Review

Hematopoietic Stem Cell Transplantation in Mucopolysaccharidosis Type II: A Literature Review and Critical Analysis

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Abstract

Mucopolysaccharidosis II (MPS II—Hunter syndrome) is an X-linked lysosomal storage disorder caused by a deficiency in iduronate-2 sulfatase. Enzyme replacement therapy does not cross the blood–brain barrier (BBB), limiting the results in neurological forms of the disease. Another treatment option for MPS, hematopoietic stem cell transplantation (HSCT) has become the treatment of choice for the severe form of MPS I since it can preserve neurocognition when performed early in the course of the disease. Even though the intravenous therapy does not cross the BBB, it has become the recommended treatment for MPS II, and HSCT was not often indicated. In an attempt to understand why this treatment modality is rejected by most specialists as a treatment option for patients with Hunter syndrome, we sought to raise all HSCT cases already reported in the scientific literature. Databases used were Medline/PubMed, Lilacs/BVS Cochrane Library, DARE, SciELO, and SCOPUS. Different combinations of the terms "mucopolysaccharidosis II," "Hunter syndrome," "hematopoietic stem cell transplantation," "bone marrow transplantation," and "umbilical cord blood stem cell transplantation" were used. A total of 780 articles were found. After excluding redundant references and articles not related to the theme, 26 articles were included. A descriptive summary of each article is presented, and the main features are summed up. The clinical experience with HSCT in MPS II is small, and most of the available literature is outdated. The available data reveal poor patient selection criteria, varied conditioning regimens, distinct follow-up parameters, and post-HSCT outcomes of interest, making impossible to compare and generalize the results obtained. Recently, after the development of new conditioning protocols and techniques and the creation of bone marrow donor registries and umbilical cord banks, HSCT has become more secure and accessible. It seems now appropriate to reconsider HSCT as a treatment option for the neuronopathic form of MPS II.

Keywords

mucopolysaccharidosis type II, hunter syndrome, hematopoietic stem cell transplantation, bone marrow transplantation, umbilical cord blood stem cell transplantation

Introduction

Mucopolysaccharidosis II (MPS II, Hunter syndrome, OMIM 309900) is an X-linked lysosomal storage disorder caused by a deficiency in the enzyme iduronate-2 sulfatase (I2 S), leading to the accumulation of the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate.[1] Mucopolysaccharidosis II affects multiple organs and systems with a variable age of onset of signs and symptoms. Two clinical presentations of Hunter syndrome have been reported, the mild, or attenuated, and the severe forms. The severe phenotype, with primary neural parenchymal disease, is referred as neuronopathic MPS II and the mild phenotype, without neural parenchymal involvement, as non-neuronopathic MPS II. The distinguishing factor between the 2 forms is the presence or absence of progressive intellectual deterioration. Both phenotypes exhibit cardiorespiratory and skeletal disease[2]

In 1968, Fratantoni et al[3] first established that substrate accumulation in the cells of patients with lysosomal enzyme deficiencies could be dramatically reduced by coculturing these cells

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with cells producing the missing enzyme.[3] The principle of "cross-correction" was subsequently used to explore both exogenous enzyme replacement therapy (ERT) and allogeneic hematopoietic stem cell transplantation (HSCT) in numerous lysosomal disorders. As HSCT also enables engraftment of donor-derived microglial cells in the brain—serving as local enzyme production units—this treatment, contrary to ERT that does not cross the blood–brain barrier (BBB), has the potential to treat central nervous system (CNS) manifestations.[4]

Hematopoietic stem cell transplantation has been tested in various disorders and become 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.[5–9] Compared to Hurler syndrome, the overall experience in the use of HSCT for treatment of other MPS types (II, III, IV, VI, and VII) is very limited, often evaluated only as part of large heterogeneous cohorts of transplanted patients with multiple metabolic diseases or as few case reports and with variable results.[10–12] Nevertheless, the scientific basis for the effectiveness of HSCT across the MPS spectrum remains the same: donor-derived cells would secrete the deficient enzyme, which would be recaptured by surrounding cells. The kinetics of cellular migration, differentiation, distribution, and effective enzyme delivery, however, may differ among MPS subtypes.

After 2006, with the approval of Elaprase (idursulfase, Shire Human Genetics Therapies, Inc., Cambridge, MA, USA), ERT has become the treatment of choice for patients with Hunter syndrome. Even though the intravenous therapy is known not to cross the BBB, being unable to prevent neurodegeneration in the neuronopathic form of MPS II, the HSCT was discouraged and no longer performed in most Western countries.[13]

In an attempt to understand why HSCT is rejected by most experts as a treatment option for MPS II, all articles and/or cases reported in the scientific literature were reviewed and analyzed.

Material and Methods

Controlled and randomized clinical trials are considered the gold standard of evidence on the effect of an intervention.[14] Due to the rarity of MPS II, controlled and randomized clinical trials evaluating the efficacy of HSCT on disease progression do not exist and are unlikely to occur. Therefore, in an attempt to evaluate the results obtained so far and to understand why HSCT has been rejected by most specialists as a therapeutic modality for MPS II, it was sought to raise all cases already reported in the scientific literature on the participant.

