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Reviews

Hematopoietic Stem Cell Transplantation for Mucopolysaccharidoses: Past, Present, and Future

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A B S T R A C T

Allogenic hematopoietic stem cell transplantation (HSCT) has proven to be a viable treatment option for a selected group of patients with mucopolysaccharidoses (MPS), including those with MPS types I, II, IVA, VI, and VII. Early diagnosis and timely referral to an expert in MPS are critical, followed by a complete examination and evaluation by a multidisciplinary team, including a transplantation physician. Treatment recommendations for MPS are based on multiple biological, sociological, and financial factors, including type of MPS, clinical severity, prognosis, present clinical signs and symptoms (disease stage), age at onset, rate of progression, family factors and expectations, financial burden, feasibility, availability, risks and benefits of available therapies such as HSCT, enzyme replacement therapy (ERT), surgical interventions, and other supportive care. International collaboration and data review are critical to evaluating the therapeutic efficacy and adverse effects of HSCT for MPS. Collaborative efforts to assess HSCT for MPS have been ongoing since the first attempt at HSCT in a patient with MPS reported in 1981. The accumulation of data since then has made it possible to identify early outcomes (ie, transplantation outcomes) and long-term disease-specific outcomes resulting from HSCT. The recent identification of predictive factors and the development of innovative regimens have significantly improved the outcomes of both engraftment failure and transplantation-related mortality. Assessment of long-term outcomes has considered a variety of factors, including type of MPS, type of graft, age at transplantation, and stage of disease progression, among others. Studies on long-term outcomes are considered a key factor in the use of HSCT in patients with MPS. These studies have shown the effects and limitations of HSCT on improving disease manifestations and quality of life. In this review, we summarize the efficacy, side effects, risks, and cost of HSCT for each type of MPS.

INTRODUCTION

Mucopolysaccharidoses (MPS) are a group of genetic lysosomal storage disorders (LSDs). Individuals with MPS lack a specific enzyme in the lysosome, which degrades glycosaminoglycans (GAGs) in numerous body tissues. Deficiency of the

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enzyme leads to an accumulation of undegraded GAGs in the body, resulting in systemic clinical manifestations unique to patients with MPS. Seven types of MPS have been identified, based on the specific enzyme deficiency and successive accumulation of specific GAGs. Common clinical manifestations of MPS include skeletal manifestations, cardiac and respiratory disease, and, in some types of MPS, central nervous system (CNS) involvement [1-4].

Two main treatments for MPS patients are available in practice: hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT). With HSCT, healthy donor cells are transplanted, and the enzymes secreted by donor cells are then taken up by the recipient's body through cross-correction [2,5-8]. Figure 1 illustrates the mechanisms of HSCT treatment in patients with MPS. In contrast, i.v. ERT delivers the specific recombinant enzyme that is deficient in the patient. These enzymes bind to the mannose-6-phosphate (M6P) receptors on the cell surface and are delivered to the lysosome, the site of action of lysosomal hydrolases.

The first stem cell transplantation in a patient with MPS, a bone marrow transplantation (BMT) performed in a 1-year-old boy with MPS type IH (Hurler syndrome), was reported in 1981 (Table 1). Initially, the boy received cells from his father, who was matched at 1 haplotype, but there were no signs of successful engraftment after 2.5 months. The boy then received cells from his mother, with a 3-loci match. After 14 days of engraftment, 88% of his white cells had an XX chromosome. However, at 8 days after engraftment, he developed graft-versus-host disease (GVHD), and manifestations of MPS I, such as hepatosplenomegaly and corneal clouding, regressed. A liver biopsy performed at 199 days post-BMT showed no signs of storage materials, and the boy's leukocyte and plasma enzyme levels reached the normal levels of his mother [9].

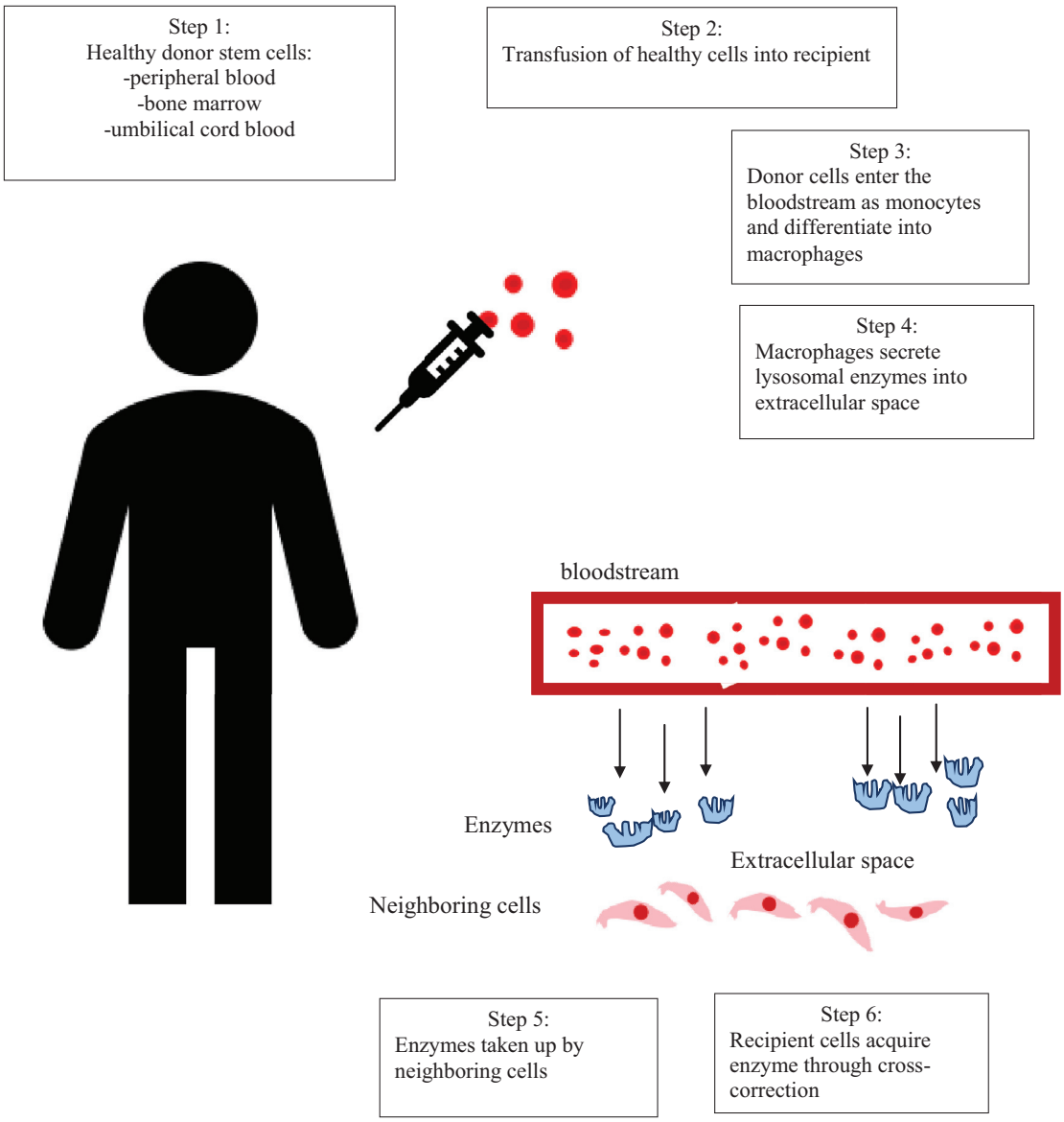

Figure 1. Process by which HSCT treats patients with MPS [2,196].

Table 1
Historical Timeline of HSCT for MPS

Year(s)	Description	Reference
1957	First documented BMT in a patient who sustained nuclear radiation exposure	[197, 198]
1969	HSCT allows cross-correction in patients with MPS I and II	[21, 22]
1981	First report of HSCT in a patient with MPS I	[56, 153]
1982-1991	First allogeneic BMTs in patients with MPS II	[56, 153]
1984	First report of successful BMT in a patients with MPS VI	[6]
1998	First report of BMT in a patients with MPS VII	[20]
2000	First report of successful HSCT in a patient with MPS II	[199]
2005	New EBMT international guidelines for HSCT in patients with MPS	[37]
2014	First report of BMT in a patient with MPS IVA	[12]

HSCT is considered the standard of care for patients those with MPS IH and an optional treatment for those with Hurler/Scheie syndrome (MPS IH/S) and Scheie syndrome (MPS-IS) (attenuated phenotypes of MPS I), MPS II, MPS IVA, MPS VI, and MPS VII [10-20].

One of the main differences between ERT and HSCT is that in ERT, only the deficient enzyme is infused, which circulates in the bloodstream with a short half-life and cannot cross the blood-brain barrier (BBB). In contrast, in HSCT, donor stem cells circulate in the bloodstream, which can cross the BBB and differentiate (eg, macrophages, microglia). The microglial cells secrete the deficient enzyme to the different parts of the brain [21]. HSCT has been shown to improve CNS impairment in patients with MPS I, II, and VII [10,13,18,20,22].

Advantages of HSCT include that it is generally a one-time procedure that provides the recipient with a continuous source of enzyme, as well as rapid clearance of GAGs [2]. Peripheral blood stem cell transplantation (PBSCT) has largely replaced BMT in adolescent patients, owing to the simplicity of donor collection, fewer complications, and better outcomes. These outcomes include reduced hematologic and immune responses, easier retrieval donor stem cells, less need for antibiotics, shorter hospital stays, and fewer donor adverse effects. However, BM remains the preferred donor source for adult patients because of the lower associated incidence of GVHD [23]. Umbilical cord blood (UCB) is another possible donor cell source, attractive because of its ease of retrieval and decreased rate of complications due to immune tolerance [3,24-26]. Nonetheless, there remain many challenges associated with HSCT, including the time-consuming process of finding an acceptable donor, as well as the mortality and morbidity associated with the procedure [2].

