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Hematopoietic Cell Transplantation in Patients with Mucopolysaccharidosis Type II

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Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is an X-linked lysosomal storage disorder caused by deficiency of the enzyme iduronate-2-sulfatase, leading to the accumulation of glycosaminoglycans (GAGs), which affects multiple organs and systems. Current treatments for MPS II include enzyme replacement therapy (ERT) and hematopoietic cell transplantation (HCT) to reduce the accumulation of GAGs. HCT has the potential advantage that donor-derived enzyme-competent cells can provide a continuous secreting source of the enzyme. However, HCT as a treatment for MPS II remains controversial because its effectiveness is unclear, particularly in terms of neurological symptoms. To date, several clinical experiences with HCT in MPS II have been reported. In this paper, we review post-HCT outcomes in the previously published literature and discuss the effects of HCT on each of the clinical signs and symptoms of MPS II.

Keywords: Mucopolysaccharidosis type II, Hunter syndrome, Hematopoietic cell transplantation

Introduction

Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is one of the lysosomal storage diseases caused by mutations in the gene encoding the enzyme iduronate-2-sulfatase (I2S). Lack of I2S enzyme activity leads to accumulation of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate both intracellularly and extracellularly. The excessive storage of GAGs leads to the clinical signs and symptoms of MPS II in the skeleton, cardiopulmonary system, central nervous system (CNS), cornea, skin, liver, and spleen in a chronic and progressive manner[1,2]. The clinical presentations of MPS II have been reported on a continuum from attenuated phenotypes to severe phenotypes. Severe and attenuated phenotypes are differentiated by the presence or absence of CNS issues, such as intellectual disability and loss of cognitive function[2,3].

Treatment Options for MPS II

Although there is no cure for MPS II, enzyme replacement therapy (ERT) and hematopoietic cell transplantation (HCT) are the main treatments to reduce the accumulation of GAGs.

1. Enzyme replacement therapy

ERT involves the intravenous administration of idursulfase, a glycosylated protein analogous to native human I2S, which is produced by genetic engineering in a continuous human cell line[4]. ERT improves the clinical symptoms of MPS II, but since idursulfase cannot cross the blood-brain barrier, the treatment cannot improve the neurological symptoms associated with severe phenotypes of MPS II. ERT also has limited effectiveness on the clinical symptoms involving heart valves, cartilage, and bones. In addition, the need for long-term treatment and high cost are disadvantages of ERT[5,6]. To treat both the somatic and neurological symptoms, a phase II/III clinical trial of intrathecal administration of idursulfase has been conducted. In Korea and Japan, collaboration research on intracerebrovascular ERT targeting severe types of MPS II has been conducted.

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2. Hematopoietic cell transplantation

Another treatment option for MPS is HCT. It involves progressively replacing enzyme-deficient hematopoietic cells with donor-derived enzyme-competent cells in the vascular and extravascular compartments of the body[7]. HCT is the treatment of choice for the severe form of MPS I (Hurler syndrome) since it can preserve neurocognition when performed early in the course of the disease, but it is less commonly used in the treatment of other MPS types (milder MPS I, II, III, IV, VI, and VII)[8]. In general, HCT has not been recommended for MPS II owing to a lack of clearly demonstrated neurological benefits and high rates of morbidity and mortality. However, encouraging developments have been reported with HCT performed very early in a limited number of MPS II patients[9-11]. HCT could be a good therapeutic option for MPS II, and it could be considered effective in resolving a broad range of clinical outcomes if performed at an earlier age[11,12].

3. Gene therapy

In recent years, gene therapy has emerged as a potential therapeutic option to overcome the limitations of HCT and ERT in the treatment of the neurological symptoms of MPS II. Encouraging results have been obtained from preclinical studies that used gene therapy in animal models of MPS II, and a phase I/II clinical trial of gene therapy for this disease has been conducted in the United States (ClinicalTrials.gov NCT03566043)[13-15].

MPS II Treated with HCT

The effectiveness of HCT for MPS II has been reported to be equivocal. Several experiences have suggested that HCT is not suitable for MPS II owing to a lack of clearly demonstrated improvements in neurological symptoms[9,16-18]. However, recent studies have shown positive outcomes in HCT for MPS II[11,19].

The literature reported previously provides mixed results of the effects of HCT on the clinical manifestations of MPS II. Clinical outcomes in MPS II patients treated with HCT are listed in Table 1.

Joint stiffness and a coarse face including thick skin and hirsutism associated with MPS II improved in most patients after HCT[9,16,20,21]. Growth also improved after HCT[9,21,22]. Patel et al.[23] described the effects of ERT and HCT on the growth of 44 Japanese patients with MPS II. The patients, who had been treated with either ERT or HCT, showed increased height compared with untreated patients, and HCT and ERT were equally effective in restoring growth in MPS II patients. MPS II patients who received HCT at 70 days of age showed normal growth charts at 7 years of age[10].

All patients showed improvements in hepatosplenomegaly on clinical manifestations or ultrasound findings after HCT. McKinnes et al.[16] described the follow-up of a transplanted patient at 29 months of age. During the period, serial liver biopsies showed a significant reduction in deposited material in all cell types. Araya et al.[24] reported the case of a 5-year-old patient who underwent HCT. Biochemical and histopathological analyses of the autopsied tissue revealed that I2S activity in the liver was 40% of the normal range, and there was no deposited material on the liver tissue.

