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Hematopoietic stem cell transplantation for metabolic storage diseases

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Abstract

Almost thirty years of hematopoietic cell transplantation for congenital enzymopathies have revealed that the transfer of relatively few hematopoietic stem cells is able to fully reconstitute the lymphohematopoietic system in conditioned recipients and to maintain long term complementation of the enzyme defect in the recipient. Despite decades of effort to illuminate the mechanisms whereby the cross correction occurs, it remains unclear why hematopoietic cell transplantation is adequate only in some enzyme deficiencies. Here we review both biochemical and clinical data on the metabolic storage diseases in which the natural history and quality of life have been changed after hematopoietic cell transplantation. The challenge ahead is to understand the pathophysiology of congenital enzymopathies resistant to correction with hematopoietic cell transplantation, and to test whether the advances in stem cell therapy and gene correction can be translated into less toxic and even more effective therapy of metabolic storage diseases for which hematopoietic cell transplantation is a standard of care today.

Keywords: hematopoietic cell transplantation, conditioning regimen for hematopoietic cell transplantation, mucopolysaccharidosis, Hurler syndrome, metachromatic leukodystrophy, globoid cell leukodystrophy, Krabbe disease, adrenoleukodystrophy, mannosidosis, late effects after hematopoietic cell transplantation

1. Introduction

Hematopoietic cell transplantation (HCT) is a prototypic stem cell therapy, and has been a life-saving measure for tens of thousands of patients. Over its relatively short history, the study of transplantation has shown that the transfer of relatively few cells can lead to the development of a fully functional lympho-hematopoietic system in the recipient, that bidirectional immunologic tolerance between post-natal tissues is possible, and that cancer can be eradicated by immunologic means.

After the seminal insight that cells with two different enzyme deficiencies can complement each other [1], a paradigm shift occurred, according to which stem cell transfer is applicable to equally fatal but non-malignant disorders [2]. This has translated into the establishment of transplantation as the standard of care for some of these enzyme disorders; monitoring of hundreds of patients with congenital metabolic disorders after transplantation has shown that long-lasting cross correction can be achieved. Conceptually, these benefits have been limited to congenital defects of enzymes, but there is no intellectual barrier to applying this strategy to other diseases where structural proteins are deficient, such as in extracellular matrix disorders.

In this review, we intend to present experiences with hematopoietic cell transplantation that have established its functionality and

benefits for children with congenital metabolic storage diseases, and to describe some limitations and open questions regarding HCT for these conditions.

2. Conditioning regimens and graft sources

HCT for malignant as well as non-malignant diseases has traditionally been preceded by myeloablative doses of total body irradiation (TBI) and chemotherapy, or more commonly in the non-malignant setting, with myeloablative doses of busulfan combined with cyclophosphamide [3-6]. These regimens were also originally designed to be effective in treating the underlying malignancy, particularly leukemia, as well as providing intensive immunosuppression to prevent graft rejection. Although effective at achieving durable engraftment in most patients, intensive chemotherapy leads to a significant risk of short-term morbidity and a 10–30% risk of transplant-related mortality in patients with inborn errors of metabolism (IEM) [7]. Additionally, exposure to high doses of these agents can lead to a risk of significant late effects (cataracts, endocrinopathies, pulmonary and cardiac abnormalities, and new malignancies) as discussed later in this chapter. For these reasons, many parents and non-transplant physicians have been unwilling to accept the risks of HCT for children with IEM.

The demonstration that stable mixed chimerism could be achieved with sub-lethal doses of TBI (approximately one-sixth of the dose administered with standard TBI) and immunosuppression with cyclosporine and mycophenolate mofetil led to the widespread development of so-called non-myeloablative or reduced intensity conditioning regimens [8]. While these regimens were initially intended for patients who were ineligible for standard high dose conditioning, the fact that these regimens avoid many of the major short and long term toxicities associated with HCT has made this approach very attractive for use in children with non-malignant disorders. Fludarabine, a relatively new chemotherapeutic agent that has been widely used for conditioning, is highly immunosuppressive and has limited non-hematologic toxicity [9]. It has been used with low-dose TBI or without TBI in combination with busulfan, melphalan, or other agents. The use of these regimens in patients who are "chemotherapy naive" and who have normal immune systems, such as patients with IEM, has been very limited and associated with high rates of graft rejection. Additionally, measures commonly employed with reduced intensity conditioning to improve or boost engraftment, such as donor lymphocyte infusions, are associated with a high risk of acute and chronic graft vs. host disease (GVHD). Despite these issues, the use of reduced intensity conditioning in patients with IEM is a desirable goal, and research continues to refine these regimens with the objective of optimizing engraftment and minimizing toxicity.

