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Original article

Hematopoietic stem cell transplantation in pediatric patients with type VI mucopolysaccharidosis

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Background: It is uncertain whether hematopoietic stem cell transplantation (HSCT), versus standard enzyme replacement therapy (ERT), is effective for type VI mucopolysaccharidosis (MPS VI).

Purpose: New related advances in HSCT prompted an examination of the transplant procedures performed in a recent cohort.

Methods: This single-center retrospective study reviewed the medical records of 17 pediatric patients with MPS VI who underwent allogeneic HSCT in 2021–2023. All conditioning regimens were myeloablative. Engraftment days, complications, and survival data were recorded. As follow-up was short, we recorded only 6-minute walk test distance before versus after HSCT.

Results: The patients underwent transplantation at a median of 6-year postdiagnosis. All were engrafted and had a full or mixed chimerism. Enzyme levels were within normal ranges. Walking tests of all evaluable patients improved at a median 9-month follow-up.

Conclusion: HSCT aims to improve the disease and provides a permanent solution at the enzyme level, eliminating ERT. Our study showed that HSCT, a less expensive and permanent treatment option, should be offered to patients with MPS VI.

Key words: Mucopolysaccharidoses, Hematopoietic stem cell transplantation, Enzyme replacement therapy, Child, Maroteaux-Lamy syndrome

Key message

Question: Could hematopoietic stem cell transplantation (HSCT) be an alternative to enzyme replacement therapy (ERT) for type VI mucopolysaccharidosis (MPS VI)?

Finding: HSCT is generally not offered due to reports of high toxicity and mortality. However, we detected fewer complications and graft-versus-host disease cases and no deaths with HSCT.

Meaning: HSCT is both less expensive than ERT and permanent; thus, it should be considered an alternative treatment for MPS VI.

Introduction

Mucopolysaccharidoses (MPS) belong to a clinically heterogeneous group of diseases that occur due to deficiencies in enzymes that degrade glycosaminoglycans (GAGs), resulting in lysosomal storage diseases (LSDs). GAGs are degraded by several enzymes, and 7 different forms of MPS are caused by deficits in each of these enzymes that require different treatment approaches.[1)] A broad spectrum of clinical symptoms, including skeletal and joint abnormalities, short stature, cardiorespiratory disease, hepatosplenomegaly, decreased hearing, and vision loss, can result from the progressive accumulation of GAGs in cells and tissues throughout the body. Certain types of disorders (MPS III) primarily involve the central nervous system (CNS), while others involve the skeletal system (MPS IV). MPS I, II, and VII affect soft tissue storage and the skeletal system with the CNS; however, MPS VI only affects soft tissue and the skeletal system without the CNS.

In certain types of MPS, certain therapies, such as hematopoietic stem cell transplantation (HSCT), are quite effective, while others show no clear benefit.[1-4)] The use of HSCT for patients with MPS IH is currently the norm because it has a significant impact on CNS disease, which cannot be treated effectively by enzyme replacement

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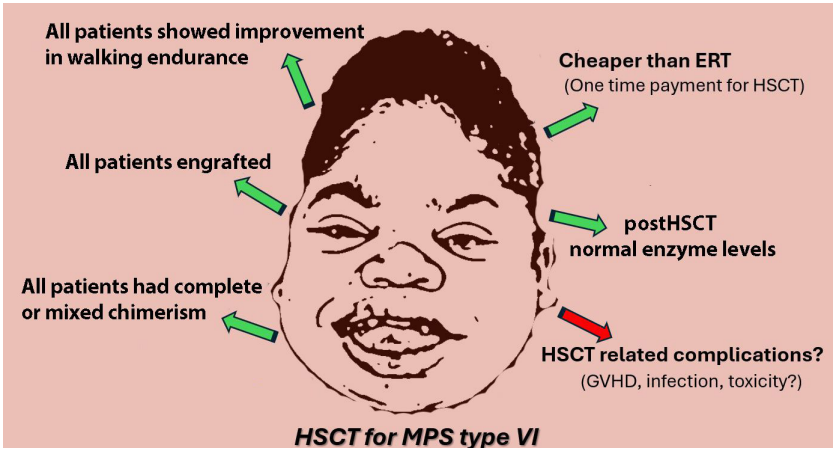