In the early years of HSCT as treatment for MPS in the 1980s and 1990s, a significant risk of mortality was associated with the procedure. However, it is important to consider some factors that contributed to this high mortality risk. Patients who underwent HSCT during this initial period were usually in the late stages of disease with significant clinical manifestations already present. In addition, advancements in medicine since then have led to a reduction in mortality risk [3,27-33]. Specific aspects of the transplantation procedure have improved, reducing mortality rates. These improvements include the availability of matched UCB grafts, enhanced HLA-matching techniques, advanced conditioning regimens, and improved supportive care [28,34-36]. Experienced HSCT centers have reported engrafted survival rates as high as 90% in patients with MPS I, due primarily to the use of updated protocols from the European Society for Blood and Marrow Transplantation (EBMT) and selection of well-suited donors [28,31,33,37,38].

ERT can cause an immune response against the infused enzyme in the recipient's body, which may result in compromised treatment outcomes [39-42]. In 2012, Saif et al. [43] reported that HSCT can overcome immune responses resulting from ERT. In their study, all patients with MPS IH who received ERT followed by HSCT had their antibodies reduced to an insignificant level by 101 days after transplantation. The presence of normal enzyme levels did not affect the antibody levels. In addition, the authors found that full-donor chimerism was required for the reduced antibody response. Allogeneic HSCT corrects the immune response to ERT by replacing the patient's immune system with the donor's immune system [44].

The age at which HSCT is performed has a significant impact on its efficacy. In 2015, Tanjuakio et al. [45] reported higher activities of daily living (ADL) scores in patients with MPS II undergoing HSCT before age 5 years compared with those undergoing HSCT after age 5 years. Therefore, transplantation at an early age is important for the overall outcome of the procedure. Increased awareness of MPS and the introduction of newborn screening (NBS) have allowed for early detection and treatment of the disease before the development of severe irreversible clinical manifestations.

In 2017, Kubaski et al. [13] reported a patient with MPS II who underwent ERT beginning at age 2.3 years and developed an IgG antibody response that caused the ERT to eventually become ineffective. At age 4.5 years, the patient underwent HSCT with full engraftment. Positive results from the HSCT included decreased urinary GAGs, decreased hepatosplenomegaly, and increased ADL scores. Thus, HSCT restored and even improved the outcomes of a patient who otherwise would have remained without treatment owing to the immune response.

As of 2018, more than 1000 patients with MPS have undergone HSCT to treat their disease [11-14,17,19,20,37,46-50]. Although the most common treatment for those with attenuated forms of MPS remains weekly 4- to 6-hour i.v. ERT infusions, HSCT is more time-efficient overall; moreover, HSCT can be a better treatment option for improving disease symptoms, because it results in better metabolic correction [10,13,18,19,31,51]. In this review article, we summarize the benefits and limitations, adverse effects, predictive factors, innovative regimens, and costs of HSCT for each type of MPS.

GENERAL ASPECTS OF HSCT

HSCT has been shown to be effective in patients with MPS type I, II, IVA, VI, and VII [10-14,18-20,45,49,52-58]. The extent to which the treatment is effective depends on the patient's age and disease stage at the time of the procedure, type of MPS, type of donor, and preparative regimen [55,59]. HSCT can improve the clinical manifestations of MPS, including reduced joint mobility, vision, hearing, and cardiopulmonary function; coarsened facial features; upper airway obstruction, impaired respiratory function; and hepatosplenomegaly [2,5-8,60-64]. However, HSCT is not able to significantly correct clinical manifestations of the disease in bone or cornea, cardiac valve abnormalities, or preexisting cognitive and intellectual effects [3,65-68]. In comparison, ERT has shown no significant effect on correcting skeletal dysplasia. Enzymes also have a short half-life, and ERT can sometimes cause an increase in

antibodies, which can decrease the overall efficacy of treatment [3,65,66,68,69]. Transplantation at an early age is important for an overall good outcome of the procedure.

Conditioning Regimens

Preparative conditioning regimens and GVHD prophylaxis are administered before HSCT to suppress the patient's immune system by eliminating immune cells and to reduce the risk of rejection of donor cells. Myeloablative conditioning (MAC), nonmyeloablative (NMA) conditioning, and reduced-intensity conditioning (RIC) regimens are available. MAC regimens usually contain some combination of cyclophosphamide and total body irradiation (TBI) or a combination of busulfan and cyclophosphamide. NMA and RIC regimens include some combination of low-dose TBI with or without fludarabine or a mixture of fludarabine with an alkylating agent, such as thiotepa, melphalan, or busulfan [70-81]. The type of preparative conditioning used before HSCT can affect the success of the procedure. Some studies have reported an increased risk of graft failure with the use of RIC regimens [35]. Table 2 summarizes published HSCT cases, detailing the conditioning regimen, donor source, and outcomes of the procedure [82]. The most recent recommendation for successful engraftment was adopted in 2012, suggesting a combination of busulfan and fludarabine as a conditioning regimen. This recommendation differs from the previous recommendation of a combination of busulfan and cyclophosphamide. Fludarabine is now considered the preferred conditioning agent because is less toxic than cyclophosphamide when combined with busulfan and has been shown to achieve the same engraftment rate success in patients [31,37,83].

Cell Sources for HSCT

HSCT recipients can acquire donor cells from 3 different sources: BM, peripheral blood stem cells (PBSCs), and UCB [24]. In 2005, the EBMT released guidelines suggesting the following donor type hierarchy: noncarrier HLA-matched related donor (MRD), matched UCB, and matched unrelated donor (MUD) [82]. In 2016, Boelens et al. [31], evaluating the best way to achieve event-free survival after an HSCT, identified the best donor sources as identically HLA-matched siblings and identical antigen-matched UCB and the next-best sources as 5/6 HLA-matched UCB and 10/10 HLA-matched unrelated donors. In 2017, Rodger et al. [84] reported a higher 8-year survival rate in patients who undergo related BMT or unrelated UCB transplantation compared with patients who undergo unrelated BMT [84]. In addition, the best combination of regimen and donor source is a busulfan-containing MAC regimen [30,35,37] and a matched UCB, noncarrier matched sibling, or fully matched unrelated donor [28]. In recent years, UCB has become a popular donor source. However, in a 2017 multicenter study, Lum et al. [82] reported an overall decreased risk of graft failure in recent years, but that the pattern has changed from previous recipient autologous reconstitution to now aplastic-type graft failure. The former reflects inadequate myelosuppression, and the latter is more common in UCB recipients, which has been proposed to represent inadequate recipient immune suppression. Overall, patients who become engrafted with UCB exhibit better donor chimerism compared with those engrafted with BM [28,82,85].

Adverse Effects of HSCT

Before 2000, reported mortality rates associated with HSCT for MPS were as high as 27% [13,18,56]. Side effects associated with HSCT include disturbances of growth and infertility [51]. The major causes of death in patients with MPS IH within the first year post-transplantation include viral infection, pulmonary hemorrhage, and GVHD [8,35,84,86,87]. Factors contributing to a high mortality rate include advanced disease stage at the time of HSCT and use of a mismatched donor. Causes of death following HSCT include infection, organ failure, graft rejection and disease recurrence, GVHD, and conditioning regimen toxicity [13,18,56]. TBI has not been used in patients with MPS IH since 2002, because TBI-containing conditioning regimens have been associated with negative effects on neurodevelopment, growth, hypothyroidism, and cataracts. However, currently used regimens can lead to secondary malignancies, especially in older patients [38]. The event-free survival rate in patients with MPS IH rose to 91% between 2005 and 2008, which has been attributed to improved transplantation protocols.

The toxicity of the drugs administered before, during, and after HSCT can have detrimental effects on the patient. Conditioning regimens are aimed at achieving optimal donor chimerism and preventing GVHD, and they have an essential role in ensuring the successful engraftment. A robust MAC regimen is needed; the absence of pharmacokinetic targeting of busulfan to achieve a myeloablative level is associated with a high risk (20% to 25%) of autologous reconstitution and late graft failure in patients with an inherited metabolic disease [63,88,89]. However, a conditioning regimen may cause further progression of a lysosomal storage disorder brain disease, thereby compromising the effectiveness of HSCT. In 2015, Aldenhoven et al. [38] suggested that toxic conditioning regimens can contribute to the ongoing disease symptoms seen in patients with MPS IH even after transplantation. In addition, in 2014, Ansari et al. [90] suggested that females may be more prone to busulfan toxicity, which may explain the increased mortality rate in females reported by Rodgers et al. [84].

In 2018, Chen et al. [89] identified the combination of fludarabine (90 mg m^{-2}), busulfan (9.6 mg m^{-2}), and cyclophosphamide (200 mg kg^{-1}) as an acceptable conditioning regimen for achieving and sustaining full engraftment in haploidentical allogeneic HSCT without any increase in complications.

The 5-year survival rate in patients with MPS I who undergo HSCT is >90% [7,55,86]. In patients with MPS IH, death is most common during the first-year post-transplantation [8,28,35,84,86,87]. Rodger et al. [84,91-93] reported a persistent steady mortality rate in adolescents and young adults at >1 year post-transplantation, and higher incidences of infection and pulmonary and cardiac complications compared with healthy counterparts even at 10-years post-transplantation. Although patients with untreated MPS IH usually die from cardiac and pulmonary causes [94], those who undergo HSCT can also die from pulmonary complications and infection during the first-year post-transplantation [8,28,35,84,86,87]. These complications are usually attributed to conditioning toxicity, GVHD, or impaired immunity. Long-term outcomes of patients with MPS IH who undergo HSCT show that the increased mortality associated with the procedure is not correlated with age at transplantation, sex, graft-recipient HLA disparity, conditioning regimen, or exposure to serotherapy [94]; however, in 2017, Rodgers et al. [84] reported a 30-year study of patients with MPS I who underwent HSCT that found a correlation between reduced mortality during the first decade post-transplantation and improvements in peri-HSCT management. Overall, the improved symptoms and higher survival rate make HSCT a good treatment option for patients with MPS IH.