The study was divided into 3 stages:

- Phase 1—Search for primary studies.
- Phase 2—Selection of articles.
- Phase 3—Data analysis.

Phase 1—Search for Primary Studies

The electronic search was performed in the following databases: Medline/PubMed, Lilacs/BVS Cochrane Library, DARE, SciELO, and SCOPUS. The abovementioned databases were selected because they cover a large number of journals from different countries.

In an attempt to identify the largest possible number of articles for inclusion in the review, a more sensitive search strategy was performed, to the detriment of specificity. Different combinations of the terms "mucopolysaccharidosis II," "Hunter syndrome," "hematopoietic stem cell transplantation," "bone marrow transplantation," and "umbilical cord blood stem cell transplantation" were used in the various databases after consultation in the Medical Subject Heading and Subject Descriptor.

Case reports presented at congresses and published in special supplements of indexed journals were included, but there was no search in the gray literature (which comprises the literature not formally published) since there would be no guarantee as to the veracity and authenticity of data.

No date limit was set for the research since the objective was to find as many articles as possible in the literature. The searches were conducted until July 2017. The oldest article retrieved was from 1986.

Phase 2—Selection of Articles

Because MPS II is a rare condition, we did not expect to find a large number of articles and/or case reports. For this reason, all articles on HSCT in patients with Hunter syndrome were included in the evaluation, excluding only those whose transplantation was performed in patients with other MPS types than MPS II and those who evaluated the HSCT animal models of MPS II.

All studies identified in the initial search, respecting the exclusion criteria, had their summaries evaluated. When these were not available, the full article was studied.

Phase 3—Data analysis

The data were synthesized in a descriptive way, based on the results presented in each article.

Results

In the absence of formal studies evaluating HSCT as a therapeutic modality for MPS II, it was sought to collect all previously published articles on the subject and to briefly describe all cases of HSCT II already described in MPS II.

After defining the terms used in the bibliographic search and consulting the selected databases, 780 articles were found (Table 1). Many electronic databases index the same periodicals, and redundant references were retrieved. The fact we used more than one search mechanism on some databases, also contributed to redundancy. Of the total number of articles retrieved, 659 were excluded after reading the title and/or summary, remaining 121. After the exclusion of the repeated

Table 1. Synthesis of the Electronic Bases Used, Search Tools Used in Each Base and Number of References Found.

Database	Number of References
Search tool	
Medline/PubMed	
Mucopolysaccharidosis II [MeSH] AND hematopoietic stem cell transplantation[MeSH]	17
Mucopolysaccharidosis II [MeSH] AND cord blood stem cell transplantation [MeSH]	2
Mucopolysaccharidosis II [MeSH] AND bone marrow transplantation [MeSH]	20
Mucopolysaccharidosis II OR Hunter syndrome AND hematopoietic stem cell transplantation	57
Mucopolysaccharidosis IIOR Hunter syndrome AND cord blood stem cell transplantation	15
Mucopolysaccharidosis II OR Hunter syndrome AND bone marrow transplantation	7
LILACS/BVS	
Mucopolissacaridose II (DeCS) AND transplante de células-tronco hematopoiéticas (DeCS)	31
Mucopolissacaridose II (DeCS) AND transplante de medula óssea (DeCS)	29
Mucopolissacaridose II (DeCS) AND transplante de células-tronco do cordão umbilical (DeCS)	7
Cochrane Library	
Mucopolysaccharidosis II [MeSH] AND hematopoietic stem cell transplantation[MeSH]	0
Mucopolysaccharidosis II [MeSH] AND cord blood stem cell transplantation [MeSH]	0
Mucopolysaccharidosis II [MeSH] AND bone marrow transplantation [MeSH]	0
DARE	
Mucopolysaccharidosis II AND hematopoietic stem cell transplantation	0
Mucopolysaccharidosis II AND cord blood stem cell transplantation	0
Mucopolysaccharidosis II AND bone marrow transplantation	0
SciELO	
Mucopolysaccharidosis II AND hematopoietic stem cell transplantation	0
Mucopolysaccharidosis II AND cord blood stem cell transplantation	0
Mucopolysaccharidosis II AND bone marrow transplantation	2
Hunter syndrome AND hematopoietic stem cell transplantation	0
Hunter syndrome AND cord blood stem cell transplantation	0
Hunter syndrome AND bone marrow transplantation	2
SCOPUS	
Mucopolysaccharidosis II AND hematopoietic stem cell transplantation	67
Mucopolysaccharidosis II AND cord blood stem cell transplantation	118
Mucopolysaccharidosis II AND bone marrow transplantation	3
Hunter syndrome AND hematopoietic stem cell transplantation	143
Hunter syndrome AND cord blood stem cell transplantation	253
Hunter syndrome AND bone marrow transplantation	7

Abbreviations: DeCS, Subject Descriptor; MeSH, Medical Subject Heading.

articles, 37 articles were read in full. Of these, 11 were still excluded because they only referred to HSCT previously described or because they dealt with ethical issues regarding HSCT in Hunter syndrome, leaving 26 articles that were included in this review (Figure 1).

A descriptive summary of each article retrieved and included in this review is presented below. The main features of the articles are also summed up (Table 2).