The other consideration regarding HCT for patients with IEM is graft source. Obviously the preference is for HLA-matched sibling donors, but this is an option for only a minority of patients. The availability may be even lower for this patient group because siblings can also be affected with the disease. Certainly many of the potential matched sibling donors may be carriers of the disease in question. The question as to whether an alternative donor should be used preferentially over a sibling shown to be a carrier remains unanswered. Alternative unrelated donor sources (bone marrow, peripheral blood stem cells, cord blood) have been routinely utilized with good results. Acute and chronic GVHD is the major limitation to the use of alternative donors, and in these patients with non-malignant disorders there is no benefit to be derived from GVHD. Methods employed to reduce the risk of GVHD include T cell depletion (TCD) and possibly the use of umbilical cord blood. Both of these methods appear to be effective in reducing the risk of GVHD, but each carries with it a higher risk of graft rejection as well as a higher risk of infectious complications (particularly from viruses).

3. Lysosomal storage diseases

3.1. Mucopolysaccharidoses

Mucopolysaccharidoses are autosomal recessive disorders characterized by deficiencies of enzymes needed for the stepwise catabolism of complex sugars termed glycosaminoglycans (GAG) [10-12]. Some of these conditions predominantly affect the viscera; the others are both neuronopathic and visceral. Many of them also exhibit a dynamic range from a less severe phenotype associated with hypomorphic mutations to severe ones generally associated with null mutations.

3.1.1. Mucopolysaccharidosis type I (Hurler Syndrome)

In mucopolysaccharidosis type I (MPS I), the deficiency of α-L-iduronidase (IDUA) results in lysosomal accumulation of the GAG heparan sulfate and dermatan sulfate. This in turn leads to progressive cellular and multi-organ dysfunction. While the clinical findings may be apparent at birth, the manifestations of the disease and onset of symptoms usually occur by six months of age. Multiple organ systems are affected, and many of these patients present with or develop hepatosplenomegaly, cardiac disease, umbilical or inguinal hernia, obstructive airway disease, chronic rhinitis and otitis, skeletal deformities, hydrocephalus, neurocognitive deterioration, and corneal clouding. If left untreated, death occurs between 5 and 10 years of age, primarily from cardiac causes.

Treatments focus on approaches to replace the missing IDUA. This can be achieved either by exogenous administration of IDUA or through the endogenous production of IDUA following stable engraftment of normal cells producing enzyme within the affected individual. The former is achieved by enzyme replacement therapy (ERT) available for MPS I since 2003 [13], and the latter by HCT, which was first shown to hold promise in 1980 [2]. The therapeutic basis for both treatment options is that IDUA can be taken up by recipient cells via the mannose-6-phosphate receptor and then be translocated to lysosomes where it mediates the hydrolysis of GAG.

HCT has been accepted as a standard of care for patients with severe forms of MPS I (Hurler Syndrome). Initially, unaffected HLA-genotypically-identical bone marrow donors were considered the optimal donors, but results with matched unrelated donors, and especially with cord blood, are encouraging. As a result of better availability of improved methods for HLA typing and supportive care, the early engraftment and survival rates have improved, and currently may be as high as 85% in institutions specializing in transplantation for metabolic storage diseases [5, 14-19].

Remarkably, donor-derived cells engraft even within the brain, thereby providing a source of enzyme to the central nervous system and halting the neurocognitive decline in most patients [20].

This is in addition to correction of most of the visceral signs of pathology, including cardiovascular function, organomegaly, and lung disease. In contrast, the heart valves and skeletal abnormalities are largely unaffected by this therapy.