Graphical abstract. ERT, enzyme replacement therapy; HSCT, hematopoietic stem cell transplantation; MPS, mucopolysaccharidosis.

therapy (ERT). However, it is uncertain whether HSCT would be a successful therapy for MPS VI instead of ERT, given that individuals with MPS VI do not appear to exhibit cognitive abnormalities resembling those reported in people with MPS IH. ERT has been shown to slow the progression of bone disease and improve endurance, pulmonary function, and growth velocity in patients with MPS VI patients.[5-7] ERT seems effective in preventing the progression of cardiac valve abnormalities, particularly when initiated earlier but without significant cardiac outcomes.[8,9] Nevertheless, since ERT requires lifelong treatment, is very expensive, requires regular hospital visits, and thus presents societal issues, HSCT, which promises to be a permanent and less expensive method, may come to the fore.

The argument for utilizing HSCT as a therapy for MPS VI is based on MPS subtypes other than VI. Most data on HSCT are based on a small number of case studies; the largest one is the study by Turbeville et al.[4] This study included patients who underwent transplantation between 1982 and 2007 (mostly before 2000) and resulted in a relatively high rate of graft-versus-host disease (GVHD) (36%) and mortality (36%). Owing to the poor results of this study, many guidelines consider HSCT as an option rather than the standard of care for patients with MPS VI.[10,11] This highlights the necessity of transplant procedures carried out in a recent cohort, in light of new advances and less toxic agents.

Methods

This was a single-center retrospective review of 17 pediatric patients with mucopolysaccharidosis type VI (MPS VI) undergoing allogeneic HSCT between March 2020 and March 2023. All patients were under ERT for at least

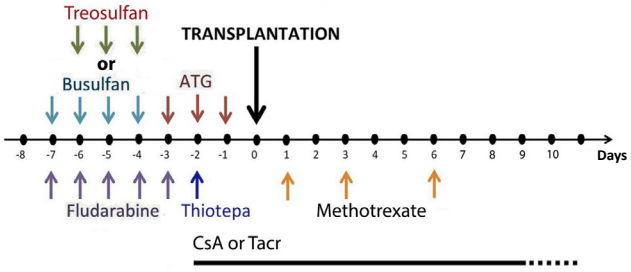

Fig. 1. Conditioning regimen. ATG, antithymocyte globulin; CsA, cyclosporine A; Tacr, tacrolimus.

6 months before HSCT and stopped treatment before the conditioning regimen. An informed consent was obtained, and approval for this study was granted by the ethics board of the Medical Park Antalya Hospital (2024/9).

All patients and donors were HLA-typed using high-resolution techniques. All sibling donors with a full HLA match (10/10) and unrelated donors with a 9/10 and 10/10 match have been accepted as donors. All myeloablative conditioning regimens were based on protocols comprising busulfan at weight-based doses (1.2 mg/kg for 9 to <16 kg, 1.1 mg/kg for 16 to <23 kg, 0.95 mg/kg for 23 to 34 kg, and 0.8 mg/kg for >34 kg). In general (Fig. 1), fludarabine was used together with busulfan at a dose of 30 mg/m^2/day for 5 days. At the beginning of the study, we added 10 mg/kg of thiotepa (5 mg/kg, twice in a day) to the busulfan-fludarabine combination; however, we were able to use it in 12 of the 17 patients due to drug shortage. In patients with poor performance, treosulfan was used instead of busulfan at doses of 12 g/m^2 for 3 days recommended for 0.5–1 m^2 body surface area. Antithymocyte globulin (ATG Grafalon, rabbit-based) was administered in a total dose of 20–25 mg/kg during the pre-transplantation period for immunoablation and *in vivo* T-cell depletion.