The first patient with Hunter syndrome treated with HSCT who had clinical and biochemical data reported was described in 1986 by Warketin et al.[15] The patient underwent HSCT at 7 years and 5 months, had an initial intelligence quotient (IQ) of 87, which dropped to 73 (mainly due to language delay), and stabilized after transplantation. He presented reduction in skin lesions and hirsutism, improvement in joint stiffness and mobility, resolution of hepatosplenomegaly, and normalization of urinary and CSF excretion of GAG. The activity at I2 S normalized in leukocytes but remained well below normal range in plasma. After 3½ years of transplantation, the patient died suddenly and necropsy revealed GAG deposition of GAG in the heart valves and in the brain.

In 1994, Bergstrom et al[16] reported the results of HSCT in a 14-year non-neuronopathic patient. Three years after the procedure, the patient presented significant improvement, both subjectively and objectively, in the symptoms of the disease. There was resolution of cutaneous nodules and hepatosplenomegaly, attenuation of facial features, improvement in joint mobility, especially in the hands and the echocardiogram showed reduction in the valvular leaflets thickness with resolution of mitral insufficiency. The patient returned to school 7 months after the transplant and continued to have gains in his intellectual function.

Another case of HSCT in a patient with non-neuronopathic MPS II was described by Imaizumi et al[17] in 1994. The patient was transplanted at 9 years and 10 months, and 1½ year later, he showed improvements in his facial appearance, joint contractures, hepatomegaly, skin lesions, and height. Cardiac valve dysfunction did not progress, but there was no improvement in sensorineural hearing loss nor in bone deformities.

Miniero et al[18] also in 1994 reported the case of a 31-month patient with the neuronopathic form of MPS II who received granulocyte colony-stimulating factor (G-CSF) after bone marrow transplantation. Complete chimerism was confirmed at 11 and 80 days after transplantation. He had no complications or graft versus host disease. Two months after transplantation, skin and liver biopsies show stabilization of the disease. Six

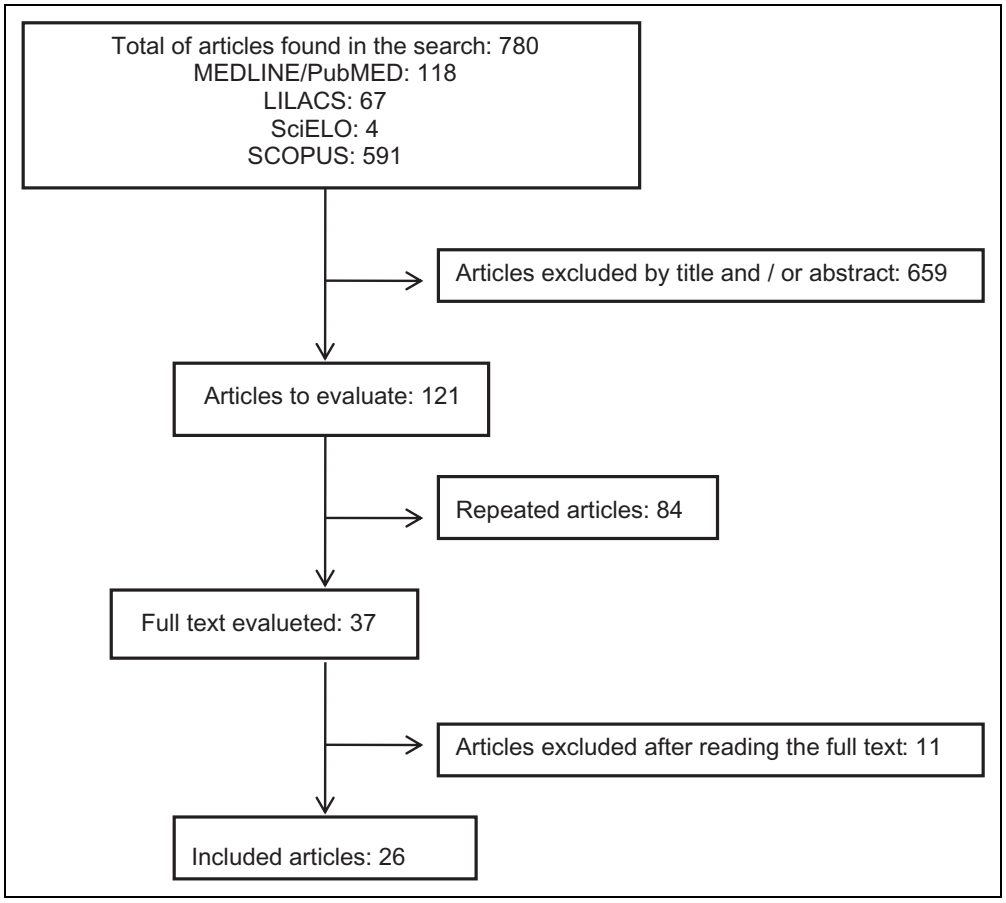

Figure 1. Flowchart of article selection.

months after transplantation, there was reduction in the urinary GAG excretion to near normal levels, and the activity of I2 S in leukocytes normalized, while in plasma remained undetectable. Administration of G-CSF did not induce proliferation of bone marrow histiocytes. This report suggested that G-CSF should be recommended for patients undergoing HSCT in order to reduce the period of neutropenia associated with the chemotherapy regimen preparatory to transplantation.