ERT has been introduced for treatment of less severe visceral forms of MPS I, and is currently the standard of care in patients without neurologic disease, since IDUA does not cross the blood-brain barrier [21]. Recent data on a combination of ERT with HCT are encouraging, however, and appear to support the possibility that combination therapy is in fact the new standard of care for patients with Hurler Syndrome [22-24]. The rationale for this approach is based on identifying risks in the pre-transplant course that are associated with increased morbidity and mortality during and after HCT [7]. Most prominent among these risks are upper and lower lung disease. It follows that if the enzyme can be provided for a sufficient time before transplantation, GAG storage in viscera can be partially cleared, and may result in fewer complications during HCT. The possibility that pre-transplant enzyme replacement therapy will result in increased graft failure because of generation of antibodies against donor cells has not been borne out. Of note, some advocate the use of combination therapy primarily for patients with higher risk disease. We and others, however, offer combination therapy for all patients with MPS I who are considered for HCT, because of the low risks associated with enzyme therapy and the potential that it may decrease life-threatening complications after HCT. In addition, it is possible that decreases in GAG, after enzyme replacement therapy, but before the HCT, can create a more permissive environment in the bone marrow niche for donor engraftment when compared to the patients who did not receive ERT.

3.1.2. Other mucopolysaccharidoses

In contrast to Hurler Syndrome, HCT has not been shown to significantly alter the natural history of patients with severe mucopolysaccharidosis type II (Hunter Syndrome). The attenuated phenotypes may benefit from stem cell therapy, but for yet unknown reasons, children with severe MPS II phenotype do not appear to gain neurocognitive benefit from the transplant. Whether transplantation before the onset of symptoms, such as in the neonatal period, may improve outcomes is as yet unclear.

Similarly, early results with HCT using allogeneic grafts have not been very encouraging in patients with Sanfilippo Syndrome (MPS III). Only limited published data exist regarding transplant results, but available data suggest that, in contrast to MPS I, the neurologic deterioration of MPS III patients is not alleviated by transplantation.
Morquio Syndrome (MPS IV), is characterized by significant musculoskeletal disease with less prominent neurologic changes, and so far has not been shown to benefit from HCT.

In contrast, the visceral findings of Maroteaux-Lamy Syndrome (MPS VI) have been shown to improve with HCT. However, the availability of enzyme replacement therapy for MPS VI limits the need for HCT.

Finally, Sly Syndrome (MPS VII), which results in bone deformities, developmental delays, and organomegaly, has been treated with HCT with some positive response [25-27].

Thus, individual mucopolysaccharidoses differ substantially with regards to their responses to HCT and ERT. While HCT, especially in combination with ERT, is a standard of care for severe MPS I (Hurler Syndrome), the efficacy of standard methods of transplantation for MPS II and MPS III has not been established.

4. Sphingolipidoses

The glycosphingolipids are an important component of the cell membrane, consisting of polysaccharide bound to lipid, primarily ceramide, which is incorporated into the membrane [28]. The polysaccharide portion contributes to cell interactions, adhesion, and signaling, in addition to other functions [29]. Degradation is accomplished through the action of lysosomal acid hydrolases, which serve to remove the carbohydrate moiety. Collectively the glycosphingolipid disorders are the most common cause of neurogenerative diseases (incidence approximately 1:18,000) in children [28]. With the exception of Fabry disease, these disorders are inherited in an autosomal recessive pattern. Based on the enzyme defect and substrate accumulation, these disorders are often divided into GM1 gangliosidosis, GM2 gangliosidoses (Tay-Sachs disease and Sandhoff disease), Fabry disease, multiple sulfatase deficiency, Gaucher disease, Niemann-Pick A and B, Farber disease, metachromatic leukodystrophy (MLD) and globoid cell leukodystrophy (GLD, also known as Krabbe disease). Most data regarding transplantation for these disorders relate to experience with MLD and GLD. These disorders will be discussed individually.

4.1. Metachromatic leukodystrophy

Metachromatic leukodystrophy (MLD) results from a decrease in arylsulfatase A (ARSA) activity, leading to the accumulation of the substrate cerebroside 3-sulfate, a component of myelin [30]. Decreased ARSA activity leads to demyelination of the white matter of the central nervous system (CNS) as well as the peripheral nerves [31]. Arylsulfatase A deficiency leading to MLD occurs with an overall incidence of approximately 1:40,000 births, while a higher frequency may be observed in specific populations [31-33]. There is significant phenotypic variation in MLD. In patients with the "late-infantile" form of the disease, neurological deterioration is initially observed within the first several years of life. Death generally ensues several years from diagnosis. Symptoms are associated with both central and peripheral demyelination, and motor-related difficulties are often apparent earlier than loss of cognition and language skills. The juvenile form of the disease has an onset from 4 years of age through adolescence [34-35]. Clinical manifestations of juvenile MLD are similar to the infantile form, although the rate of progression is slower. The adult form of the disease may become apparent as late as the seventh decade, and represents approximately 20% of cases of MLD [36]. Rather than presenting with motor-related difficulties, patients with late-onset disease may have emotional lability, progressive dementia, psychosis, and difficulties with substance abuse. There is a phenotype-genotype correlation in MLD, with more severe mutations resulting in more rapid accumulation of sulfatides and disease progression [37].

