease and progressive neurodegeneration are the main clinical features. There is a single

case report of a 5-month-old girl who underwent BMT. Developmental delay was already present at the time of BMT and its progression was not arrested. However, interestingly, there was significant reduction of the clinical features of storage [110]. This cannot be explained on the basis of correction of the abnormal cholesterol trafficking. Partial sphingomyelinase deficiency has been recently demonstrated in this condition [111]. The reason for this is unclear but it is possible that the reduction in storage results from the correction of this partial enzyme deficiency.

α-mannosidosis

Grewal and colleagues recently reported four patients with follow-up ranging from 1 to 6 years. There was stabilization of intellectual decline with improvement in some aspects of cognitive function and normalization of hearing [112]. Longer follow-up is required to determine whether, in carefully selected patients, BMT might be a feasible option.

Fucosidosis

The results of BMT in the canine model suggest that it should be a good therapeutic option [113]. While short-term follow-up reports are encouraging [114,115], the long-term results of the first patient to undergo BMT are less so. After 12 years of relative stability, albeit with cognitive impairment, this patient is developing progressive cerebellar and posterior column involvement; magnetic resonance imaging scans show progressive cerebellar atrophy.

Aspartylglucosaminura

Aspartylglucosaminura is predominantly a Finnish disease. Autti and colleagues described two patients who received BMT [116]. There was histological and radiological evidence of improvement. However, both patients had cognitive impairment at the time of BMT and the period of follow-up was relatively short, given the relatively slow clinical progression. In the mouse model, there was efficient uptake of enzyme by glial cells [117] and BMT was effective in correcting CNS storage in younger mice (3-week-old) [118] but not in older (8-week-old) mice [119].

Wolman disease

Krivit and colleagues reported a successful outcome in an infant following BMT. The follow-up was relatively short but there was significant improvement in storage [120].

Farber disease

Three patients have undergone BMT; one with the infantile variant [121] and two with milder non-neurological disease [122]. Although there was no slowing of intellectual decline in the first patient, there was dramatic resolution of the subcutaneous nodules and hoarseness in all three. Given the high morbidity and mortality, even in the non-neurological variants, and the lack of ERT at present, BMT may well be an appropriate therapy for this condition.

Disadvantages of bone marrow transplantation

The main disadvantages of BMT are the need for a matched donor and the transplant-related morbidity and mortality.

Fewer than 30% of patients requiring BMT have HLA-compatible sibling [123]. Even fewer will have a matched, unrelated donor. Umbilical cord blood is now considered an acceptable alternative to the use of bone marrow as a source for HSCs for pediatric HSC transplantation, and is being investigated in adults. The major advantages of umbilical cord blood include the speed of availability compared with unrelated donor bone marrow and tolerance of 1–2 HLA mismatch, which offers the opportunity to extend the donor pool. Umbilical cord blood transplantation is associated with durable engraftment and a low incidence of severe graft-versus-host disease, even in the 1–2 HLA mismatched setting [2].

Infections, veno-occlusive disease of the liver (VOD) and graft-versus-host disease remain the major complications of BMT and are well reviewed elsewhere [123–128]. What is not as well appreciated is the high incidence of neurological complications associated with BMT. Two studies, both looking at the incidence of neurological complications following BMT, have been reported recently. In a prospective study of 71 adult patients performed by Sostak and colleagues, 65% developed neurological sequelae. Of these, 18% were acute and defined, resulting in death in 8%, while 47% developed subacute complications, mainly affecting the peripheral nervous system [129]. The second study, performed by Faraci and colleagues, was confined to children. It was a retrospective study of 272 patients undergoing BMT over a 6-year period. A total of 37 children (13.6%) developed severe neurological events (SNE) after a median of 90 days (range: 5 days to 8.8 years) following HSCT. Cyclosporine A (CSA) neurotoxicity was the most frequent SNE (n = 21), followed by irradiation or chemotherapy injury (n = 7), CNS infections (n = 7), cerebrovascular events (n = 3) and immune-mediated etiology SNE (n = 2). A total of 11 patients (30%) died of neurological complications. These findings have two implications. First, there may be a risk of exacerbation of the underlying disease and, second, there may be difficulty in interpreting neurological progression.

Conclusion

It is clear that while BMT is capable of providing a permanent source of enzyme, it is more effective in some tissues than others and not every disease responds equally. The most important factors governing outcome are the type of tissue predominantly involved (i.e., mesenchymal, neuronal or reticuloendothelial), the disease severity at the time of BMT (dictated not just by storage, but by secondary events as well) and the natural history (i.e., rapidly or slowly progressive). Significant challenges remain, particularly with regard to mesenchymal and neurological correction.