All patients were administered a calcineurin inhibitor (CNI) starting on day -2 (cyclosporine A or tacrolimus

level kept at 100–200 and 5–8 ng/mL, respectively) in combination with short-course methotrexate (10 mg/m^2 on days 1, 3 and 6) for GVHD prophylaxis. CNIs were used till 6th month of HSCT and tapered in 3 months. Our institutional policy for sinusoidal obstructive syndrome prophylaxis consists of continuous heparin infusion combined with ursodeoxycholic acid and N-acetylcysteine for 1 month.

Neutrophil engraftment was considered the first of 3 consecutive days with an absolute neutrophil count ≥0.5×10^9/L, and platelet recovery was defined as a platelet count greater than ≥20×10^9/L for 7 days without transfusion support. Infection prophylaxis and microbiological screening were performed as previously described.[12] Briefly, all patients used kinolon and fluconazole prophylaxis for 6 months. Trimethoprim-sulfamethoxazole and aciclovir were used for 1 year. Neutropenic fever and viremias were treated according to the previously described relevant guidelines.[12,13] Briefly, cefepime monotherapy was initially used for febrile neutropenia, but if fever persisted, carbapenems were used, with liposomal amphotericin-B replacing fluconazole for broad-spectrum antifungal protection. Preemptive treatment with ganciclovir was given for a minimum of 21 days in cases of increased viral load of cytomegalovirus (CMV). When immunoglobulin G levels fell below 400 mg/dL, intravenous gamma globulin was administered. The use of granulocyte-colony stimulating factor was limited to prolonged neutropenia, and it was not routinely used. The diagnosis of acute GVHD (aGVHD) and assessment of organ involvement were based on the modified Glucksberg criteria devised at the Keystone Conference.[14] The diagnosis of chronic GVHD and the assessment of organ involvement were based on the 2014 National Institutes of Health Consensus Criteria (NIH-CC) recommendations.[15]

As Akyol et al.[1] recommended the follow-up after HSCT in their guideline, all patients' arylsulfatase B levels in leukocytes, as well as endurance testing, cardiorespiratory function, and ophthalmic findings, were collected before HSCT and at least 3 months after HSCT, if applicable. Demographics, disease and transplant characteristics, acute or chronic GVHD severity, and survival data at the last follow-up were recorded. Having a steady course or improvement of the disease and a normal enzyme level assessed at least 6 months following HSCT, without ERT, was defined as disease and GVHD-free survival (DGFS).

All statistical analyses were performed using SPSS ver. 16.0 (SPSS Inc., USA). Descriptive statistics for the qualitative variables are expressed as frequencies and percentages. A Wilcoxon signed-rank test was conducted to determine whether there was a statistically significant difference between the initial and post-HSCT enzyme level and the 6-MWT. Statistical significance was set at P<0.05.

Results

The patient and transplant characteristics are summarized in Table 1. Patients underwent transplantation at a median of 6 years after diagnosis, mostly with a matched unrelated donor (76%). All the patients were engrafted and had full or mixed chimerism at the last follow-up. All patients had their enzyme levels assessed at least 3 months after HSCT, and all were within normal ranges (Tables 2 and 3) (initial level (0.1 [range, 0.1–1.0] and post-HSCT 100 nmol/mg.h [range, 40–230 nmol/mg.h]; P<0.05). The median follow-up period of the patients was 14 months (range, 9–29 months).