Krivit reported the results of the first transplant for MLD in 1990 [38]. Subsequently, reports of the success of transplantation for MLD generally have been limited to a small numbers of patients,

and these data are difficult to assess due to variations in phenotype (late-infantile, juvenile, or adult forms) as well as the state of the disease at the time of transplantation [34]. Assessment of these outcomes is further limited by the lack of a universal standard for clinically assessing these patients both prior to and after transplantation. Obtaining such data will be critical to determining the utility of therapy, as asymptomatic patients or those early in their disease course are more likely to have better outcomes [16]. Similarly, those with less severe phenotypes may respond better to therapy. In regards to symptomatic late-infantile disease, while sulfatide levels decrease in urine and cerebrospinal fluid and the rate of progression may be less than observed in untreated siblings, the available data do not support the claim that transplantation has the capacity to stabilize disease [39]. The inability to deliver sufficient amounts of enzyme into the CNS is likely a primary limitation, as enzyme delivery is dependent on engraftment of cells such as the microglial population in the brain, which may take months following transplant [12, 27, 34]. In addition, despite engraftment of allogeneic cells, patients with infantile disease also appear to have progressive peripheral disease. Whether asymptomatic patients identified by neonatal screening or by family history who would be predicted to develop infantile disease can benefit from transplantation within the newborn period is debatable. Data available to address this question suggest that these patients continue to have progressive motor disabilities [34, 40-41]. In contrast, reports of the outcome of transplantation of later-onset disease (juvenile and adult forms) suggest that stabilization of the central nervous system may be achieved, even if patients are symptomatic at the time of transplantation [39, 42-43]. As may be expected, the rate of decline prior to transplantation and the status of the disease at transplant are likely to affect outcomes [44].

4.2. Globoid cell leukodystrophy

The disorder known as globoid cell leukodystrophy (GLD) was initially described in 1916 by Krabbe, who reported infants developing spasticity and sclerosis of the brain [45]. Krabbe also described the characteristic "globoid cell" present in the white matter of affected patients. In 1970 the enzyme defect responsible for GLD was identified as the lysosomal enzyme galactocerebroside β-galactosidase (GALC) [46], also commonly referred to as galactocerebrosidase. In 1990 Zlotogora localized the gene to chromosome 14 [47], and the gene was cloned by Wenger's laboratory in 1993 [48]. The primary substrate that accumulates in GLD is galactocerebroside, which is degraded by GALC to ceramide and galactose [49]. The metabolite psychosine accumulates as well in GLD, as it is a substrate for GALC [35]. Psychosine has been thought to contribute to cytotoxicity of cells in the CNS, including oligodendrocytes [50-52].

Globoid cell leukodystrophy has an incidence of 1:70,000–100,000, and presents with a varied phenotype, similar to MLD. Historically, 85–90% of patients with GLD develop symptoms as infants [35]. Patients with infantile GLD characteristically become increasingly irritable, with increased sensitivity to stimuli, developmental arrest and subsequent regression [35]. Protein levels in the cerebro-spinal fluid are high. Hypertonicity is apparent, with feeding difficulties and visual changes; increased deep tendon reflexes and seizures may be observed. Death generally results within a few years of the onset of symptoms. Other patients have less severe disease, and have been divided into late infantile (onset from 6 months to 3 years) and juvenile forms (ages 3–8 years), while some patients are not diagnosed until their second or third decades, and occasionally later [35]. As might be expected, these later onset patients have a less rapidly progressive disease course.