Rodgers et al. [84] also found higher mortality in females than in males, regardless of the time period in which HSCT was

Table 2
Summary of HSCT Conditioning Regimens, Donor Sources, and Graft Types

Study	MPS Type(s)	Number of Patients	Conditioning Regimen	Donor Source	Graft Type	Donor Chimerism	Incidence of GVHD	Survival
Souillet et al., 2003 [8]	MPS IH	27	27 Bu/Cy/ATG for MMUD BMT	13 MRD; 14 MUD	2 UCB; 17 BM	70% ≥95% donor chimerism	5 aGVHD	85%
Boelens et al., 2007 [35]	MPS IH	146	68 Bu/Cy 200 mg/kg; 30 Bu/high-dose Cy 240-260 mg/kg; 15 Bu-targeting; 17 Flu-based MAC; 18 RIC	96 HLA-MD	103 BM; 20 PBSC; 23 UCB	71% full donor chimerism after initial HSCT	26 aGVHD grade I; 15 aGVHD grade II; 3 aGVHD grade III; 5 aGVHD grade IV; 8 cGVHD	85% after first transplantation
Tuberville et al., 2011 [17]	MPS VI	45	6 Cy/TBI ± other; 30 Bu/Cy ± other; 1 Flu/Mel; 7 other	15 HLA-MSD; 3 MRD; 27 MUD	34 BM; 1 PBSC; 10 UCB	N/A	15 aGVHD grade II-IV; 34 aGVHD grade III-IV; 19 cGVHD	78% at 100 d; 66% at 1 and 3 yr
Aldenhoven et al., 2015 [37]	52 MPS IH; 2 MPS II; 2 MPS III; 2 MPS VI	62	29 Bu/Cy; 33 Flu/Bu	44 HLA-MD	41 UCB; 21 BM or PBSC	88.2% full donor chimerism	8 aGVHD grade II-IV; 8 cGVHD	95.20%
Wang et al., 2016 [18]	12 MPS I; 12 MPS II; 4 MPS IVA; 4 MPS VI; 2 unknown	34	21 Bu/Cy/ATG; 8 Bu/Cy/Flu/ATG	11 4/6 to 6/6 HLA-MUD; 4 MSD; 2 MRD; 17 MUD	11 UCB; 23 PBSC	31 full donor chimerism	14 aGVHD grade II to IV; 4 aGVHD grade III-IV; 2 moderate-severe cGVHD	84.8% ± 6.3% at 3 yr
Lum et al., 2017 [82]	MPS IH	240	145 Bu/Cy ± serotherapy; 40 Bu/Flu ± serotherapy; 55 other	67 MRD; 151 MUD; 22 MMD	132 BM; 16 PBSC; 92 UCB	80% full donor chimerism of 85 patients assessed	70 aGVHD grade I-II; 22 aGVHD grade III-IV; 14 cGVHD	85.20%
Rodgers et al., 2017 [84]	MPS IH	134	35 targeted Bu; 99 nontargeted Bu	35 MRD; 97 MUD	83 BM; 49 UCB; 2 PBSC	100 ≥90%; 21 10%-89%; 12 <10%; 1 unknown		70% at 1 yr

MSD indicates matched sibling donor; MD, matched donor; MMUD, mismatched unrelated donor; Cy, cyclophosphamide; Flu, fludarabine; Mel, melphalan; ATG, thymoglobulin; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; Bu, busulfan.

performed. When evaluating causes of death up to 25-years post-transplantation, pulmonary-related causes accounted for 27% of the deaths, making this the highest single-organ cause of death. Infection-related causes accounted for 11.6% of deaths, and cardiac-related causes of death accounted for 8.3% deaths. It is important to note that while GVHD was not identified as the main cause of death, it could have contributed to these single-organ causes of death. The report also found no correlation between the level of alpha-L-iduronidase (IDUA) enzyme measured at 1 year post-transplantation and long-term survival in patients with MPS I.

Along with the general risks and adverse effects of HSCT, there may be increased risks associated with receipt of more than 1 HSCT. In a 2017 study of patients with MPS IH, Lum et al. [94] found a correlation between receipt of 2 HSCTs and the severity of cardiac dysfunction. In addition, patients with MPS I who have serious lower respiratory tract disease or pneumonia before HSCT have an increased risk of mortality [95].

The reported 5-year survival rate was 88.5% in patients with MPS II who underwent HSCT in Japan between 1990 and 2003 [3]. However, subsequent reports have suggested even higher survival rates today. In 2016, Wang et al. [18] reported a 100% survival rate in a 10-year follow-up study of 12 Chinese HSCT recipient with MPS II [13].

Patients with MPS IVA typically have a severely narrowed airway and pulmonary compromise. These airway abnormalities, which have a tortuous appearance in the trachea, bronchi, and small lungs, complicate the use of anesthesia in procedures and can lead to difficulty with intubation and extubation as patients age, especially after adolescence [12,96]. Therefore, careful selection for HSCT is necessary in patients with MPS IVA. Although the number of treated patients is low, no deaths clearly due to HSCT have been reported in patients with MPS IVA [18,19].

In patients with MPS VI, HSCT can result in complications including GVHD, graft failure, infection, endocrine, and gonadal failure. In 2011, Tuberville et al. [17] reported that 36% of patients with MPS VI who underwent HSCT between 1982 and 2007 developed acute GVHD by 100 days post-transplantation, with a resulting survival rate of 78% at 100 days post-transplantation and 66% at 1 year after transplantation.

Predictive Factors of HSCT Cost

Accurately estimating the cost of HSCT is difficult because of the many factors that affect this cost. These factors include the country in which HSCT is performed, type of donor, preconditioning regimen, potential complications, and out-of-pocket expenses. In the United States, the cost of HSCT is often underestimated because such cost categories as outpatient medication, home infusions, donor search, graft procurement, and physician charges are not considered when calculating the total cost of the procedure. Most studies evaluating the cost of HSCT focus only on the short-term costs of the procedure, and thus there are insufficient data for determining the financial impact of long-term care or chronic GVHD [97]. The majority of costs associated with transplantation are incurred within 5 months post-transplantation [98].

One of the main determinants of the cost of HSCT is the duration of hospitalization associated with the procedure. Hospital length of stay has been reported to account for 80% of the total cost of HSCT by 1 year post-transplantation [23,99,100].

Another factor in the cost of HSCT is the graft donor source. The difference in cost between different donor types is related to the disparity in the costs of cell acquisition. For example, the cost difference between UCB and MRD is related to the longer engraftment period and higher graft failure rate with UCB, which result in longer hospital stays and, consequently, a higher total cost [101]. Cell acquisition from MRDs involves donor evaluation, apheresis, graft processing, and storage. Cell acquisition from UCB includes searching the cord blood bank for a suitable match, confirming HLA typing in the donor, and shipping of cord blood. With a median cost of $69,000, the acquisition of UCB is significantly more expensive than cell acquisition from either MUDs or MRDs. Cell acquisition from MRDs is the least expensive option, with a median cost of $9500 [101].

There is also a cost difference between PBSCT and BMT, as well as between MAC regimens and RIC regimens [99]. Patients receiving an NMA conditioning regimen typically have a shorter initial length of hospital stay than those who receive an MAC regimen; however, over time, patients receiving an NMA regimen end up having to be hospitalized more than those receiving an MAC regimen due to an increased rate of complications, such as secondary GVHD and infections. NMA-conditioned HSCT recipients usually end up spending significantly more money by 6 to 12 months post-transplantation because of the costs associated with complications and readmissions [99]. Another factor to consider in the cost of HSCT is the complications that can result from the procedure, including GVHD, urinary tract infection, sepsis, and pneumonia, which can incur additional costs [102].

The location where HSCT is performed is another significant factor affecting cost. A 2006 study in Sweden reported a total average cost of HSCT of $145,000 with related donors and $182,000 with unrelated donors [103,104]. In 2007, the reported 1-year median cost of HSCT in Thailand was $23,000 [103,105]. In Mexico, in 2015, the median cost of allogeneic HSCT in pediatric patients was $13,000 and the total cost by 1 year post-transplantation, including follow-up and out-of-pocket expenses, was $16,000. The median duration of inpatient stay was 6 days, at a median cost of $1400, and the average for out-of-pocket expenses was $2000 [23]. In 2016, Gale et al. [106] reported that the cost of HSCT in Latin America ranged from $25,000 to $75,000 [106]. The reported cost per HSCT in Japan is between $70,000 and $205,000 [13,47,49,107-109].

The cost of ERT in patients with MPS is generally much higher. In 2017, the reported annual cost of ERT in a patient weighing 25 kg was $218,000 for MPS I, $340,000 for MPS II, $578,000 for MPS IVA, $476,000 for MPS VI, and $550,000 for MPS VII [110] (Table 8).

Combination Therapy with ERT and HSCT

Combination therapy with ERT and HSCT is a newer, more effective approach for minimizing the clinical manifestations of MPS, as well as for improving some of the patients' clinical manifestations before transplantation [44,111,112]. In Australia, guidelines in place suggest that patients with MPS I should receive ERT up to 12 weeks before HSCT and for up to 15 to 17 weeks after HSCT [2,113]. ERT can improve some pretransplantation conditions in recipients, such as reduced respiratory and cardiac manifestations, leading to better results overall [24,54]. ERT does not affect the overall engraftment of HSCT [42,44,54,67,111,114-118]. The combination of ERT with HSCT decreases transplantation-related complications for patients with MPS I [119,120] and may be able to reduce the mortality caused by the transplant itself [44,111,112]. The pretransplantation use of ERT gives the patient time to find a donor without worrying about worsening of the disease [120]. However, there is concern that ERT could potentially initiate

Table 3
Reports of HSCT for MPS I

Author	Details	Results
Yasuda et al., 2015 [137]	UCBT at age 2 yr, 10-yr follow-up	- Normal ADL and cognitive function
		- Bone deformity continued
		- Improved bone lesion
		- Reduced GAG levels
Aldenhoven et al., 2015 [21, 38]	- 217 patients with MPS IH	- Early transplantation correlated with significant cognitive development
	- Patients from various centers	- Many achieved normal enzyme levels
	- Transplantations performed between January 1985 and February 2011	- Enzyme levels below the reference limit in 26 patients
	- Patients followed for a median of 9.2 years	- Persistent disease manifestations in some patients
		- TBI and older age correlated with little neurodevelopmental improvement
		- 71% of patients with severe cognitive impairment had DQ/IQ <70 post-transplantation
		- 15% of patients with DQ/IQ >70 developed severe cognitive impairment post-HSCT
		- Mild developmental impairment post-transplantation
Rodgers et al., 2017 [84]	- 134 patients with MPS IH	- Survival rate after transplantation: 70% at 1 yr, 62% at 10 yr, 32% at 25 yr
	- HSCT performed at University of Minnesota in 1983-2013	- Survival rates before 2004: 65% at 1 yr post-transplantation; 57% at 8 yr post-transplantation - Survival rates after 2004: 84% at 1 yr post-transplantation; 81% at 8 yr post-transplantation - Preferred treatment changes led to an increase in rate of normal IDUA enzyme level from 54.8% before 2004 to 75.9% after 2004
	- In 2013, follow-up data were obtained for 122 patients	
	- Median duration of follow-up was 10.7 yr (IQR, 5.0-17.2 yr) post-transplantation	
	- Longest follow-up was 28.97 yr	
Lum et al., 2017 [82]	- 240 patients with MPS IH	- 85.2% survival rate
	- HSCT performed between 1983 and 2015	- 85 patients alive and engrafted
	- 102 patients received pretransplantation ERT	- 60 patients experienced graft failure
		- UCBT associated with graft failure
Lum et al., 2017 [94]	- 54 patients	- 18 patients experienced graft failure
	- HSCT performed between 1985 and 2008	- 9 died
	- Median patient age 15.1 months	- 17 received second transplantation
		- 12 alive and engrafted after second transplantation
		- 73.7% survival rate at 20 yr post-transplantation
		- 9 normal cardiac assessments
		- 4 on angiotensin-converting enzyme inhibitors
		- 2 had mild cardiomyopathy
		- 2 had aortic valvular replacement

an antibody response, which in turn could affect the outcome of HSCT [44,111,112].