There are various results on the effects of HCT on skeletal deformities, and two reports showed no improvement in skeletal manifestations even when HCT was administered at the age of less than 3 years[16,20]. McKinnes et al.[16] reported that skeletal deformities did not improve after HCT, but did not progress either.

In several studies, improvements in cardiac function and heart valve insufficiency, and normalization of ventricular size on echocardiography have been reported[21,25]. Tanaka et al.[19] reported that cardiac valvular regurgitation improved in 32% of valves and stabilized in 56% of valves after HCT. However, there was a report of four boys with a severe phenotype of MPS II, in whom cardiovascular involvement was unchanged after receiving HCT[20].

It has been reported that the behavioral problems of MPS II did not improve after HCT. Three studies reported that hyperactivity and behavioral problems did not improve in patients with the severe form of MPS II after HCT[10,16,24], and Muschol et al.[26] reported a case of progression of hyperactivity and aggressive behavior after 6 months of HCT.

The effects of HCT on hearing loss and cognitive function have various results in several studies. In one report, there were mixed results with improved or worsened neurological symptoms[17]. Several previous experiences suggested that HCT was not effective in preventing the neurologic progression of the disease in children with the severe phenotype of MPS II1[6,24]. In a report by Muschol et al.[26], neurological decline with progressive cerebral atrophy was observed in one of two patients, and the other patient showed developmental delay with reduction in white matter changes. However, there have also been reports that HCT stabilized the intelligence quotient (IQ) of patients with MPS II after transplantation[21,25]. Barth et al. reported a boy with a family history of a severe form of MPS II who underwent HCT at 70 days of age[10]. Despite low measured IQ (measured IQ of 47), the patient was quite functional with consistent improvements in cog-

Table 1. Summary of clinical outcomes in patients with MPS II treated with HCT

Number of patients	Phenotype	Age at HCT	Facial feature	Joint stiffness	Skeletal deformity	Height	Hepatosplenomegaly	Cardiac valve dysfunction	Cognitive function	Behavior problem	Hearing loss	Reference
1	NA	2 y 9 m	I	I	I	I	I	I	I	NA	I	Coppa et al.[21]
1	SF	2 y 5 m	I	I	U	NA	NA	NA	U	U	U	McKinnes et al.[16]
1	SF	5 y	NA	I	NA	NA	I	I	I	NA	NA	Li et al.[25]
10	NA	10 m to 5 y 1 m	NA	NA	NA	NA	NA	I	Variable	NA	NA	Vellodi et al.[17]
1	AF	10 m	NA	NA	I	I	I	NA	I	NA	NA	Mullen et al.[22]
8	AF/SF	3 y 9 m to 16 y 4 m	I	I	I	I	I	I	Variable	NA	I	Guffon et al.[9]
1	SF	5 y 11 m	NA	NA	NA	NA	I	NA	U	U	NA	Araya et al.[24]
21	AF/SF	2 y to 19 y 8 m	NA	NA	NA	NA	NA	I	I	NA	NA	Tanaka et al.[19]
4	SF	2 y 6 m to 2 y 11 m	I	I	U	NA	I	U	I	NA	U	Annibali et al.[20]
18	AF/SF	2 y to 18 y	NA	NA	NA	I	NA	NA	NA	NA	NA	Patel et al.[23]
12	NA	NA	Variable	Variable	Variable	I	I	I	I (2 to 6 y)	NA	Variable	Wang et al.[29]
2	NA	2 y 1 m to 4 y 3 m	NA	NA	NA	NA	I	NA	U	U	NA	Muschol et al.[26]
1	SF	70 days	I	I	I	I	I	NA	I	U	U	Barth et al.[10]
27	AF/SF	2 y 0 m to 21 y 5 m	NA	NA	NA	NA	NA	NA	I	NA	NA	Kubaski et al.[11]

HCT, hematopoietic cell transplantation; SF, severe form; AF, attenuated form; I, improved; U, unimproved; NA, not available.

nitive, language, and motor skills. In addition, previous reports mentioned that donor-derived cells were found in the autopsied brain tissue of an MPS II patient after HCT[24] and that improvements of abnormal findings on brain MRI, including cystic lesions, white matter signal changes, ventricular enlargement, and/or brain atrophy, were noted in patients after HCT[11,19]. Additionally, it has been reported that HCT has a positive effect on activities of daily living (ADL) (movement and cognition) in patients with MPS II and that early HCT is associated with a higher ADL score than late HCT[27]. In a report of Wang et al.[28], HCT was also beneficial in improving mental development in MPS II patients aged 2 to 6 years.

Combined Treatment with HCT and ERT

Prior or overlapping ERT treatment in MPS II patients who received HCT had an additive effect on growth[23]. In addition, it has been reported that the combination of HCT and ERT was additive in reducing GAGs in several visceral organs in an MPS II mouse model. However, HCT and ERT alone or even as a combination had a limited positive effect on brain disease[29].

Conclusion

A potential advantage of HCT for treating MPS II is that donor-derived enzyme-competent cells can provide a continuous secreting source of the enzyme. However, HCT as a treatment for MPS II remains controversial owing to a lack of clearly demonstrated neurological benefits and high rates of morbidity and mortality. The effects of HCT on neurological symptoms have various results in the previously reported literature, but there are reports that HCT performed at an earlier age provides better neurological outcomes. The clinical consequence of HCT relies on the age of the patient at the time of transplantation and the severity of the clinical phenotype. HCT should be considered as a treatment option for MPS II with careful consideration of the clinical characteristics of the patient and the risk/benefit ratio.

Conflict of Interest

The author has no financial conflicts of interest.

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