Coppa et al,[19] in 1995, reported the 2-year follow-up of a patient transplanted with 2 years and 9 months. During the period, there was normalization of hepatosplenomegaly, resumption of growth curve, reduction in skin thickness and hirsutism, and important improvement in joint mobility. The evaluation of the bone inventory showed stabilization of clinical condition in relation to the pretransplantation state, as well as brain magnetic resonance imaging (MRI) and audiometry. The echocardiogram showed ventricular size normalization; the urinary GAG excretion decreased progressively over the first 6 months and stabilized at levels close to normal. Enzymatic activity in leukocytes normalized but remained well below the normal range in plasma. The longitudinal neuropsychological evaluation showed significant worsening after the third month of transplantation, especially regarding verbal capacity. Twenty months after transplantation, there was partial recovery in motor and interpersonal skills, while verbal performance remained unchanged.

In 1996, McKinnes et al[20] reported the case of a transplanted patient in 1988 at 29 months of age. After 5½ years, leukocyte I2 S levels were normal whereas in plasma they were only 25% of normal. Urinary GAG excretion decreased to levels near to the upper limit of normal. Serial liver biopsies showed a significant reduction in deposited material in all cell types; however, serial rectal biopsies demonstrated GAG deposition in neural structures, with reduction in deposition in non-neural structures. There was improvement in some somatic symptoms such as the face and hair and in joint mobility, but skeletal deformities and auditory deficit did not improve, although did not progress either. Despite the clinical success of the transplant, with good grafting, normal levels of I2 S and physical improvement, the intellectual status continued to deteriorate. At 8 years of age, cognitive test results showed an IQ <20, compatible with a 6-month-old child. There was loss of intellectual capacity, adaptive functions, and language skills associated with behavior problems.

Also in 1996, Li et al[21] described the follow-up of a patient with the neuronopathic form of MPS II submitted to HSCT at 5 years. Liver and spleen returned to normal size and urinary GAG excretion normalized 1 year after transplantation. Three

Table 2. Summary of the Main Features of the Articles.

Author/Year	N° Pat.	Age at HSCT	Deaths	Phenotype	GAG	I2S	Neurol. Evaluation	Graft Failure	GVHD	Conclusion
Warketin et al, 1986	1	7 years 5 months	1		X	X	X			Necropsy: GAG deposits on heart and brain
Bergstrom et al, 1994	1	14 years		NN			X			Somatic and neurological benefit
Imaizumi et al, 1994	1	9 years 10 months		NN						Somatic benefit (except on hearing and bones)
Miniero et al, 1994	1	2 years 7 months			X	X				Uses of granulocyte colony stimulating factor
Coppa et al, 1995	1	2 years 9 months			X	X	X			Somatic and some neurological benefit
McKinnes et al, 1996	1	2 years 5 months			X	X	X			Somatic benefit but IQ reduction
Li et al, 1996	1	5 years		N	X	X	X			Somatic benefit and IQ stabilization
Vellodi et al, 1999	10	10 months-5 years 1 month	7				X			IQ reduction in 2 pat. and stabilization in the third
Coppa et al, 1999	1	3 years		NN	X	X	X			Somatic benefit and IQ stabilization
Mullen et al, 2000	1	10 months		NN						Somatic benefit but hemolytic anemia
Ito, 2004	5	4 years-11 years								Dermatological evaluation (papules)
Ochiai et al, 2005	3	5 years-8 years								Ultrastructural evaluation of peripheral nerves
Escolar et al, 2007	5	3 month-3 years 4 month	1				X	X (1)	X (1)	Neurological benefit. Uses of cord blood
Guffon et al, 2009	8	3 years-16 years	1	N(4)/NN(3)	X	X	X			Somatic benefit. Distinct neurological outcomes
Araya et al, 2009	1	6 years	1	N						Necropsy: I2 S activity in microglia
Poe et al, 2011	9	1.5 month-3 years 11 month	2				X			Neurological benefit but with some delay
Escolar et al, 2012	9	1.5 month-3 years 11 months					X			Continuous benefit, although slower
Tanaka et al, 2012	21	2 years-19 years		N/NN						Valid before cerebral atrophy and cardiac disease
Annibali et al, 2013	4	2 years 6 months-2 years 11 months		N			X			Neurological deterioration slower than expected
Patel et al, 2014	18									Only growth was evaluated
Tanjuakio et al, 2015	20			N/NN						Activities of daily living in MPS II
Cagle, 2015	1	3 years 1 month								No signs of regression until 4 years
Wang et al, 2016	12	2 years-6 years					X			Neurological benefit
Muschol et al, 2016	2	2 years 1 month-4 years 3 month			X	X				Neurological decline in 1 and stabilization in another
Barth et al, 2017	1	70 days		N	X	X	X			HSCT seems effective and can be considered
Kubaski et al, 2017	27			N/NN	X					HSCT seems effective and can be considered

Abbreviations: GAG, glycosaminoglycans; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation; I2 S, iduronate-2 sulfatase; IQ, intelligence quotient; MPS, mucopolysaccharidosis; N, neuronopathic; NN, non-neuronopathic; No. Pat, Number of patients.

years after HSCT, there was improvement in joint mobility and motor capacity and stabilization of the neurocognitive and cardiac functions. Plasma I2 S activity reached the normal limit 4 years after HSCT and remained around 60% of the normal value in leukocytes.