Because HSCT cannot entirely correct secondary musculoskeletal disorders [120] but can improve cognitive and central nervous system function [8,55,64,121-126], the combination of ERT with HSCT can result in better outcomes than either treatment can produce alone.

In 2010, Whitley et al. [127] reported the outcomes of a male with MPS VI who had received HSCT at age 18 months from an HLA-identical sibling who was a heterozygous carrier. At 20 years post-transplantation, this patient was still fully engrafted but had symptoms of progressive corneal opacification. The patient was then given galsulfatase via i.v. infusion at a dose of 1 mg/kg. As a result of the ERT treatment, urinary GAG levels were reduced from 7.63 mg/mmol creatinine to 4.4 mg/mmol creatinine by just 10 days after treatment. These results are surprising for a one-time treatment with galsulfatase and may suggest the possible use of ERT with HSCT for a better outcome in patients with MPS VI [127].

In 2014, Ferrara et al. [120] reported that ERT administered pretransplantation reduced the amount of soft tissue forming around the odontoid causing dural and cord compression in the spine. Magnetic resonance imaging (MRI) after transplantation showed a reduction of pressure in the spine. Based on this finding, Ferrara et al. suggested that ERT should be given to patients with MPS I pretransplantation, during marrow aplasia, and post-transplantation until successful engraftment is observed.

Furthermore, in 2016, Ghosh et al. [112] investigated the effect of the combination of ERT and HSCT in patients with MPS I at the University of Minnesota and the Royal Manchester Children's Hospital, between September 2004 and June 2014. ERT treatment was started immediately after diagnosis of MPS I and continued until successful transplantation. All patients received .58 mg/kg of laronidase weekly. Patients at the University of Minnesota's Division of Pediatric Blood and Marrow Transplantation received ERT for an average of 8 weeks post-transplantation, whereas patients at the Royal Manchester Children's Hospital

stopped laronidase treatment after engraftment. The median number of doses of laronidase given pretransplantation was 13 doses. The overall survival rate in this study was 86%, and the overall event-free survival rate was 80%. ERT reduced urinary GAG levels, which were further reduced after HSCT. The continuous decrease in urinary GAG levels could be attributed to substrate reduction after transplantation, as has been reported in previous studies [51,112]. The results from this study show that the combination of HSCT and ERT did not decrease the rate of GVHD in patients with MPS I.

In a 2017 study reported by Lum et al. [94], 52.2% of HSCT recipients with normal/mild cardiac valve insufficiency had received pretransplantation ERT, compared with none of the HSCT recipients with moderate valve insufficiency and only 1 HSCT recipient (25%) with severe valvular insufficiency/cardiomyopathy. That study supports the claim that pretransplantation ERT can help reduce cardiac manifestations of the disease compared with HSCT alone.

Two case reports of patients with MPS VI reported benefits of combining ERT and HSCT. In 1 case, a 3-year old girl with MPS VI showed positive effects on respiratory function, hepatosplenomegaly, and joint range of motion with the combination of ERT and HSCT; however, her musculoskeletal manifestations and cardiac valve disease continued to worsen [128,129]. In the other case, ERT administered 10 years after HSCT in a patient with MPS VI resulted in improved joint range of motion and endurance [128,130].

HSCT FOR EACH TYPE OF MPS

MPS I

MPS I is caused by deficiency of the IDUA enzyme, leading to the accumulation of heparan sulfate (HS) and dermatan sulfate (DS) [84]. Clinical manifestations of the disease include neurocognitive, orthopedic, cardiac, and pulmonary symptoms. As a result of these manifestations, the median age of survival of untreated patients with MPS I is 6.8 years [1,84,131]. HSCT has been shown to modify the course of disease in patients with MPS I, as well as to increase the lifespan and improve clinical parameters [21,31,38,94,120]. For this reason, HSCT is an effective treatment for MPS I [120], recommended by the EBMT for patients age <2.5 years with MPS I [117].

Successful engraftment of donor cells improves many clinical manifestations of MPS I, including obstructive airway disease, hepatosplenomegaly, cardiovascular function, hearing, vision, linear growth, and others. HSCT also can stabilize or prevent hydrocephalus and prevent the deterioration of psychomotor functions [21,31,38,85], and also has been associated with improvements in cognitive function and CNS manifestations [8,21,31,36,38,55,64,85,87,120-126,132].

In 2015, Aldenhoven et al. [38] reported a long-term study of 217 patients with MPS IH. The patients were followed for a median of 9.2 years after treatment. The study examined the long-term effects of HSCT in more than 70% of the patients who underwent successful transplantation. The overall outcomes included significant cognitive development after HSCT in those who underwent transplantation earlier in life. Many of the patients achieved normal enzyme levels, suggesting that HSCT can greatly improve possible organ manifestations of the disease. However, in another report, some patients experienced continued manifestations of the disease even after transplantation, [21] (Table 3).

The most critical factors contributing to overall outcomes and long-term effects of HSCT in patients with MPS IH are baseline status before transplantation, age at transplantion, and enzyme levels post-HSCT. Enzyme levels after transplantation can be a good predictor of outcomes after HSCT, except for neurodevelopmental outcomes. The most important factor determining neurocognitive outcomes after HSCT is the severity of CNS damage before transplantation. Factors contributing to normal enzyme levels after transplantation include receipt of cells from a noncarrier donor and full donor chimerism [28,38,51].

HSCT cannot alter any preexisting CNS symptoms of MPS I [31,38,85]; however, if performed early enough, it may preserve neurocognitive function [10,38,42,112,117,133]. HSCT can prevent deterioration of the psychomotor system, thereby supporting normal neurodevelopment [31,38,85]. In a 1998 study of patients with MPS I treated before age 2 years, those with an IQ of >70 responded more favorably to HSCT compared with those with an IQ <70 [13,36]. It is imperative that HSCT be performed as early as possible because it takes considerable time (roughly 1 year) for donor-derived cells to enter the brain and replace the existing microglial cells [88]. This delayed delivery might be the reason for the corresponding slow improvement in or even worsening of CNS symptoms seen in some patients [31].

The effectiveness of HSCT depends on the amount of enzyme activity occurring after transplantation. A 2012 study found decreased effectiveness in patients with MPS IH who had low enzyme activity after HSCT [49,134]. Another study from 2015 reported better overall HSCT outcomes in recipients with >50% donor chimerism [135]. It is very likely that the enzyme level achieved is a better predictor of outcome [135,136].

Although HSCT improves CNS manifestations of the disease, it does not seem to correct these manifestations entirely and cannot correct corneal clouding owing to insufficient delivery of enzymes to the eye [136]. Even when performed between 1 and 2 years of age, HSCT cannot repair the preexisting or progressive bone and cartilage manifestations in patients with MPS IH [136]. Consequently, surgery is often necessary to fix secondary musculoskeletal disorders such as genu valgum, thoracolumbar kyphosis, hip dysplasia, carpal tunnel disease, and ribcage, finger, wrist, knee, and tibia irregularities [8,55,87,121-126]. Cervical or lumbar stenosis resulting in spinal cord compression is often observed during the second decade of life after HSCT [136].

In 2015, Yasuda et al. [3,137] examined the skeletal manifestations of a patient with MPS I who had undergone HSCT (Table 3). At 10 years post-HSCT, spinal manifestations of the disease persisted, necessitating surgery. The patient's ability to perform ADL remained stable, and after a series of surgical procedures, he became ambulatory and independent in ADL. GAG levels in blood were normal. Later pathology revealed no vacuolization in chondrocytes with normal size [3]. Overall, skeletal abnormalities in this patient were much milder than those seen in untreated patients with MPS I.

In a 2017 report, results of a long-term study showed persistent cardiac and pulmonary manifestations of MPS I, including mitral and aortic valve insufficiency, mild cardiomyopathy, and arrhythmia, even after HSCT [94]. Some patients required angiotensin-converting enzyme inhibitors or cardiac surgery. A smaller percentage of patients had hypoxia or required respiratory support. Although HSCT cannot fix all cardiac manifestations of MPS I, a correlation between higher enzyme levels and greater donor chimerism with better cardiac outcomes after transplantation has been reported [94]. This correlation likely explains the improved quality of life reported in patients with MPS I who receive cells from UCB donors [138].