The first description of the outcomes of GLD patients treated by allogeneic transplantation were provided by Krivit et al in 1998 [53]. Four of the 5 patients reported had late onset disease, while one had typical infantile GLD. For the older patients, the patients appeared to stabilize, or even improve, in regards to their disease. The patient with infantile disease was transplanted at 2 months of age. By now there is sufficient experience with transplantation of symptomatic patients with infantile disease to state that transplantation is not effective at arresting disease progression, although the clinical course may be attenuated [39]. In addressing this question, Escolar reported a staging system for clinically assessing patients with GLD in the pre-transplant period, and correlated this to outcomes [54]. There has recently been great interest in the outcomes of patients with presumed infantile GLD if these patients are transplanted in the neonatal period [55]. These very young and asymptomatic patients who would be predicted to have a severe phenotype, clearly have a different clinical course after transplantation than would be expected without transplantation [56]. Based on this observation, there has been significant discussion regarding the use of newborn screening as a means of identifying these patients prior to the onset of symptoms [57, 58]. However, it remains unclear how patients who have severe genotypes and are transplanted in the first weeks of life will do as they age [55]. It is of interest that many of the difficulties these patients face are motor limitations, and this is likely at least in part due to peripheral nerve demyelination. Such a finding would be in keeping with observations in the twitcher mice, a model for GLD [59-61]. Thus far there has not been universal agreement to move towards neonatal screening for GLD with the intention of identifying and transplanting patients predicted to have severe disease soon after delivery, although screening is currently being done in New York, and is likely to be in place soon in several other US states. It should be noted that due to the severe time limitations in attempting to transplant asymptomatic neonates, a large proportion of these infants will require cord blood grafts. This has been suggested to be a preferred graft source, not only because of the expediency of moving to transplantation, but also because of the possibility of an increased ability of cord blood to transdifferentiate into a variety of non-hematopoietic stem cells or progenitor cells [16]. Additional clinical information will be required to determine if this will be the case.

The efficacy of transplantation in patients with later onset GLD remains less well delineated than would be expected. It has previously been stated that patients with later onset disease are likely to benefit from transplantation [62]. In some cases, improvement has been reported [26]. However, data related to large series of patients focused on the function and neurocognitive outcomes are not available. It would be important to review the genotypic findings of an individual diagnosed by GALC activity to determine whether it is reasonable to pursue transplantation in an asymptomatic patient, as it is not necessarily clear what the anticipated course will be. However, if a patient with later-onset disease is early in the course of the disease, transplantation seems a reasonable option. It has been suggested that for a number of these

diseases, multi-institutional trials with standard methods of analysis would prove very beneficial to the field [63], and despite the difficulties inherent in developing and funding these large trials that could require decades to complete, it is difficult to argue with this view.

Other related lysosomal disorders have been treated with transplantation, although less data are available than for MLD and GLD. Niemann-Pick A and B result from a deficiency in sphingomyelinase. In Niemann-Pick A rapid neurologic progression is often observed. For these patients, who are severely affected and deteriorating rapidly, there are insufficient data to confirm that transplantation modifies the course of neurologic disease. In Niemann-Pick B, there is little published data, but our group and others have observed improvement in the marrow and lung pathology of these patients after transplant [64-65]. Niemann-Pick C has been shown to have 2 subtypes, both associated with accumulation of cholesterol. Niemann-Pick C1 is the most frequent form, but is not due to a lysosomal enzyme defect and therefore is less likely to respond to transplantation. In contrast, Niemann-Pick C2 disease is associated with a deficit in a lysosomal enzyme [66]. While it has been reported that there is an insufficient response of Niemann-Pick C to transplantation [67], the ability to separate the genotypes has only recently become available. Although it might be expected that type C2 may respond to transplantation, results have not been reported in individuals confirmed to have this genotype. As the C2 genotype is much less common than C1, genetic analysis prior to intervention will be of importance.

GM1 gangliosidosis is characterized by seizures and psychomotor deficits, and has infantile, juvenile, and adult onset forms [35, 68]. While little information is available regarding the utility of transplantation, a report describing a juvenile patient suggests there is little benefit from transplantation [69]. GM2 gangliosidosis disorders (Tay-Sachs and Sandhoff) are due to abnormalities within the hexosaminidase (HEX) gene [68]. In the case of Tay-Sachs, HEX A is deficient, while in Sandhoff HEX A and B are deficient. Unfortunately in most cases these disorders are rapidly progressive, and there is little information to suggest that symptomatic patients benefit from transplantation [40, 70]. However, it is as yet unclear as to whether those with late-onset disease or newborns predicted to have early-onset disease would benefit. Gaucher disease has been shown to benefit from transplantation [71-74], but as there is enzyme replacement therapy available for Gaucher, there is little enthusiasm for the morbidity and mortality associated with transplantation for this disorder. However, as the neuropathic form of Gaucher does not benefit from ERT [75], there may be interest in evaluating transplantation in patients with Gaucher who show evidence of neurologic deterioration [40]. Fabry disease is an X-linked disorder of the lysosomal enzyme α-galactosidase A, which results in accumulation of substrate in the kidneys, heart, eyes, and blood vessels, but does not have a significant neurological component. As enzyme replacement therapy is available for Fabry, there is currently no enthusiasm for transplantation [41].