Vellodi et al[22] reported, in 1999, the long-term follow-up of 3 patients with MPS II undergoing HSCT from an initial cohort of 10 transplanted patients. Of these, 7 died after transplantation (performed between 1982 and 1985). Of the 3 patients who survived, 2 (1 transplanted at 20 months and another transplanted at 5 years and 1 month) showed progression of the neurodegenerative process. The third patient, submitted to HSCT at 10 months, presented stabilization of the neurological condition. After 7 years of transplantation, he had a borderline IQ of 78, a certain difficulty in concentration, but continued to attend regular school. The latter patient presented a positive family history for MPS II and comparatively post-HSCT presented a better outcome than his affected maternal uncle.

Also in 1999, Coppa et al[23] reported a 4-year follow-up of a patient with the non-neuronopathic form of MPS II submitted to HSCT at 3 years. There was attenuation of facial features, skin was less thick, abdominal ultrasonography showed resolution of hepatosplenomegaly, and he presented only small joint limitation. His IQ remained stable at 70, he spoke short phrases and knew some letters of the alphabet. Ultrastructural analysis of hepatocytes and fibroblasts showed only a few remaining vacuoles. Regarding the biochemical parameters, the urinary GAG excretion and the activity of I2 S in leukocytes normalized.

Mullen et al[24] described the long-term outcome of HSCT in a 10-month boy with non-neuronopathic MPS II. There was resolution of hepatomegaly, and his growth and development were normal; however, after 9 months, transplantation was complicated by the development of autoimmune hemolytic anemia. The patient required corticoid and other immunosuppressive treatment for 2 years and remained with positive direct Coombs test.

In 2004, Ito et al[25] evaluated 5 patients with MPS II, aged 4 to 11 years, submitted to HSCT. They found that the white-yellow papules characteristic of the disease disappeared completely within 35 days after transplantation (mean of 18 days) in all patients. They also observed that skin thickness tended to normalize after HSCT.

The ultrastructural assessment of cutaneous nerve involvement in 3 patients with MPS II before and after HSCT was published in 2005 by Ochiai et al.[26] Two patients underwent HSCT at 5 years and the third at 8 years. Electron microscopy studies showed that clear vacuoles were present in the cytoplasm of endoneurial fibroblasts and Schwann cells, 2 months and 2 years, respectively, after transplantation. On the other hand, only a few vacuoles remained in the dermal fibroblasts 2 months after HSCT and disappeared after 2 years of transplantation. The results suggested the existence of a hemato-neural barrier (such as BBB in the CNS) that may be responsible for preclude enzymatic correction in the internal environment of cutaneous nerves and thus not preventing psychomotor degeneration in patients undergoing HSCT.

In 2007, Escolar et al[27] reported the neurological development of 5 children submitted to umbilical cord cell transplantation. The ages at the time of transplantation ranged from 0.26 to 3.4 years, and the follow-up period ranged from 1.7 to 3.9 years. Four patients presented complete grafting and 1 presented mixed chimerism. This patient died after a second HSCT due to complications related to graft versus host disease. The 4 patients who survived presented cognitive, motor, language, and adaptive skills gains. The older patient, who required the placement of ventriculoperitoneal shunt due to increased intracranial pressure, presented the slower rate of improvement. The authors concluded that, despite the mild auditory deficit present in all 4 patients, they continued to show neurological improvements in all areas. Long-term follow-up is needed.

A long series of cases of patients with Hunter syndrome treated with HSCT was reported in 2009 by Guffon et al.[28] The report involved 8 patients aged 3 to 16 years at the time of transplantation. Five boys had the neuronopathic form (diagnosis before 4 years of age and IQ <80), 2 had the non-neuronopathic form (diagnosis at 5 years and normal IQ), and 1 was considered to have an intermediate phenotype (diagnosis before 4 years and IQ $\geq$80 and <90). One of the patients with the neuronopathic form, transplanted at 3 years and 11 months, died suddenly at the age of 10 years of nontransplant-related cause. The remaining 7 patients were followed for periods ranging from 7 to 17 years and presented between 9 and 24 years in the last evaluation. All had normal I2 S activity in leukocytes and low in plasma. Urinary GAG levels were close to the upper limit of normal. There was resolution of hepatosplenomegaly and joint stiffness in all; there was also improvement in persistent rhinorrhea and upper airway obstruction. Valvular changes were detected in all of them before HSCT, but deterioration following transplantation was observed. Neuropsychological outcomes were distinct. The 2 boys with the non-neuronopathic form reached adulthood with normal IQ, normal school, and social development, without language impairment. Four patients with the neuronopathic form deteriorate after HSCT; 3 lost their ability to walk in early adolescence, 2 lost their language skills at 9 and 11, and 2 developed epilepsy. The other 2 patients required special education and had few social and language skills. Regarding auditory impairment, sensorineural deficit remained stable after transplantation and the transmission deficit improved. Four boys were using hearing aids at the last evaluation.