Table 4
Reports of HSCT in Patients with MPS II

Author	Details	Results
Tanaka et al., 2012 [49]	- 26 patients with MPS II	- 88.5% 5-year survival rate
	- Treated between 1990 and 2003 in Japan	- Category I and III brain lesions positively altered
	- 21 questionnaires collected	- Attenuated phenotype improved ADL, IQ/DQ, FIM, and brain MRI finding
	- Mean age at transplantation 64.2 ± 30.2 mo	- 32% less valve regurgitation
	- Average duration of follow-up 115.7 ± 41.4 d	- 56% valves stabilized
		- Category IV lesions continued to progress in 6 patients
Tanjuakio et al., 2015 [45]		- Average ADL score 27.9 ± 11.4
		- Early ERT mean ADL score 21.6 ± 9.0
		- Late ERT mean ADL score 9.5 ± 10.5
		- HSCT before age 5 yr mean ADL score 33 ± 7.0
		- HSCT after age 5 yr mean ADL score 21.2 ± 13.0
Yasuda et al., 2015 [3,137]	- Patient underwent HSCT at age 2 yr	- Normal blood GAGs
		- ADL score maintained at normal level
		- Present height and weight 162 cm and 55 kg at age 15 yr
		- Milder symptoms compared with untreated patients
		- Several manifestations still present at 10 yr post-HSCT
		- At age 13.5 yr, no vacuolization in chondrocytes, chondrocytes of normal size in spine
Kubaski et al. 2017 [13,27,49]	- HSCT performed in 146 patients with MPS II	- From the previously published cases: 8 (9%) of 85 had GVHD; 9 (8%) died from transplantation-related complications
	- Results compared with those in 51 ERT-treated patients and 15 untreated	
	- Mean age at transplantation 5.5 yr	
		- Of the 27 new patients: 76% age <6 yr at time of HSCT; 3 developed GVHD
		- 100% survival
		- All had ERT before HSCT
		- Improvements in somatic features, joint movements, and ADL score compared eith those treated with ERT
		- Improvement or stabilization of lesions located in categories III and IV
		- Donor cells found in the brain of 1 patient, along with positive hydrocephalic changes and perivascular enlargement decrease
Barth et al., 2017 [10]	- Patient age 7 yr underwent HSCT at age 2 mo with UCB from unrelated donor	- Improved cognitive function and skeletal manifestations
		- Improved ADL
		- 80% chimerism
	- Bu/Cy/ATG conditioning regimen	- Slowed speech development
		- Moderate hearing loss
		- No coarse facial features, corneal clouding, or hepatosplenomegaly
		- Normal cardiac function
		- Mild dysostosis multiplex

In 2017, Rodgers et al. [84] investigated the long-term effects of HSCT in 134 patients with MPS IH (Table 3). The survival rate was 70% a 1 year post-HSCT, 62% at 10 years post-HSCT, and 37% at 25 years post-HSCT. Males had a better survival rate than females at 25 years post-HSCT. The higher mortality in females could be related to their higher rates of pulmonary complications and infections.

In 2018, Walker et al. [139] reported a 14% incidence rate of airway complications patients with MPS I treated with HSCT, compared with 57% in patients with MPS I treated with ERT. Frawley et al. [140] reported similar post-HSCT findings in a smaller group of patients with MPS IH. Another study reported no intubation failures in patients with MPS I who had undergone HSCT [141]. These findings indicate that HSCT significantly improves the ease of airway management during anesthesia and the safety of anesthesia.

It is important to note that preferred treatments changed significantly between 1983 and 2013. These changes included increased targeted busulfan dosing, reduced used of TBI/total lymphoid irradiation, increased use of UCB, and the use of peri-HSCT ERT. As a result, the percentage of patients who underwent HSCT and reported normal IDUA enzyme levels increased after 2004. Survival rates also increased after 2004, indicating that longer-term survival rates are likely to improve. Even after the new regulations were in place, more females have died (n = 5) compared with males (n = 2). Promising results in preclinical studies using ex vivo gene therapy in MPS I and MPS IIIA mice have led to Phase I/II clinical trials of ex vivo therapy in patients with MPS IH and MPS IIIA [142]. The goal of these trials is for patients to express supranormal amounts of enzymes for these enzymes to have a greater effect on the clinical manifestations of the disease.

Because MPS I is included in NBS programs in several states of the United States, some European countries, and Taiwan, patients can be treated within the first few months of life, which is expected to minimize most of the limitations seen in patients treated at later disease stages.

MPS II

Patients with MPS II have a deficiency of the enzyme iduronate-2-sulphatase (IDS), causing the accumulation of undegraded DS and HS [2]. The major clinical manifestations of the disease are due to the accumulation of GAGs in the CNS, skeletal system, and visceral organs [13,27,49,143]. During the first several years of life, patients with MPS II may exhibit overgrowth in both height and weight [144]. The most serious damage to cognitive and motor function [13,27,49,143], as well as to skeletal, pulmonary, and cardiac function [145], occurs in patients with the severe phenotype. Patients with the attenuated phenotype of MPS II also may develop mild neurologic symptoms and retinal deterioration later in life [13]. ERT cannot treat the CNS symptoms of individuals with the severe phenotype, because the infused enzyme cannot cross the BBB [10,146,147]; however, ERT remains the recommended treatment option in patients with MPS II to improve organomegaly because of its less invasiveness and fewer risks [13,107,108]. A 2010 report noted that HSCT in patients with MPS II led to the appearance of donor cells in the microglia by 10 months after transplantation [27,103], whereas other studies have questioned the effectiveness of HSCT to alter the course of neurologic decline in patients with MPS II.

HSCT decreases urinary and blood GAG levels [10,148] to a greater degree than ERT, and also normalizes or stabilizes IDS enzyme activity in leukocytes [13,149]. HSCT has proven successful not only in improving disease manifestations and slowing overall disease progression, but also in correcting most disease manifestations [6,45,49,53-56,58]. Of note, there is no question that HSCT improves somatic and skeletal symptoms of the disease [2,52,149,150]. HSCT has been deemed a treatment option for patients with MPS II in Japan and China [13,37,45,49,53,103]. More recently, Brazil has changed their guidelines for HSCT to make the treatment accessible and efficient for patients with MPS II [103,151]. However, in the United States, HSCT is not currently used regularly in patients with MPS II [24,29,152].

In 2012, Tanaka et al. [49] reported a study evaluating the long-term effects of HSCT (Table 4). Overall, the findings suggested that HSCT should be considered an effective treatment option for patients with MPS II if performed before the development of brain atrophy and heart valve regurgitation. The reported 5-year survival rate after HSCT was 88.5%. Evaluated categories included ADL, IQ/developmental quotient (DQ), Functional Independence Measure (FIM), brain MRI, valvular regurgitation, and urinary GAG levels, which were measured at baseline and at the most recent follow-up visit [49]. It is important to note that those patients with severe MPS II had low IQ/DQ scores at their baseline report, further suggesting that HSCT does not effectively impact brain involvement of MPS II if developmental delays are already present before transplantation. Brain MRI demonstrated that category I and III brain lesions were positively altered by HSCT. Category I brain lesions are caused by the enlargement of perivascular spaces from GAG-loaded cells. Category III brain lesions are caused by insufficient cerebrospinal fluid (CSF) absorption or by brain atrophy. Two patients with the severe MPS II phenotype showed deterioration in ADL, IQ/DQ, FIM, and brain MRI parameters. Some results of this study call into question the long-term efficacy of HSCT in patients with MPS II. Based on the decline of DQ scores, HSCT might not improve brain manifestations of the disease in some patients. Category IV lesions, which are caused by neuronal cell loss, continued to progress in 6 patients, possibly because donor cells cannot reach deep brain tissue. These findings demonstrate that HSCT does not improve brain MRI findings in more severe cases. After HSCT, 32% of the patients had less valve regurgitation, and 56% showed valve stabilization. Valvular insufficiency is the most significant cause of death for patients with MPS II [49]. These patients usually experience overgrowth in height and weight in their early years, but by age 14, they begin to show below-average height compared with an age-matched control group. In 2014, Patel et al. [53] reported that HSCT allows for similar improvement of growth in long bones compared with ERT in patients with MPS II.

In 2015, Tanjuakio et al. [45] compared the effectiveness of ERT and HSCT in Japanese patients with MPS II, focusing mainly on ADL (Table 4). They reported that patients with the severe MPS II phenotype had more clinical manifestations of the disease in cognitive function compared with those with the attenuated MPS II phenotype. In addition, those with the severe phenotype showed decreasing ADL scores over time [3,12]. ADL scores tended to be higher in patients treated with HSCT compared with those treated with early ERT. Results from that study also suggested that patients treated as a later age had better ADL scores if treated by HSCT than if treated by ERT. Patients who underwent HSCT early in life had the highest ADL scores. Furthermore, those who underwent HSCT had substantially better ADL scores in the “movement” and “movement and cognition” categories, although their “cognition” scores remained low [45].

In 2016, Wang et al. [18] reported improvements in speech and neurologic symptoms in patients with the severe MPS II phenotype after HSCT. These benefits allow patients with MPS II to continue to develop cognitive, adaptive, and language skills. Although these HSCT recipients still developed these skills at a slower pace, they showed significant improvements compared with untreated patients.

In 2017, Barth et al. [10] reported a relatively stable IQ in a 7-year-old patient with MPS II who underwent HSCT at age 2 months. The improvement in the patient's cognitive function and skeletal manifestations allowed him to attend regular school. Although he was still behind in school compared with his peers, he can gain skills and interact well with others. The improvements observed were supported by the Pediatric Evaluation of Disability Inventory, on which he scored 156 out of 197 in the skills section, considered a very good score for an individual with MPS II. His ADL score was 43 out of 60, which is high than scores seen in children with severe MPS II [10].

HSCT can improve hearing in patients with MPS II if the procedure is performed before age 25 months [10,154]. The patient reported by Barth et al. developed sensorineural hearing loss, but it is important to note that he experienced a cytomegalovirus infection at 75 days after transplantation, which was treated with a 6-month course of ganciclovir 10 mg/kg/day. He also had an upper airway infection during the neonatal period, which was treated with gentamicin. The possibility of drug toxicity as a contributing factor to his hearing loss cannot be ruled out [10,154].