4.3. Adrenoleukodystrophy

While GLD and MLD are autosomal recessive lysosomal enzyme deficiencies, adrenoleukodystrophy (ALD) is an X-linked disorder of the peroxisome that results in abnormal metabolism of very long chain fatty acids (VLCFA) due to decreased beta-oxidation. These VLCFA accumulate in the testes, adrenal gland, and white matter of the central nervous system [76]. For reasons that are not clear, approximately 40% of individuals with ALD under 20 years of age show a clinical course of rapid neurologic deterioration [77]. This condition, representing the cerebral form of ALD, is an inflammatory process present in the CNS, with a mixed cellular infiltrative process, although CD8+ T cells are prominent [78-79]. Eichler stated that the bulk of the inflammation occurs behind the area in which demyelination is seen, and he proposed that the infiltrative process occurs in response to demyelination rather than being its cause [80]. The beneficial effects of HCT are thought to be related at least in part to elimination of the active inflammation present in the CNS, although recent early findings of a gene therapy approach suggest that there is a corrective process provided by hematopoietically-derived cells [81]. Another important issue in regards to the early identification of ALD relates to adrenal insufficiency. Primary adrenal insufficiency (AI), or Addison's disease, which precedes cerebral manifestations of ALD, occurs with an estimated prevalence of 43% in asymptomatic boys with X-ALD [82]. In our center's experience, 7 boys who have been evaluated for transplantation for cerebral ALD since 2002 had previously been diagnosed with adrenal insufficiency, but VLCFA testing was not performed expeditiously, resulting in a delay in diagnosis and presumably disease progression that either rendered the patient ineligible for transplantation or put him at higher risk for a poor outcome (Polgreen et al., unpublished observations).

Transplantation early in the course of cerebral ALD has been shown to stabilize the disease process, although it is clear that in more advanced patients the outcome is inferior [4]. An MRI scoring system was developed by Loes to quantitate the extent of the disease [83], and this allows the identification of patients who are at high risk for poor outcomes of transplantation. Due to the importance of the extent of disease in the ability of transplantation to arrest the disease process [84], it is recommended that boys with biochemically proven ALD be monitored with serial MRI scans, and to proceed with transplantation when patients show evidence of early progression to cerebral disease [4]. It is not known whether transplantation plays any role in preventing the evolution of other manifestations of ALD, such as the peripheral nervous system condition termed adrenomyeloneuropathy (AMN). In addition, there are no data to show that transplantation prior to the onset of cerebral ALD will prevent its occurrence. Therefore the risks of transplantation are not justified in patients without evidence of evolving cerebral ALD, as a majority of boys will not develop cerebral ALD [85]. The use of Lorenzo's oil in patients who have not yet developed cerebral ALD may decrease the risk of its occurrence [86].

5. Oligosaccharidosis: Mannosidosis

Alpha-mannosidosis presents with hepatosplenomegaly, vomiting, immune deficiency, and dysostosis multiplex. Affected patients also have mental retardation and ocular clouding. Approximately 20 patients have been transplanted to date, some of whom had pulmonary and airway complications during the first several months after HCT. Remarkably, the mental development as well as cardiopulmonary function appear to have been preserved, suggesting that HCT is a valid treatment option for alpha-mannosidosis [87].

6. Enzyme localization defect: Mucolipidosis Type II (I-Cell Disease)

Mucolipidosis Type II results from a defect in a phosphotransferase that is integral to the localization of numerous lysosomal hydrolyses. In the absence of this targeting mechanism, these lysosomal enzymes are secreted rather than retained in the lysosome. This results in lysosomal substrate accumulation, while extremely high serum levels of these enzymes are observed in the plasma. The phenotype resembles MPS I, but the response to HCT has been much less favorable [88]. It remains to be determined whether early identification of these patients, before the damage to visceral and neuronal tissue is irreversible and profound, and expedient transplantation may improve outcomes.