Expert commentary

Bone marrow transplantation will continue to be a therapeutic option for several LSDs. While gene therapy may become a realistic option, this is unlikely to be in the near future and

many countries will simply not possess the necessary technology. The pluripotential nature of bone marrow cells holds great therapeutic promise for many conditions previously considered untreatable. While newer therapies, such as ERT and SRT, may become the treatment of choice for many conditions, cost is, sadly, a major issue. However, the correct approach is to ensure that they become available in poorer countries through humanitarian efforts.

Five-year view

The past decade has welcomed the arrival of two new therapies: ERT and SRT. There is therefore now a range of therapeutic options for several conditions, of which BMT is just one. ERT has revolutionized the treatment of Gaucher disease [130], Fabry disease [131] and MPS I [132]. Although there is little or no clinical evidence that it crosses the BBB, a study in the MPS VII mouse suggests that it is transported in younger mice across the BBB by transcytosis involving the M6P receptor [133]. This receptor appears to be downregulated at an early age. However, a more recent study in the same model has shown that larger doses of enzyme delivered over a longer period can clear neuronal storage [134]. Similar results have been reported following ERT in mouse models of aspartylglucosaminuria [135] and metachromatic leukodystrophy [136]. Improvement in function was also seen in the latter. While these results are interesting, they should be interpreted with caution until more data are available, preferably in large animal models. In the meantime, other avenues should be explored. SRT offers a unique therapeutic approach to the treatment of the glycosphingolipid disorders [137]. It is licensed for use in selected patients with type I Gaucher disease. However, it also appears to cross the BBB [138,139]; this finding has prompted clinical trials in several LSDs affecting the CNS. Results from these trials are expected over the next 12 months. Based on the results of preclinical studies in the Tay-Sachs and Sandhoff mouse models [138,140], a combination of BMT and SRT may offer hope in the presymptomatic stage of conditions currently considered unresponsive to BMT alone, such as GM1 gangliosidosis [141] and Tay-Sachs disease.

The results of BMT have prompted several preclinical studies of gene therapy in the LSDs. Several excellent recent reviews have been published [142–144]. Gene therapy has several advantages over BMT. HSC gene therapy, if successful, would obviate the need for a donor, although conditioning will still be required. Transgenic overexpression of enzyme (something that conventional BMT cannot do) has been shown to correct storage in mouse models of metachromatic leukodystrophy [145] and galactosialidosis [146] more effectively than conventional stem cell transplantation. Higher levels of enzyme to drive axonal transport may therefore be required to achieve better results in the CNS, although overexpression may not be without risk [147].

The BBB is likely to continue to present a challenging obstacle. In an effort to bypass this, direct CNS gene therapy has been performed in several animal models, using different vectors. Decreased storage [148,149] and, importantly, improved function have been reported [150,151]. Remarkably, correction of storage occurs over a far wider area than localized gene delivery would imply [151,152]. Human trials of direct CNS gene therapy are now underway [153]. These are outside the scope of this review but are worth mentioning here, as the potential therapeutic implications are significant for BMT. It has been shown that, although donor-derived cells appear in the CNS after BMT, they are slow to do so [36]. Thus, there is a gap after BMT, during which the underlying disease might well progress. If found to have even a temporary benefit, direct CNS gene therapy might bridge this gap.

There is increasing evidence that adult bone marrow cells can differentiate into many types of tissue, including skeletal muscle, cardiomyocytes and endothelia, neurons and glia, hepatocytes and bile duct epithelia, renal epithelia and podocytes, and gut mucosal cells and associated myofibroblasts [154]. It is possible that some of these are the result of the fusion of bone marrow cells with the differentiated cells in the new organ [155,156] and, clearly, care must be taken in interpreting results. Nevertheless, these are exciting findings, and raise the distinct possibility that bone marrow cells may be a useful vehicle for the delivery of therapeutic genes to diseased organs.

Key issues

- Bone marrow transplantation (BMT) provides donor-derived enzymes for most organs, including the CNS.
- BMT is capable of clearing storage.
- However, the clearing of storage does not necessarily equate to clinical benefit.
- Response in animal models is not always reflected in clinical practice.
- Patient selection is a key factor; identifying the patients who are unlikely to respond at an early stage is a high priority.
- BMT should not be considered in isolation when considering therapeutic options for lysosomal storage disorders; rather, it should be considered as part of a therapeutic armoury, which now includes enzyme replacement therapy and possibly substrate reduction therapy.

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