In 2017, Kubaski et al. [13] reported the effects of HSCT in 146 patients with MPS II (27 new cases and 119 previously published cases) compared with 51 patients treated only with ERT and 15 untreated patients (Table 4). The patients who underwent HSCT had more positive outcomes in the long-term

Table 5
Reports of HSCT in Patients with MPS IVA

Author	Details	Results
Chinen et al., 2014 [3,12,58]	- Allogeneic BMT performed at age 15 yr 8 mo	- At 5 yr after HSCT, recipient GALNS enzyme activity matched donor activity
		- Return to walking after osteotomy with digression of a narrow airway resulting in shortness of breath
		- Recovery in pulmonary function, no snoring, and increase of bone mineral density in the lumbar vertebrae (L2-4)
		- Some physical activities remained restricted
		- Mineral density in the lumbar spine increased by 50% at yr post-HSCT
		- Unchanged epiphyseal dysplasia in trochanter major and minor and joint hyperlaxity
Yabe et al., 2016 [19]	- Long-term study of 4 patients with MPS IVA, 3 with severe phenotype and 1 with attenuated phenotype	- Transplantation successful in all 4 cases
	- Allogeneic BMT performed at a mean age of 10.5 yr with HLA-identical sibling or HLA-identical unrelated donors	- No serious reports of GVHD
		- All patients achieved full engraftment
		- Two patients achieved normal enzyme activity
		- Two patients achieved the same enzyme level activity as a carrier donor
		- Improved clinical course of MPS IVA
		- Earliest transplantation associated with greatest improvement in ADL score (59 of 60)
		- One patient required bilateral osteotomies after transplantation
		- Reduced bone manifestations
		- Lessened impact on growth and joint laxity for those with severe MPS IVA
		- Three patients reported improved or stabilized walking
		- No spinal cord compression
Wang et al., 2016 [18]	- HSCT performed in 4 patients between 2004 and 2015	Remission in hepatosplenomegaly; stable spinal cord compression; joint laxity and hypermobility; improvements in upper airway obstruction, otitis media, height, and thoracic deformity
	- MAC regimen with Bu/Cy/Flu/ATG	

evaluation compared with those who were treated with ERT alone and those who were untreated. Overall, HSCT had an impact on brain involvement when performed before the manifestation of developmental delays. That report suggests that HSCT can be an effective treatment option even for older patients with MPS II. Moreover, some reports suggest that HSCT might even be as effective for patients with MPS II as it is for those with MPS I [13,27,149].

It is important to mention that most published studies are limited by the patients' age at transplantation. It is not possible to measure the precise benefits of HSCT on the CNS if symptoms are present before the procedure. Further studies in younger patients will help elucidate whether HSCT can improve and/or prevent CNS decline in patients with MPS II. Taiwan is already screening for MPS II in their NBS program, data from which will likely help clarify the benefits of early HSCT.

MPS III

MPS IIIA and MPS IIIB are caused by a deficiency of HS N-sulfamidase and N-acetylglucosaminidase, respectively [155]. Patients with MPS III usually exhibit neurocognitive impairment by age 4 years. There have been very few reports of HSCT in patients with MPS III, and effectiveness has been mixed.

In 1995, Klein et al. [156] reported that HSCT was unsuccessful in preventing neurocognitive symptoms in a patient with MPS III who underwent transplantation after manifestation of neurocognitive symptoms. HSCT was reported in a patient age <2 years with MPS IIIB in 1992 [157] and in a patient age <1 year with MPS IIIB in 1999 [158]. These patients did not exhibit any neurocognitive symptoms before HSCT; however, transplantation was unsuccessful in preventing neurocognitive decline. In 2008, Prasad et al. [25] reported that HSCT performed early in patients with MPS III can have some positive effect on neurocognitive decline. In 2014, a patient with MPS IIIB underwent HSCT at age 1 year 10 months, and the treatment was deemed successful in improving clinical manifestations. At age 15 years, her disease symptoms were good compared with those in untreated peers with MPS IIIB patients, and she had normal blood levels of O-sulfated HS and N-sulfated HS [148].

In 2014, Welling et al. [159] reported a 5-year follow up study of 2 patients with MPS III, 1 with the severe phenotype and 1 with the attenuated phenotype, after early UCBT [159]. In these patients, UCBT did not prevent the neurologic effects of the disease, even though transplantation was performed before each patient exhibited any neurologic symptoms. Manifestations included diminished cognitive skills and behavioral disturbances. At 2 years post-HSCT, the concentration of HS in CSF in the patient with the attenuated phenotype remained very high, in the range of that seen in untreated patients with MPS III. However, at 5 years post-HSCT, urinary GAG levels were normal in both patients.

Overall, HSCT for patients with MPS III has not shown definitively positive results. Because of the difficulty of early

detection, there are no reports of HSCT performed within the first months of life in patients with MPS III .

MPS IVA

MPS IVA is caused by a deficiency of N-acetylgalactosamine-6-sulfate sulfatase (GALNS), leading to the accumulation of chondroitin 6-sulfate (CS) and keratan sulfate (KS) [1,58,144,160,161]. Unlike other MPS types, MPS IVA is not associated with mental impairment. One unique manifestation of MPS IVA is joint hypermobility [55,161-163]. In 2014, Chinen et al. [12] reported a patient with MPS IVA who underwent allogeneic BMT at age 15 years 8 months [12] (Table 5). At 5 years post-HSCT, the patient's GALNS enzyme activity in lymphocytes had reached the level measured in the donor, accompanied by several clinical improvements and an increased bone mineral density [3,12].

In 2016, Yabe et al. [19] reported successful allogeneic BMT in 4 patients with MPS IVA (1 of whom was a patient in the study reported by Chinen et al. [12]) (Table 5). All 4 patients achieved full engraftment, and 2 patients demonstrated normal enzyme activity. HSCT improved the clinical course of MPS IVA in these patients. ADL scores were significantly improved after HSCT and remained elevated thereafter. Only 1 patient required a bilateral osteotomy after transplantation. In addition, in patients with severe MPS IVA, HSCT reduced the bone manifestations and also lessened the impact on growth and laxity of joints. After HSCT, orthopnea and loud snoring ceased, and overall respiratory function improved. Based on the results in these 4 patients, Yabe et al. [19] have deemed HSCT a potential treatment option for those with MPS IVA.

In 2016, Wang et al. [18] reported on patients with MPS IVA treated with HSCT in China. Improvements seen in 1 of these patients included reductions in joint hypermobility, hepatosplenomegaly, upper airway obstruction, and recurrent otitis media, and slight improvements in height and thoracic deformity. After transplantation, the patient's spinal cord compression was stabilized. The patient needed surgery at 1 year after transplantation for genu valgus [18]. At the time of this report, HSCT had been used to treat 9 patients with MPS IVA (median age, 3 years; range, 1.5–8 years) at Shanghai Children's Medical Center. At the time of this report, all patients had achieved full donor chimerism with normal enzyme activity without severe complications and were alive with significantly reduced joint hypermobility. Two patients underwent surgery for genu valgum, spinal cord compression, and hip dislocation; no long-term post-transplantation results are available at this time.

MPS VI

MPS VI is caused by a deficiency of N-acteylgalacosamine-4-sulfatase, which leads to accumulation of DS and CS [1,2]. Misdiagnosis of MPS VI has been reported, which can occur because some individuals without MPS VI can have elevated total urine GAG levels similar to those of age-matched patients with MPS VI [148,164]. MPS VI produces skeletal manifestations, including dysostosis multiplex [127], but no mental impairment [1,2]. Other sign and symptoms of MPS VI include progressive arthropathy, hepatomegaly, pulmonary disease, cardiac abnormalities, corneal clouding, and cervical spinal cord compression [127]. The most serious complications are cardiopulmonary complications, which cause death in most patients during the second decade of life [165-167]. Although ERT is the recommended first-line treatment option for patients with MPS VI, ERT has had little success in reducing the cervical spine compression [127,168,169].

The reported effectiveness of HSCT in patients with MPS VI varies [6,61,128]; therefore, HSCT is recommended for these patients only after the use of ERT has proven ineffective [7,86,128]. In patients with MPS VI, HSCT is associated with

Table 6
Reports of HSCT in Patients with MPS VI

Author	Details	Results
Turbeville et al., 2011 [17]	- HSCT performed in 45 patients between 1982 and 2007	- 85% survival rate at 6 mo post-HSCT
		- 56% alive and engrafted at 6 mo post-HSCT
	- Most common conditioning regimen Cy/Bu	- 34 patients developed aGVHD
	- Most common donor source BM from unrelated donor	
Behfar et al., 2017 [62,165]	- HSCT with a nonsibling donor in 3 patients with severe MPS VI	- Two patients achieved 95% chimerism
		- Patient 1: underwent BMT with donor cells from carrier mother
		- Increased enzyme levels
		- Improved joint mobility and ability to walk and climb
		- Improved pulmonary function
		- Decreased overall facial coarseness and finger stiffness
		- Corneal clouding remained unchanged
		- Patient 2: underwent PBSCT from related donor (grandmother)
		- Developed grade II aGVHD
		- Normal spleen size and liver size
		- Improved walk test
		- Persistent mild tricuspid regurgitation and mitral regurgitation
		- Patient 3: underwent UCBT from a 5/6 HLA-matched unrelated UCB donor
		- Experienced graft failure
		- Died of pneumonia at 11 mo post-transplantation

Table 7
Reports of HSCT in Patients with MPS VII

Author	Details	Results
Yamada et al., 1998 [20]	- 12-yr-old female	- No GVHD
	- Donor source: HLA-identical unrelated female	- Congestive heart failure at day 6, resolved at day 55 post-transplantation
	- Multiple disease symptoms at transplantation	- Interstitial pneumonia from cytomegalovirus 37 days after transplantation
	- Wheelchair-bound	- Uronic acid decreased from 44 mg/g to 14 mg/g
	- Rectal mucosa swollen with lysosomal storage material	- Swollen lysosomal storage material in the rectal mucosa removed
		- Recurrent infections ceased
		- Improved motor function, shortness of breath, recurrent infections and snoring
		- IQ not significantly altered (IQ of 47 reported after BMT)
		- No significant changes in brain atrophy and ventricular enlargement
		- Moderate aortic valve and mitral valve regurgitation stabilized
		- No changes in vertebrae or hip joints
		- Quality of life improved
Montano et al., 2016 [180]	- 5 patients	- Patient 1: moderate clinical and skeletal manifestations, normal intelligence, overall slow progression of disease
	- Patient 1: underwent first BMT at age 2 yr, failed; underwent second BMT at age 4 yr, successful	- Patient 2: died from complication of BMT
	- Patient 2: age 7 yr with severe disease manifestations	- Patient 3: died few years after BMT
	- Patient 3: diagnosed at age 4 mo	- Patient 4: moderate phenotype at age 15 yr; clinical and skeletal manifestations; hydrocephalus with language impairment
	- Patient 4: underwent BMT at age 3 yr	- Patient 5: No clinical manifestations at age 15 mo; hepatomegaly disappeared, normal intelligence and walking; cardiomyopathy with mild atrial enlargement
	- Patient 5: underwent BMT at age 7 mo	
Sands et al., 2018 [182]	- 2-yr-old female	- Developed aGVHD
	- First transplantation with an MUD and RIC with Flu/Mel/alemtuzumab	- Graft rejection at 1 yr after first HSCT
	- Second transplantation with matched UCB and MAC with Bu/Cy/ATG	- Full chimerism at 6+ years after second HSCT; normal motor function, stabilized skeletal dysplasia; no neurologic symptoms

increased survival, as well as improvements in joint movement and cardiopulmonary function [6,7,61,165].