7. Late effects after HCT for Metabolic Storage Disease

As discussed previously, the majority of patients with IEM who undergo HCT do so following traditional high-dose, chemotherapy-based conditioning regimens. The combination of busulfan and cyclophosphamide is the most common regimen utilized. Patients with IEM are unique, however, in that they also have to face the potential of long-term complications related to their underlying disease that may not be reversed or prevented by successful HCT. One can assume that they are at the same risk as other patients going through HCT for the common conditions seen after exposure to high-dose chemotherapy in the conditioning regimen, but there are little data that describe those findings. Additionally, there may be unique long-term effects of some of the preparative regimens in patients with IEM, but again for the most part these have not been reported to date. Limited long-term follow-up data in some subsets of IEM patients (Hurler's syndrome in particular) related to amelioration of disease-associated conditions are available and will be briefly summarized.

Endocrine issues. There are minimal IEM-specific data, but some patients have been found to have primary ovarian failure [19]. It is unclear if this is related to the disease or HCT since both may contribute. Other endocrine issues seen in children after HCT include gonadal failure in males, hypothyroidism, and growth failure. While some of these conditions may be more frequently encountered after exposure to TBI, they can also be seen with non-TBI containing regimens. Patients with Hurler's syndrome have growth problems to begin with, and while some reports suggest that linear growth may be maintained early after HCT, others suggest growth may not be maintained on a long-term basis [19, 89].

Pulmonary. Patients with IEM have high rates of pulmonary complications during HCT that may be related to a pro-inflammatory state within the lung [90]. While busulfan can lead to pulmonary fibrosis, this is not a common complication in children after HCT. In patients with Hurler's it has been demonstrated that they do have relief of their obstructive airway symptoms and improvement in sleep apnea with improved pulmonary function [19, 91]. A reduction in the risk of pulmonary deterioration in a patient successfully transplanted for I-cell disease has also been reported [92].

Cardiac. Long-term cardiovascular complications are rarely associated with exposure to cyclophosphamide and busulfan alone. Certainly for several of the IEM disorders, progressive cardiac dysfunction is common. For patients with Hurler's, long-term follow-up after HCT has shown that myocardial function is preserved and hypertrophy has been seen to regress, and patients have not developed heart failure or coronary artery disease. However, mitral and aortic valve deformities have persisted and frequently progressed [93].

Neuropsychological and cognitive function. In the absence of exposure to radiation during conditioning, children typically do not have significant neuropsychological sequelae secondary to HCT. In the case of children with IEM, post-HCT neurologic outcome depends upon the specific disease, age at time of HCT, specific genotype of the disease, cognitive status at the time of HCT, engraftment status, and donor enzyme activity after HCT. The goal, of course, is to perform HCT early in the course of the disease before any extensive neurologic damage or deterioration has occurred. When this can be done, neurocognitive function can be stabilized (or in some cases improved) and further progressive neurologic deterioration can be prevented [5, 19, 89, 91, 94].

Bone and joints. HCT conditioning can affect bone health leading to osteopenia and osteoporosis. This may be reversible on its own over time or may require further intervention with vitamin D and calcium supplementation or occasionally treatment with bisphosphonates. These effects have not been studied to date in children with IEM. Other disease-specific orthopedic complications, such as odontoid dysplasia in patients with Hurler's, have been shown to improve over time [95]. However, other complications such as genu valgum, carpel tunnel syndrome, and acetabular dysplasia have not improved after HCT and frequently require surgical intervention [96-97].

Post-transplant malignancies. It has been well described that patients after HCT are at life-long increased risk of developing malignancies that is estimated at nearly 10-fold greater than that in the general population [98-99]. Whether this same risk applies to patients with IEM is not known, but we are aware of some patients who have developed malignancies years after HCT.

Late Mortality. After allogeneic HCT patients have twice the risk of mortality of the general population [100]. Data submitted for publication from the Center for International Blood and Marrow Transplant Research demonstrate that patients with IEM have a higher risk of mortality between 2–6 yrs after HCT and that this increased risk persists even 6 yrs after HCT. This increased risk is highest in patients who have received unrelated or HLA non-identical related donor transplants. Causes of death include GVHD, infection, and organ failure.