Araya et al,[29] in 2009, described the case of a 6-year-old patient with the neuronopathic form of MPS II submitted to HSCT. He died 10 months after the procedure due to laryngeal lymphoproliferative disease. During the posttransplant follow-up period, there was no improvement in hyperactivity, IQ, or brain MRI findings. Biochemical and histopathological analyzes on autopsied tissues showed the presence of distended cells with deposited material in the brain but not in the liver. Iduronate-2 sulfatase activity in the brain remained very low

while in the liver it was 40% of the normal range. Tandem repeat analyzes showed weak bands, derived from the donor, not only in the liver but also in the brain. In addition, I2 S immunoreactivity was recognized not only in Kupffer cells but also in hepatocytes. Immunoreactivity of I2 S has also been found in microglial cells located predominantly in the perivascular spaces and some in the cerebral parenchyma. The efficacy of HSCT 10 months later was considered insufficient for the brain, but detection of donor-derived cells in the cerebral parenchyma suggests the potential of HSCT for the treatment neurological symptoms in patients with MPS II.

The neurodevelopment of 9 patients underwent HSCT was reported in 2011 by Poe et al.[7] Patients were between 1.5 and 47 months at the time of transplantation and were followed for periods ranging from 7 months to 7 years. Two patients died after transplantation. During the evaluation period, the patients performed between 3 and 12 neuropsychological evaluations. Of the 7 living patients, 5 continued to show gains in some or all of the developmental domains. One patient had normal development in 4 of the 6 domains evaluated. The study concluded that neurodevelopment was delayed after HSCT, although more research is needed to clarify the reason for this variability.

In 2012, Tanaka et al[30] published the results of a retrospective evaluation of the efficacy of HSCT performed between 1990 and 2003 in 21 patients with both forms of MPS II. The ages at the time of transplantation ranged from 2 to 19 years and 8 months (mean of 64.2 $\pm$ 30.2 months), and the 5-year survival rate was 88.5%. The authors concluded that HSCT is a valid treatment for patients with MPS II when performed before the onset of cerebral atrophy and heart valve disease.

Also in 2012, Escolar et al[31] reported the development of 9 patients with the neuronopathic phenotype of Hunter syndrome, transplanted with ages ranging from 1.5 to 47 months. They were followed up for 8 years and compared to 35 non-transplanted patients. The results showed that transplanted children aged <18 months had very close to normal cognitive, adaptive, and language skills. All early transplanted children showed continuous gains in these skills, albeit at a slower rate than normal children. The development of boys transplanted after 18 months of age reached a plateau and then declined to functional ages between 1 and 3 years. More consistent clinical data are not available.

The long-term follow-up of 4 patients with the neuronopathic form of MPS II undergoing HSCT was reported in 2013 by Annibali et al.[32] Patients were between 2 years and 6 months and 2 years and 11 months of age at the time of transplantation. Neuropsychological assessments showed IQ stabilization in 3 of the 4 patients in the first 5 years after transplantation, followed by a worsening in neurological status. Two patients who had mild mental retardation (MR; IQ = 70) before transplantation remained stable for 5 years and then had moderate MR until the last evaluation, 16 and 7 years after HSCT (IQ = 35 and IQ = 40), respectively. The third patient, who had moderate MR prior to transplantation (IQ = 49), presented neurological deterioration and 8 years later presented very severe MR (IQ = 15). The fourth patient, who had mild MR before HSCT (IQ = 80), remained stable up to 8 years after transplantation (IQ = 73). Patients with the neuronopathic form of MPS II submitted to HSCT showed improvement or stabilization of somatic symptoms while neurological impairment showed progression, albeit much slower than expected.

The impact of ERT and HSCT on the growth of 44 Japanese patients with Hunter syndrome was evaluated by Patel et al in 2014.[33] Twenty-six patients were treated with ERT, 12 with ERT, and 6 received ERT and HSCT. Weight and height were compared with those of untreated patients and controls from previous studies. Patients who received treatment with both ERT and HSCT had weights and heights higher than untreated patients. Enzyme replacement therapy and HSCT were equally effective in restoring growth in patients with MPS II. According to the authors, HSCT should be considered as one of the first therapeutic options for the early treatment of MPS II since positive effects on brain and heart valves have also been reported.

In 2015, Tanjuakio et al[34] tested a new questionnaire to assess the clinical phenotype and therapeutic efficacy of ERT and HSCT in patients with Hunter syndrome. The group developed a questionnaire of activities of daily living with 3 domains: "movement," "movement with cognition," and "cognition." The questionnaire was initially applied in 138 healthy controls (0.33 and 50 years) and successively in 72 patients with MPS II (4-49 years), 51 with the neuronopathic form, and 23 with the non-neuronopathic form. Twenty patients were treated with HSCT, 23 were treated with ERT initiated before 8 years of age, 25 started ERT after 8 years of age, and 4 patients never received specific treatment. The scores of patients with neurological impairment were lower than controls and patients with the non-neuronopathic form, in all categories. Among patients with the neuronopathic form, there was a tendency for transplant patients to present higher scores than patients who started ERT $\leq$ 8 years, and there was a significant difference in the score between the group that received ERT after age 8 and the group that performed HSCT, with the latter group achieving higher scores. The questionnaire showed the benefits of early treatment, with HSCT showing better results compared to ERT, although the differences were not statistically significant.