Only 1 patient experienced grade 3 aGVHD, and none of the patients had moderate or severe chronic GVHD (Tables 2 and 3). The most frequent complications were CMV viremia and, to a lesser extent, engraftment syndrome, autoimmunity, and hemorrhagic cystitis (Table 2). All complications, including GVHD, resolved after treatment, excluding one patient's autoimmune hemolytic anemia

Table 1. Patient and HSCT characteristics

Characteristic	Value
Age at diagnosis (yr)	1.8 (0.3–6.4)
Age at Tx (yr)	7.4 (1.0–15.9)
Duration of ERT (mo)	68 (1–144)
Sex	
Male	6 (35)
Female	11 (65)
Donor relation	
MSD	4 (24)
MUD	13 (76)
HLA match	
10/10	10 (59)
9/10	7 (41)
Conditioning regimen	
Busulfan Flu	5 (30)
Busulfan Flu TT	10 (59)
Treo Flu TT	2 (11)
GVHD prophylaxis	
Tacr+Mtx	11 (65)
CsA+Mtx	6 (35)
Stem cell source (×10^6/kg)	
BM	5 (29)
CD34	8.9 (5.5–34.7)
PBSC	12 (71)
CD34	9.0 (5.1–32.0)

Values are presented as median (range) or number (%).
HSCT, hematopoetic stem cell transplantation; Tx, transplantation; ERT, enzyme replacement therapy; MSD, matched sibling donor; MUD, matched unrelated donor; HLA, human leukocyte antigen; Flu, fludarabine; TT, thiotepa; Treo, treosulfan; GVHD, graft-versus-host disease; Tacr, tacrolimus; Mtx, methotrexate; CsA, cyclosporine A; BM, bone marrow; PBSC, peripheral blood stem cell.

Table 2. HSCT characteristics and outcomes (n=17)

Characteristic	Value
Engraftment (day)	
Neutrophil	14 (11–20)
Platelet	11 (7–15)
Chimerism (%)	
First (4 wk after HSCT)	99 (86–100)
Last (at the last follow-up)	98 (78–100)
Acute GVHD grades 2–4	
100 Days	4 (24)
Acute GVHD grades 3–4	
100 Days	1 (6)
Chronic GVHD (mild)	2 (12)
Complications	
CMV	6 (35)
Engraftment syndrome	2 (12)
Autoimmune	1 (6)
Hemorrhagic cystitis	1 (6)
VOD	0 (0)
Pre-HSCT enzyme levels	0.1 (0.1–1.0)
Post-HSCT enzyme levels	100 (40–230)
Change in 6-MWT after HSCT (n=9)[a]	
Change (m)	290 (50–498)
Follow-up for 6-MWT (mo)	9 (6–22)
Follow-up (mo)	14 (9–29)
Survival	17 (100)
DGFS[b]	17 (100)

Values are presented as median (range) or number (%).
HSCT, hematopoetic stem cell transplantation; GVHD, graft-versus-host disease; CMV, cytomegalovirus; VOD, veno-occlusive disease; 6-MWT, 6-minute walk test; DGFS, disease and GVHD-free survival.
The enzyme level in the first evaluation (median 4th month of HSCT [range, 3–11 months]; [N>10 nmol/mg.h])
[a]Available for only 9 patients due to lack of pre-HSCT test or refusal to undergo new test. [b]Disease- and GVHD-free survival: having a stable or improved disease and a normal enzyme level at least 6 months post-HSCT without ERT.

(AIHA), possibly driven by a major blood group mismatch. No improvements or decreases in any of the patients' echocardiographic findings were found during the first 6 months following HSCT (n=12). Thirteen of the 14 patients who underwent ophthalmic examination for corneal opacity before HSCT were reevaluated during the median 10 months after HSCT and did not show any change. Three patients had hepatomegaly before transplantation, and 2 of them remained unchanged in the first year, while one regressed by 2 cm after 11 months of follow-up. Due to the lack of regular multidisciplinary follow-up of patients before HSCT and the refusal to undergo the test after HSCT, only 9 patients performed the 6-minute walk test (6-MWT) for comparison, and it was observed that all