Summary

Obtaining clear data regarding the outcomes of transplantation in patients with IEM has proven difficult due to the rarity of these diseases, their variable phenotypes/genotypes, and differences in stem cell sources, preparative regimens, supportive therapy, and assessment of "successful" outcomes. Multi-institution trials with a common approach and outcome measures will be important in this regard. In earlier years HCT in these populations used standardized regimens designed for patients with malignant disorders. For disorders such as Hurler's syndrome and early cerebral ALD, this approach has been successful. However, for other disorders, the ability to achieve satisfactory outcomes with standard trans-

plant regimens has proven elusive. Reduced-intensity conditioning strategies may prove more successful in decreasing morbidity and mortality, particularly in patients with ongoing neurologic injury. It is anticipated that future investigations will test the use of combination therapy with or without transplantation, including substrate inhibition [101-102], chaperone therapy [103-105], enzyme replacement [24, 106], modification of anti-inflammatory therapy [107], or biologic response modifiers [108-110]. In addition, the interest in neonatal screening will provide the opportunity to intervene early in the course of these diseases, as this appears critical in achieving optimal outcomes [4, 111-114]. Finally, modifying the transplant procedure, using selectively expanded cell populations, or using cytokine manipulation may enhance microglial engraftment [115-118], which could make a substantial difference in the delivery of enzyme to the CNS. Significant progress is required to enhance transplant results and to determine optimal therapy in individuals with these devastating congenital disorders.

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Клеточная терапия и трансплантация, том 2, номер 7, 2010

Трансплантация гемопоэтических стволовых клеток при метаболических болезнях накопления

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Резюме

В данной обзорной статье представлены сведения о трансплантации гемопоэтических стволовых клеток (ТГСК) у детей с врожденными метаболическими болезнями накопления (ВМБН), и о нерешенных вопросах ТГСК при этих состояниях. Обсуждаются как миелоаблативные, так и менее интенсивные режимы кондиционирования. Показана выгода стандартизированного подхода к ТГСК при болезни Хурлера и ранней адренолейкодистрофии (АЛД) головного мозга. Режимы кондиционирования со сниженной интенсивностью могут оказаться более успешными в плане снижения смертности и развития осложнений, особенно у больных с развивающимся неврологическим дефектом. В ситуациях с ТГСК при наследственных заболеваниях можно ожидать, что потенциальные доноры-сибсы могут быть носителями мутации данного гена. Нерешенная проблема состоит в том, может ли альтернативный донор иметь преимущество в сравнении с сибсом, который может быть носителем заболевания. Обычно применяют стволовые неродственные донорские клетки из различных источников (костного мозга, периферических клеток, пуповинной крови) с хорошими результатами. Рассматривается эффективность энзим-заместительной терапии по сравнению с ТГСК в качестве подходящего лечения при менее тяжелых формах мукополисахаридозов (МПС), и ТГСК признано стандартом терапии для больных с тяжелыми клиническими формами МПС типа I. В противоположность синдрому Хурлера, ТГСК не выявила существенного влияния у больных с тяжелым МПС типа II (синдром Хантера), т.е. дети с тяжелой формой МПС типа II, по-видимому, не имеют преимуществ в нейрокогнитивном развитии при ТГСК. Что касается метахроматической или глобоидноклеточной лейкодистрофии, то данные об эффективности ТГСК здесь более скудные. Получение четких данных об исходах ТГСК у больных с ВМБН оказалось сложной задачей из-за редкости этих заболеваний, вариабельности их генотипов и фенотипов, различий в источниках стволовых клеток, кондиционирующих режимах и оценке «успешных» результатов. Дальнейшие

исследования установят полезность комбинированной терапии с/без трансплантации, включая субстратное ингибирование, терапию шаперонами, энзимотерапию и т.д. Кроме того, интерес к неонатальному скринингу обеспечит раннее вмешательство в течение этих болезней, т.к. это очень важно для получения оптимальных результатов. Наконец, модификация процедуры ТГСК или применение селективно размножающихся клеточных популяций, или обработка цитокинами могут усилить приживление микроглии, что может существенно облегчить достаку энзимов в центральную нервную систему. В это отношении будут важны многоцентровые исследования с общим подходом и оценкой клинических исходов.

Ключевые слова: наследственные болезни накопления, мукополисахаридозы, трансплантация гемопоэтических клеток, режимы кондиционирования, клинический эффект