Cagle[35] briefly reported, in 2015, the case of a patient who underwent HSCT at 37 months. Up to 4 years of age, he showed no signs of neurological regression. The author mentions the need for the development of more reliable biomarkers for monitoring both disease and treatment.

In 2016, Wang et al[36] published an article on allogeneic HSCT in 34 Chinese patients with MPS. Of these, 12 patients had MPS II and were transplanted between the ages of 2 and 6 years. After HSCT, follow-up evaluations showed improvement in airway obstruction, recurrent episodes of otitis media, joint stiffness, and hepatosplenomegaly. The auditory deficit showed some improvement, the valve impairment showed improvement in some patients and progression in others, while there were no benefits in the bone disease. Regarding the CNS,

4 patients had significant improvement in motor skills and 2 patients showed small improvements in language skills. The results suggest that allogeneic HSCT is beneficial for the neurological development of patients with MPS II.

Muschol et al[37] also, in 2016, summarized the clinical outcomes of 2 patients undergoing HSCT at 2.1 and 4.25 years. Both patients presented good grafting, normalization of I2 S activity, and decline in urinary GAG excretion. After 2 years of transplantation, hepatosplenomegaly disappeared in both. One of the patients showed signs of hyperactivity and aggressive behavior 6 months after HSCT, lost the ability to talk 2 years later, and after 3 years of transplantation presented progressive cerebral atrophy. The other showed developmental delay but maintained the motor and language skills; imaging examinations revealed a reduction in white matter changes.

Recently, in 2017, Barth et al[13] reported the 7-year follow-up of a prenatally diagnosed MPS II boy with positive family history of severe MPS form, submitted to HSCT with umbilical cord blood cells at 70 days of age. Engraftment after 30 days revealed mixed chimerism with 79% donor cells; after 7 years, engraftment remains at 80%. The I2 S activity 30 days post-transplant was low in plasma and normal in leukocytes, and the same pattern is observed to date. At age 7 years, growth charts are normal, and he is very healthy, although mild signs of dysostosis multiplex are present, as well as hearing loss. The neuropsychological evaluation disclosed an IQ of 47. Despite this low measured IQ, the patient continues to show improvements in cognitive, language, and motor skills, being quite functional. The authors believe HSCT is a therapeutic option for patients with MPS II having the severe phenotype, as it could preserve neurocognition or even halt neurodegeneration when strict selection criteria are followed.

Also in 2017, Kubaski et al[38] compared the clinical and biochemical data of patients with MPS II who received HSCT and/or ERT. Demographics of 130 patients undergoing HSCT were compared to those of 54 patients treated with ERT and 11 untreated patients. Daily living activities were also evaluated in these patients. A greater number of transplanted patients presented improvement in somatic symptoms, joint stiffness, and daily living activities compared to those who received ERT. Both treatments provided significant reductions in GAG levels, but in general patients undergoing HSCT had lower GAG levels. Two patients with the non-neuronopathic form presented improvement in brain MRI after transplantation. The authors state that despite the need for controlled studies, HSCT seems to be effective and may be considered as a therapeutic option for patients with MPS II.

Discussion

Hematopoietic stem cell transplantation is the only currently available treatment capable of preventing progressive neurodegeneration that occurs in some metabolic diseases.[4,39,40,41] It has become the treatment of choice for the severe form of MPS type I since it is able to preserve neurocognition when performed early.[5,6,9,42] Since 1980, more than 600 HSCT have been performed in patients with Hurler syndrome.[4]

Clinical experience with HSCT in MPS II is small. Most of the available literature is outdated, and the few articles available refer to heterogeneous cohorts of patients transplanted with different metabolic diseases or to reports of isolated cases. The available data reveal poor patient selection criteria; many were already at advanced ages at the time of transplantation, some had the non-neuronopathic form while others presented the neuronopathic form of MPS II, already with neurological impairment. The conditioning regimens used were quite varied, as was the source of cells for transplantation. In addition, follow-up parameters and post-HSCT outcomes of interest were also varied, making it impossible to compare and generalize the results obtained.

After 2006, with the approval of Idursulfase alfa (Elaprase), ERT became the treatment of choice for MPS II. Although it is known not to cross the BBB, being unable to prevent the neurodegeneration that occurs in the neuronopathic form of MPS II, ERT has become the treatment of choice for patients diagnosed with Hunter syndrome, and HSCT was discouraged and no longer.[13]

It is important to remember that more than 10 years, HSCT was limited by the lack of available donors, high percentage of graft failure, and high rates of morbidity and mortality. In 2005, an international collaborative study developed guidelines for HSCT in patients with MPS, based on the identification of mortality predictors.[43] In 2012, the busulfan-based conditioning regimen was modified by replacement of cyclophosphamide with fludarabine leading to less toxicity with similar efficacy.[44] Other reduced toxicity regimens that improve patients survival presently being used include fludarabine/melphalan and treosulphan/fludarabina (EBMT/ESID Guidelines for HSCT, 2017).