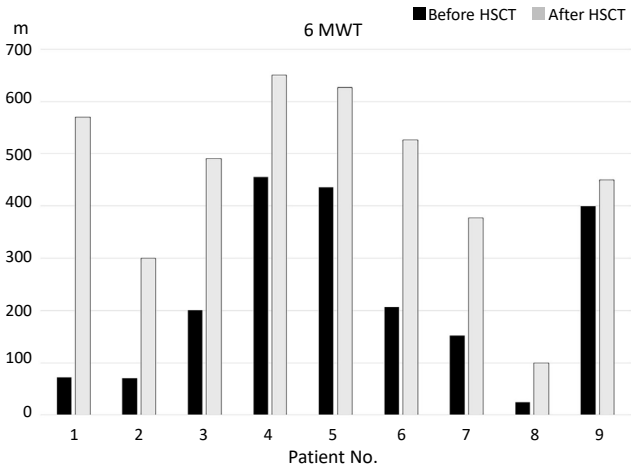

Fig. 2. Comparison of 6MWT. HSCT, hematopoetic stem cell transplantation; 6-MWT, 6-minute walk test.

Table 3. Patients' characteristics

Patient No./ sex/age (yr)[a]	ARSB gene mutation	Donor	Stem cell source	Conditioning regimen	ATG	aGVHD	cGVHD	Chimerism (%)[b]	Enzyme level	Improvement in post-HSCT 6-MWT (m)/status
1/F/7.2	c.962 T>C	MUD	PBSC	Flu+Bu	+	Grade 2	-	99	Normal	498/Alive, No GVHD
2/F/3.5	c.903 C>G	MSD	PBSC	Flu+Bu	+	-	-	82	Normal	-/Alive
3/F/9.8	c.962 T>C	MUD	PBSC	Flu+Bu+TT	+	-	-	99	Normal	-/Alive
4/F/14.3	c.962 T>C	MSD	BM	Flu+Treo+TT	+	-	-	100	Normal	230/Alive
5/M/13.7	c.962 T>C	MUD	PBSC	Flu+Bu+TT	+	-	-	98	Normal	290/Alive
6/F/3.5	c.478 C>T	MUD	BM	Flu+Bu+TT	+	-	-	100	Normal	195/Alive
7/F/10.3	c.1575delC	MSD	BM	Flu+Bu+TT	+	Grade 2	Mild cGVHD	99	Normal	191/Alive, No GVHD
8/F/10.9	c.962 T>C	MUD	BM	Flu+Treo+TT	+	-	-	100	Normal	-/Alive
9/F/7.2	c.962 T>C	MUD	PBSC	Flu+Bu+TT	+	-	-	89	Normal	-/Alive
10/F/2.6	c.962 T>C	MUD	PBSC	Flu+Bu+TT	+	-	-	78	Normal	320/Alive
11/M/1.0	c.962 T>C	MSD	BM	Flu+Bu+TT	+	-	-	84	Normal	-/Alive
12/F/10.9	c.962 T>C	MUD	PBSC	Flu+Bu	+	Grade 3	-	99	Normal	-/Alive, No GVHD
13/M/5.7	c.962 T>C	MUD	PBSC	Flu+Bu+TT	+	-	-	98	Normal	225/Alive
14/F/7.4	c.962 T>C	MUD	PBSC	Flu+Bu	+	Grade 2	-	97	Normal	75/Alive, No GVHD
15/M/2.8	c.962 T>C	MUD	PBSC	Flu+Bu+TT	+	-	-	99	Normal	50/Alive
16/M/8.2	c.962 T>C	MUD	PBSC	Flu+Bu	+	-	Mild cGVHD	98	Normal	-/Alive, No GVHD
17/M/15.9	c.962 T>C	MUD	PBSC	Flu+Bu+TT	+	-	-	99	Normal	-/Alive