Reported outcomes of HSCT in patients with MPS VI include increased enzyme activity and decreased urinary GAG level [63,167,170]. HSCT can decrease the overall progression of skeletal manifestations, but some reports indicate that it does not affect the progression of dysostosis multiplex [3,11,63,171,172], musculoskeletal complications, or corneal clouding [99,128,173,174]. Additional positive effects of HSCT include improved endurance, joint mobility, puberty and growth, pulmonary/airway function, facial features, hepatosplenomegaly, and survival [17,170,175]. Although patients with MPS VI normally do not exhibit intellectual disabilities [167,170,176], HSCT has been shown to reduce CNS abnormalities [6,170,172,175,177,178]. Whether HSCT can substantially improve cardiac dysfunction and short stature remains unclear, although some impact on those manifestations has been reported [165].

A 2013 report suggested that haploidentical stem cells are an effective donor source for HSCT in patients with MPS VI [170]. Two siblings with MPS VI had undergone unrelated UCBT, both of which resulted in graft failure. Subsequently, these patients then underwent haploidentical HSCT with PBSC grafts obtained from their father. Both patients had successful engraftment and achieved donor chimerism, although 1 patient had a mixed B cell chimerism [170].

In 2017, Behfar et al. [165] reported the results of HSCT with unrelated donors in 3 patients with severe MPS VI (Table 6). They concluded that an MAC regimen with either a PBSC or UCB graft is an effective combination for providing a continuous enzyme level. Two of the patients achieved >95% chimerism after transplantation. Patient 1 received BM cells from his carrier mother and exhibited increased enzyme levels. Patient 2 received PBSCs from his grandmother and developed grade II acute GVHD after transplantation. Effects of transplantation included normal-sized spleen and liver and improvement on the walk test, although mild tricuspid regurgitation and mitral regurgitation persisted. Patient 3 underwent HSCT with an unrelated UCB graft that was 5/6 HLA-matched, but experienced graft failure and patient died of pneumonia 11 months after transplantation. There is a need for more studies of HSCT in younger patients with MPS VI to evaluate whether HSCT is the best treatment option for these patients.

MPS VII

MPS VII is caused by a deficiency of β-glucuronidase, leading to the accumulation of DS, HS, and CS. Cognitive impairment to varying degrees is one manifestation of the

Table 8
Cost of ERT by Type of MPS, United States [2,110]

Type of MPS	Deficient Recombinant Enzyme	Drug Name	Dosage, mg/kg Body Weight	Annual Cost for 25-kg Patient, $
MPS I	Larondiase	Aldurazyme	.58 weekly	218,000
MPS II	Idursulfase	Elaprase	.5 weekly	340,000
MPS IVA	Elosulfase alfa	Vimizim	2 weekly	578,000
MPS VI	Galsulfase	Naglazyme	1 weekly	476,000
MPS VII	Vestronidase alfa	Mepsevii	4 biweekly	550,000

The overall annual cost for ERT differs slightly by country; for example, the annual cost of ERT in Japan for a 25-kg patient with MPS II is $400,000 [13].

disease [2,179-182]. HSCT has been reported to be successful in slowing the progression of MPS VII [20,180,182].

In 1998, Yamada et al. [20] reported a 12-year-old girl with MPS VII who underwent BMT from an HLA-identical unrelated female (Table 7). The patient presented multiple symptoms pretransplantation and was wheelchair-bound due to worsening bone symptoms. After BMT, her uronic acid levels decreased, and motor function, shortness of breath on movement, recurrent infections, snoring, and quality of life all improved. The BMT did not reverse the patient's preexisting neurologic damage, but did stabilize her cardiac manifestations.

In 2016, Montaño et al. [180] reported the outcomes of HSCT in 5 patients with MPS VII [180]. The first patient underwent HSCT at age of 2 years, but failed to engraft. At age 4 years, the patient had successful engraftment, with mild symptoms of the disease present; however, outcome was not reported. The second patient underwent HSCT at age 7 years, at which time severe manifestations of the disease were already present, and died from transplantation-related causes. The third patient underwent HSCT at an unknown age and died 2 years after the procedure. The fourth patient underwent HSCT at age 3 years, with symptoms of the disease already present. At age 15 years, he still only exhibited mild symptoms of the disease; however, a more recent examination found swift progression of disease manifestations. The fifth patient underwent HSCT at age 7 months with some symptoms of the disease present, including fetal cardiac distress, hydrops fetalis, and tachycardia. At age 1 year, she had achieved age-appropriate developmental milestones. At 15 months, the patient did not have any clinical manifestations of the disease, and her hepatomegaly had digressed.

Sands et al. [182] reported successful HSCT after initial graft failure in a 2-year-old child with MPS VII who first received an RIC regimen before BMT from an MUD. The second transplantation involved an MAC regimen before a matched UCBT. At 6 years after transplantation, the patient had normal motor function, no neurologic symptoms, and stabilized skeletal dysplasia [182].

These limited reports on HSCT in patients with MPS VII demonstrating variable outcomes make it difficult to draw any conclusions about the suitability of this treatment for MPS VII.

COST OF HSCT VERSUS ERT

We have reported the cost of HSCT in previous sections. Compared with ERT, HSCT is a much more cost-effective treatment option. HSCT and ERT are both expensive treatments for MPS, but ERT is more expensive than HSCT because of the nature of the weekly or biweekly regimen required throughout the patient's lifetime. The exact cost of ERT varies by the type of MPS. Table 8 presents the approximate costs of ERT for each type of MPS in the United States.

FUTURE OF HSCT

Future breakthroughs in HSCT will involve infusion of the patient's own cells modified by gene therapy in a process termed ex vivo gene therapy. Current clinical trials for different types of MPS are ongoing in the United States, Europe, and Australia [183-189]. In patients with MPS, BM, myoblast, and/or fibroblast cells are obtained, altered to repair or add back the affected gene, and then returned to the patient, where they then cross-correct all other cells in the body. The major benefit of using the patient's own cells is a reduced risk of adverse effects such as GVHD; however, there is still a need for a conditioning regimen [142]. The most promising vector used to alter patient's cells is the lentivirus vector, as has been reported by Visigalli et al. [190] in MPS I mice. Use of the lentivirus vector allows for transduction of the deficient enzyme (IDUA) for cells including nondiving cells, resulting in significantly increased enzyme activity [190]. In 2018, a Phase I/II clinical trial was opened at San Raffaele Scientific Institute to evaluate the safety, tolerability, and efficacy of autologous IDUA LV-transduced $CD34^+$ cells in 6 patients with MPS IH receiving an MAC regimen [191] (https://clinicaltrials.gov/ct2/show/NCT03488394). Hematopoietic recovery is accelerated via the introduction of G-CSF/plerixafor mobilized PBSCs, which are engineered according to a novel, shortened ex vivo manipulation protocol featuring prostaglandin E2 to boost transduction efficiency [192]. Moreover, the genetically engineered cell product is cryopreserved, allowing its characterization before conditioning and facilitating its future application in multicenter trials. The primary endpoint of efficacy is represented by IDUA activity in peripheral blood up to supraphysiological levels at 1 year post-transplantation. Included patients will lack a nonheterozygous (for mutated IDUA) HLA-matched sibling donor or $\geq$7/8 HLA-matched UCB with good cellularity after a 1-month-long search and will have an IQ/DQ $\geq$70. The first treated patient is showing encouraging preliminary results.

DISCUSSION

HSCT has been shown to provide effective results for patients with MPS; however, the associated risks have limited the use of HSCT as a therapeutic option for MPS. Recent increases in understanding of MPS and improvements in medical technology have allowed for the use of HSCT at an earlier age and have increased the safety of the procedure.

With HSCT, the enzyme is expressed and circulated infinitely in the recipient's body. GAGs can be rapidly cleared [2]. Advantages of HSCT include its ability to correct certain disease symptoms that cannot be fixed with i.v. ERT, penetration of the BBB via microglial cells, and lower cost compared with ERT, as well as the possibility of a one-time procedure when successful. With advances in procedural technology and new guidelines in place, HSCT has reduced mortality rates and can be considered a therapeutic option even for those with an attenuated phenotype of MPS. The use of HSCT in combination with

Table 9
Summary of Clinical Effects of HSCT by Type of MPS

Type	CNS	Bone Growth	Airway	Joint Mobility; Rigidity	Heart	Cornea	Liver, Spleen	Overall Clinical Effect	Recommendation	Condition	Remarks
MPS I	++ to +++	++	+++	Upper joints: ++ to +++; lower joints: + to ++	++ to +++	+	+++	++ to +++	Yes	Patients age <2.5 yr; elimination of immune response against infused enzyme with ERT	Approved and/or conducted as standard of care
Reference(s)	[38]	[136]	[142-144]	[5,8,21,64,87, 122,124,200, 201]	[5,8,21,87,202-204]	[136]	[5,8,21,87,202-204]	Better than ERT			
MPS II	+ to ++	++	++	++	++	NA	+++	++	Yes	Early stage; elimination of immune response against infused enzyme with ERT	Approved and/or conducted in Japan, China, Brazil, Europe, and the US; reported impact on CNS less than that in MPS I
Reference(s)	[49]	[3, 12]	[18]	[13]	[149]		[149]	Better than ERT		[13,37,45,49,53,109]	
MPS III	–	NA	NA	NA	NA	NA	NA	–	No	No significant positive effect; insufficient information	
Reference(s)	[155]									[158]	
MPS IVA	NA	+	++	Joint hypermobility; + to ++	++	Unknown	+++	++	Yes	Optional treatment at an early stage; elimination of immune response against infused enzyme with ERT	Approved and/or being conducted in Japan and China
Reference(s)		[12,19]	[12,18, 19]	[12,18,19]	[12,18, 19]		[12,18, 19]	Better than ERT		No criteria	
MPS VI	NA	+ to ++	++	+ to ++	++	+	+++	++	Yes	Optional treatment; elimination of immune response against infused enzyme with ERT	Approved and/or being conducted in Japan, China, Europe, and US
Reference(s)		[172]	[17,170, 172,175]	[6,7,61,164]	[164]	[97,127, 172,173]	[3]	Similar to ERT		No criteria	
MPS VII	++	++	++	+ to ++	++	Unknown	+++	++	Yes	Optional treatment; elimination of immune response against infused enzyme with ERT	Several reports of significant improvements
Reference(s)	[20,180, 182]	[20,180, 182]	[20]	[20,180,182]	[20,180,182]		[20,180, 182]	[20,180, 182]		No criteria	

+ indicates least effective; +++, most effective; –, no improvement; N/A, not applicable; ref,

ERT has also demonstrated significant improvements in disease and decreased mortality rates. Another advantage of HSCT is the possibility to resolve immune responses, such as a high-titer antibody against ERT, by replacing recipient cells with donor cells [2,3,13,21,27-36,38,44].