The implementation of these new guidelines resulted in graft survival rates of more than 90%. Over the last decade, umbilical cord blood has been used with increasing frequency in the transplantation of children with metabolic diseases. Cord blood offers several advantages when compared to bone marrow as a source for transplantation, such as shorter time to donor searching, greater tolerance for human leucocyte antigen (HLA) incompatibilities, lower incidence and severity of graft versus host disease, and lower probability of viral infections transmission. Recent studies suggest that the highest event-free survival rates are achieved in patients receiving compatible sibling cords or fully compatibles cords (6/6) of related donors, followed by compatible 5/6 cords (or compatible cords 4/6 with high cell dosages) or with 10/10 compatibility of nonrelated donor. It is important to note that many of the related donors also carry mutations, which influence posttransplant enzyme levels. Lower enzyme levels appear to influence long-term outcomes, such as neurocognitive development. Patients with normal enzyme levels in leukocytes show better results such as higher growth, less need for orthopedic interventions, and respiratory care.[8,4]

It has already been proven that the results of HSCT in metabolic disorders (both transplantation outcomes and long-term outcomes) are better when it is performed earlier in the course of the disease. This has already been demonstrated in MPS I, metachromatic leukodystrophy, X-linked adrenoleukodystrophy, Krabbe's disease, and probably it is also true for other metabolic diseases.[4]

The high grafted survival rates observed after HSCT together with the low toxicity in patients with MPS would allow the indication of transplantation for other types of MPS, in addition to the severe form of MPS I. In addition, the scientific basis for its effectiveness remains the same: The donor cells would secrete the deficient enzyme that would be captured by surrounding cells, thus correcting the underlying enzyme deficiency.

Regarding the CNS, HSCT appears to be the only treatment capable of preserving neurocognitive function. Hematopoietic stem cell transplantation appears to be beneficial since monocytic/phagocytic cells are able to cross the BBB and host in the brain as microglia. Microglia derived from donor cells would be able to secrete the deficient enzyme that would be captured by receptor neurons correcting enzyme deficiency.[45] Araya et al[29] demonstrated the presence of donor cells in the microglia of patients with MPS II 10 months after transplantation. These cells were found not only in the perivascular spaces but also in the cerebral parenchyma, suggesting the potential of HSCT to treat the neurological symptoms of Hunter syndrome.[29]

The case reported by Barth et al showed favorable neurological outcome with early HSCT in the neuronopathic form of MPS II.[13] It is generally agreed that younger patients benefit most from HSCT. Thus, early diagnosis is fundamental to the success of transplantation since much of the morbidity associated with the disease is not reversed with HSCT. Because it takes a few months for the microglia to be replaced by cells from the donor, there seems to be some delay in the benefits of transplantation to the brain. Therefore, transplantation only offers clinical benefits when instituted in presymptomatic phases but may be as effective for MPS II as it is for MPS I when the patient is transplanted prior to the onset of neurological symptoms.[29]

Currently, with the high rates of graft survival and reduction in toxicity and complications related to HSCT with the new techniques and transplantation protocols, together with a superior metabolic correction when compared to ERT,[8,36] associated with the more careful selection of patients, HSCT should be considered as an alternative option to ERT.

In China and Japan, HSCT is a standard therapy, being even listed in the guideline for MPS II treatment in Japan.[30,34,38] In Brazil, a new guideline for HSCT has recently been approved, which will make it easier for patients with MPS II to have access to this procedure in a timely manner.[46]

In addition to a potentially more favorable effect on disease progression, there would be a gain in quality of life for patients and relatives who would not need to attend a hospital/infusion center weekly over 3 to 4 hours for lifelong infusions.

Economic evaluations of HSCT are difficult to compare between countries because of differences in health-care systems, transplantation coverage, and payment policies. However, US$350 000 to US$800 000 is a reasonable approximation for an allotransplant in the United States. Comparable cost in Latin America ranges from US$25 000 to US$75 000).[47] In Europe, in a single-institution study from Sweden, Svahn et al found costs for HCT with related donor transplantations compared with HSCT with unrelated donor transplantations of €129 133 versus €160 658.[48] In France, Cordonnier et al examining costs over a 12-month period found that myeloablative allogeneic transplantations cost less than reduced intensity conditioning transplants; €74 900 versus €78 700.[49] In Thailand, Ngamkiatphaisan et al[50] found a median cost for allogeneic HCT of €22.593 over 1-year posttransplantation.[50]

Regarding public health policy, the HSCT could be considered a very interesting option since the estimated mean annual cost of idursulfase for a 25Kg patient with MPS II is €290 000/ $325 000; a lifelong cost much higher than that of the HSCT which is a procedure usually performed once.[51]

Conclusion

After little more than a decade of experience, the benefits and limitations of ERT for MPS II are known. Intravenous ERT is able to provide benefits for some of the somatic signs and symptoms of the disease, but, being incapable to cross the BBB, it does not improve or even halt the neurological symptoms and neurodegeneration that occur in patients with the neuronopathic form of Hunter syndrome.

Hematopoietic stem cell transplantation has become more secure and accessible after the development of new protocols and techniques and the creation of bone marrow donor registries and umbilical cord banks. Thus, HSCT should be considered as a treatment option to ERT in patients with MPS II. It is the only currently available treatment potentially capable of providing neurological benefits when rigid selection criteria are followed and it also should be thought for somatic treatment as it has lower cost compared to ERT for life and would provide better quality of life for the patients and their families. Longer follow-up and more reports of early transplanted patients are still necessary.

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