ATG, antithymocyte globulin; GVHD, graft-versus-host disease; aGVHD, acute GVHD; cGVHD, chronic GVHD; HSCT, hematopoetic stem cell transplantation; 6-MWT, 6-minute walk test; MUD, matched unrelated donor; MSD, matched sibling donor; PBSC, peripheral blood stem cell; BM, bone marrow; Flu, fludarabine; Bu, busulfan; TT, thiotepa; Treo, treosulfan.
[a]Age at HSCT (yr). [b]Chimerism at the last follow-up visit; skin aGVHD in patients 7 and 14; skin and GIS (lower gastrointestinal system) aGVHD in patients 1 and 12.

patients' test performance improved, between 50 and 498 meters longer than before HSCT (median [range], 2.48 times [1.1–7.9 times]; $P<0.05$) (Fig. 2), at a median follow-up of 9 months (Table 2).

Discussion

LSDs are caused by specific enzyme deficiencies that result in defective lysosomal hydrolysis of endogenous macromolecules, leading to cellular injury stemming from the primary accumulation of undigested substrates within the lysosomes. The principle of HSCT in LSDs is the cross-correction of enzyme-deficient host cells with a continuous source of enzymes produced by donor-derived myeloid cells, especially in organs where ERT is inefficient to reach.[11] This makes HSCT crucial in MPS IH due to the currently available ERT's inefficiency in crossing the blood-brain barrier at a sufficient dose to prevent cognitive decline. However, since cognitive defects due to the ineffectiveness of enzyme therapy were not observed in the ERT of MPS VI, the definite superiority of HSCT over ERT, as in MPS IH, cannot be mentioned in MPS VI.[1,2] ERT for MPS VI has shown positive results in terms of survival, quality of life, respiratory function, joint mobility, physical resistance, and growth; however, the results are inconclusive for cardiac valve disease, sleep apnea, and liver and spleen size.[16] The uncertainty of ERT in various symptoms and the high cost of this lifelong treatment may bring HSCT to the fore. Both HSCT and ERT are costly therapies for MPS VI; however, owing to the weekly regimen needed for the rest of the patient's life, ERT is more expensive than HSCT. For a patient weighing 25 kg, ERT costs $476.000 per year, while HSCT only requires a one-time payment of $500.000.[17]

However, the use of HSCT for MPS VI is currently limited owing to the significant risks of graft failure, GVHD, and infection during immune suppression.[4,11] In the study of Turbeville et al.,[4] which included HSCT performed before 2007, the probability of survival (95% confidence interval) at 100 days, which can be attributed to transplant-related mortality (TRM), was 78% (65%–89%). In our study involving HSCTs after 2020, the probability of survival at 100 days was 100%, showing the positive effect of supportive treatment and recent advancements in HSCT procedures. Furthermore, we encountered less acute and chronic GVHD in our study; all were resolved at the last follow-up, pointing to better donor screening strategies and GVHD prophylaxis and the less toxic properties of the conditioning regimen.

Patients with MPS VI frequently develop cardiac valve dysfunction driven by valve thickening from storage material deposition, which is a leading cause of morbidity and mortality.[11,18,19] Total body irradiation (TBI) or cyclophosphamide (Cy) were the conditioning regimens most frequently used in HSCT (80%) in the the study of Turbeville et al.[4]; however, we did not use these well-known cardiotoxic techniques in our patients, which may help explain the absence of TRM. One of the expected outcomes of HSCT for MPS VI is an improvement in cardiovascular events; however, owing to the short follow-up period to determine the effect of HSCT on cardiac outcomes, cardiac symptoms were stable, which is consistent with the literature. None of the corneal opacities regressed after HSCT after at least 10 months of follow-up. A longer observation period is needed to observe the effects of HSCT on corneal and cardiac involvement. Indeed, it is becoming increasingly important to monitor these patients and perform HSCT even before organ involvement develops to determine whether these organs are affected after HSCT. It is also important to follow-up to determine whether HSCT will result in long-term improvement.