HSCT can correct or improve disease symptoms such as joint mobility, vision, hearing, cardiopulmonary functions, coarse facial features, upper airway and respiratory function, and hepatosplenomegaly [2,5-8]. Table 9 summarizes HSCT recommendations for each type of MPS.

In patients with MPS I, HSCT can reduce obstructive airway symptoms and hepatosplenomegaly and improve cardiovascular function, hearing, vision, and linear growth [21,31,38,85]. It also can improve cognitive function and CNS manifestations [8,21,31,36,38,55,85,87,120-126,132,193] and either stabilize or prevent the deterioration of psychomotor functions [36,120,121,132]. Consequently, HSCT has been deemed an effective treatment for MPS I [120], and the EBMT recommends HSCT as a treatment method for patients with MPS IH who are age <2.5 years and have an IQ >70 [88,117]. NBS for MPS I has been implemented in some US states and some European countries, and Taiwan allows the treatment of affected patients with HSCT within the first few months of age [136].

A 2012 nationwide study in Japan identified HSCT as an effective treatment when performed before the manifestation of brain atrophy and heart valve regurgitation symptoms in patients with MPS II [49]. In addition, patients with MPS II who undergo HSCT early in life typically have higher ADL scores than those who do not. HSCT has also proven more effective than ERT in patients who are treated later in life [45] and to more effectively diminish GAGs [49]. HSCT also has been associated with improved speech and neurologic symptoms [13,18], somatic symptoms [2,52,149,150], hydrocephalic changes, and perivascular enlargement [13,49]. HSCT can either diminish or halt the progression of category III and IV brain lesions [13] and positively alter category I and III brain lesions in patients with MPS II. In addition, HSCT has been shown to either stabilize or improve cardiac valve regurgitation contributing to heart failure, the most common cause of death in patients with MPS II [49]. In patients with MPS IVA, HSCT has been shown to improve digression of narrow airways, pulmonary function, snoring, bone mineral density, and walking ability. A correlation between receipt of HSCT earlier in life and better ADL scores has been reported [12]. Despite the risks involved in transplantation, HSCT performed early in life will lead to better clinical improvement of the disease [55].

Owing to the lack of data on the overall cost of HSCT for patients with MPS, the best way to estimate the cost of HSCT for MPS patients is to examine studies performed in patients with the same clinical background as patients with MPS. Consequently, the information presented in this review focuses on the cost of allogenic HSCT in pediatric patients.

The cost of ERT depends on the type of MPS, which dictates the type of drug needed for ERT. In 2017, the annual reported cost of ERT in a patient weighing 25 kg was $218,000 for MPS I, $340,000 for MPS II, $578,000 for MPS IVA, $476,000 for MPS VI, and $550,000 for MPS VII [110] Overall, HSCT is significantly cheaper than ERT.

One of the main risks of HSCT is associated with the use of toxic conditioning regimens. In patients with MPS I, Rodgers et al. [84] reported a positive correlation between mortality during the first decade after transplantation and improvements in peri-HSCT management. Given the significantly improved safety of HSCT, there is some conversation about whether HSCT should be explored as a possible treatment option for milder phenotypes of MPS [153,194].

There are certain disadvantages associated with HSCT for MPS, including the time- and cost-intensive search for a donor, the urgency of performing HSCT in younger patients in good health, risk of mortality, and inability to reverse preexisting symptoms. An acceptable matched donor might not always be readily available at the appropriate time for transplantation [36,86], and early transplantation is associated with better outcomes and consequently higher ADL scores [3,45].

The main disadvantage of HSCT is its relatively high mortality rate. Before 2000, reported mortality was as high as 27% [13,18,56]. However, improvements in HSCT techniques have yielded a survival rate of >90% for patients with MPS IH [28,31,37,38]. Several factors affect survival in patients with MPS. The type of donor cells used in transplantation can affect the overall success of the procedure. Unrelated UCB has become the favored source for donor cells [24]; however, UCB can cause delayed engraftment in the recipient and consequently more frequent graft failures [101]. The toxicity of certain conditioning regimens can affect mortality and effectiveness in patients by causing neurologic complications that can counteract the effects of HSCT [88]. The recent change to the use of less-toxic fludarabine in conditioning regimens shows promise [31,37,83]. There is also an increased risk of degraded cardiac function in patients with MPS IH who undergo more than 1 transplantation [86,95].

Owing to the nature of the treatment, there are certain complications that decrease the safety and effectiveness of HSCT. These complications include infection, organ failure, graft rejection, and GVHD [13,18,56], resulting in growth disturbance and infertility complications [51]. The most frequent causes of death during the first year post-HSCT for MPS IH are viral infection, pulmonary hemorrhage, and GVHD [8,35,84,86,87]. In addition, the drugs used to combat complications such as cytomegalovirus also can decrease the effectiveness of HSCT [10]. One of the main characteristics of MPS IVA is severe bone deformities in the airway and pulmonary system, which pose a potential problem in patients who require intubation owing to other complications of transplantation [12,96]. HSCT cannot treat many of the symptoms of MPS, including manifestations in the bone, cornea, heart, and any preexisting cognitive effects [2,5,7,8,60,62,64].

With the improvement of technology and research on HSCT, the use of HSCT in combination with gene therapy may be a more effective treatment option for MPS than either HSCT or ERT alone. Gene therapy takes the patient's stem cells and genetically engineers them to produce and deliver the enzyme in which he or she is deficient by gene transfer vectors [88]. The advantage of HSCT coupled with gene therapy lies in the use of the patient's own cells, which decreases the risk of such complications as GVHD. Moreover, because gene therapy uses the patient's own cells, there is no need for full- intensity conditioning regimens. Gene therapy can decrease the mortality and morbidity rates normally associated with HSCT [88]. Although gene therapy as a treatment option for MPS remains in the experimental stages, its use with HSCT for metachromatic leukodystrophy, another lysosomal storage disorder, has shown positive results [38,88].

CONCLUSION

HSCT has proven to be an effective therapeutic option for various types of MPS. Previous concerns about the safety of the procedure have kept HSCT from being more widely used in patients with different types of MPS. However, improvements

in medical technology and increased understanding of the disease have brought significantly improved survival post-HSCT in patients with MPS. The more frequent use of HSCT in various types of MPS should be considered with careful patient selection, given that HSCT has been shown to correct more clinical manifestations of the disease compared with ERT alone. Moreover, the one-time administration of HSCT makes it a more cost-effective option.

In summary:

- Factors contributing to high mortality in patients with MPS include progressive disease at the time of HSCT, improper donor selection, infection, organ failure, graft rejection, GVHD, and toxicity of conditioning regimens [13,18,56].
- The best conditioning regimen for HSCT is an MAC regimen with a combination of busulfan and fludarabine due to lower toxicity [31,37,83].
- UCB is the best source of donor cells owing to a higher rate of full donor chimerism and normal enzyme levels, ready availability, and tolerance for HLA mismatch [24,25,28].
- HSCT is the recommended treatment for patients age <2.5 years with MPS IH [117].
- HSCT is approved for patients with MPS II in Japan and other countries [13,37,45,49,53,151] and should be explored as an acceptable treatment option [24,29,152].
- Although the number of reported cases is limited, HSCT could be a potential therapeutic option for patients with MPS IVA, given the positive results reported in recent studies [19].
- Data on the effects of HSCT in patients with MPS VI are variable [6,61,128].
- Combination therapy with HSCT and ERT has been associated with improvement in somatic symptoms, as well as GAG levels and enzyme levels, in patients with MPS I and MPS VI [24,42,44,54,67,94,111,114-118,120,127].
- HSCT can eliminate the immune response against ERT in patients with MPS via replacement with donor cells [14,46].
- The mean health care costs for allogeneic HSCT in pediatric patients are approximately $500,000 in the United States and $100,000 in Japan [195].

Overall, HSCT is a cost-effective therapeutic option for some groups of patients with MPS, providing affordability with careful selection and management [196]. A multidisciplinary team is needed to coordinate the management of patients with MPS. Management of patients with MPS should be based on the type of MPS, clinical severity, disease stage, and the patient's age and socioeconomic status with support from government agencies and nonprofit organizations independent of pharmaceutical companies.

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APPENDIX. THE INTERNATIONAL INVESTIGATIONAL TEAM FOR HSCT IN MPS

We have established a clinical research team to evaluate HSCT for treating patients with MPS, leading to accurate and feasible evaluation of the prognosis, therapeutic efficacy, and costs associated with HSCT. This multidisciplinary team comprises experts in the fields of transplantation, genetics, pediatrics, metabolism, pharmacokinetics, and molecular biology in Brazil, China, Europe, Japan, and the United States. Collectively, the team has more than 300 publications related to MPS in both basic and clinical research for MPS, including transplantation, identification of biomarkers, diagnosis, and treatments encompassing orthopedic and tracheal surgeries, ERT, HSCT, and gene therapy. This investigational team includes basic and clinical experts on MPS who have abundant experience in gene cloning, clinical diagnosis, ERT, and HSCT for MPS. Thus, our investigational team members are internationally recognized in this field for their expertise ranging from basic science to clinical care.

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