We encountered only 1 case of severe acute GVHD and 2 cases of mild chronic GVHDs, which resolved completely during follow-up. The reduced severity of GVHD may have resulted from avoiding toxic approaches of TBI and Cy; however, the use of ATG in all patients, improvement of supportive treatment, and appropriate donor selection may have contributed to the decrease in this severity. The complications were not above expectations for CMV viremia, engraftment syndrome, and hemorrhagic cystitis and resolved during follow-up. It seems that the administration of busulfan or treosulfan with fludarabine and, in some of our patients, the addition of thiotepa did not cause toxic consequences; moreover, the early engraftment days of neutrophils and platelets during recovery and normalized enzyme values after HSCT showed the success of this conditioning regimen. Although patients with MPS VI are not predisposed to immunological disorders, one of our patients experienced AIHA. It is well known that immunological reactions can result from enzyme therapy in patients with ERT[20,21]; however, our patient did not have a history of such reactions, nor did she exhibit chronic GVHD, which could have been the cause of AIHA. One possible explanation for AIHA is the high frequency of the development of immune cytopenia in patients treated with HSCT with inherited metabolic disease, possibly due to the lysosomal dysregulation of antigen expression.[11,18,19] In fact, her anemia was linked to a major blood group mismatch; sirolimus and methylprednisolone eliminated the requirement for transfusions, and at the time of her last visit, she had not needed a transfusion for 2 months.

The major limitation of our study, owing to the short follow-up period was that we were unable to evaluate the

physical improvement of the patients after HSCT; however, our goal was to make a general assessment of the patients improvement after HSCT with the 6-MWT. However, it could only be done in 9 patients since some of the patients did not have adequate follow-up prior to transplantation or had refused this long-distance walking test after transplantation. The test performance of all patients was observed to improve by a median of 290 m (median, 2.48 times) more than before HSCT at a median follow-up of 9 months (Fig. 2, Table 2). Further follow-up with musculoskeletal and cardiopulmonary measurements is needed to compare this physical improvement with ERT.

A review of the literature reveals that to prevent graft rejection in HSCT for inherited metabolic diseases, cord blood is preferred as a source of stem cells, and a myeloablative regimen should be preferred for the conditioning regimen.[11,22,23] Since the median age of our patients was 7 years, we considered that bone marrow would be a better option as a stem cell source because the CD34+ cell count of cord blood would not be sufficient. However, because peripheral blood donation was favored by MUD donors, 71% of the patients received peripheral blood, while the remaining patients received bone marrow; cord blood was not used in any of the patients. Contrary to the report by Turbeville et al.,[4] who reported an increase in GVHD after HSCT for MPS VI, no serious GVHD developed in our patients despite frequent use of peripheral blood as a stem cell source. In addition, Boelens et al.[22] reported a higher rate of normal enzyme levels in HSCT with cord blood than in other types of stem cell sources; however, although no cord blood was used in our study, the enzyme levels returned to normal within a short period of 3 months after HSCT in all patients who could be evaluated. Further studies comparing different sources of stem cells are needed to determine the results with a longer follow-up period.

In conclusion, outdated research that led to the MPS VI guidelines to consider HSCT as an optional treatment must be reconsidered using newer conditioning regimens and supportive treatment after HSCT. HSCT not only aims to improve the disease, but also provides a permanent solution to the enzyme level by providing regular blood levels of enzyme, putting an end to ERT treatment, which causes patients to be hospitalized every week and therefore causes parents to reduce their workforce or quit their jobs. Our study showed that HSCT, which is a cheaper and permanent treatment option, should be an alternative treatment for patients with MPS VI.

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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Author contribution: Conceptualization: VU,GK,AY Data curation: VU, KY, HD, SÖ, SÇ, SZ Formal analysis: VU, KY, HD, SÖ, SÇ, SZ, Funding acquisition: VU, AY Methodology: VU, AY Project administration: VU, AY, GK Visualization: VU, Writing - original draft: VU Writing - review & editing: VU, AY

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