Biol Blood Marrow Transplant 21 (2015) 1106–1109

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Hematopoietic Cell Transplantation for Mucopolysaccharidosis Patients Is Safe and Effective: Results after Implementation of International Guidelines

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Article history:
Received 20 October 2014
Accepted 10 February 2015

Key Words:
Hematopoietic cell transplantation
Mucopolysaccharidosis
Hurler syndrome

A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT) is the only treatment able to prevent progressive neurodegenerative disease in a selected group of mucopolysaccharidosis (MPS) disorders. However, its use was historically limited by the high risk of graft failure and transplantation-related morbidity and mortality. Therefore, since 2005 new international HCT guidelines for MPS disorders were proposed. The survival and graft outcomes of MPS patients receiving HCT according to these guidelines in 2 European centers of expertise were evaluated. Two consecutive conditioning regimens were used, busulfan/cyclophosphamide or fludarabine/busulfan-based, both with exposure-targeted i.v. busulfan. A noncarrier matched sibling donor (MSD), matched unrelated cord blood (UCB), or matched unrelated donor (MUD) were considered to be preferred donors. If not available, a mismatched UCB donor was used. Participants were 62 MPS patients (56 MPS type I—Hurler, 2 MPS type II, 2 MPS type III, and 2 MPS type VI) receiving HCT at median age 13.5 months (range, 3 to 44). Forty-one patients received a UCB donor, 17 MSD, and 4 MUD. High overall survival (95.2%) and event-free survival (90.3%) were achieved with only low toxicity: 13.3% acute graft-versus-host disease aGVHD) grades II to IV and 14.8% chronic GVHD (1.9% extensive). A mismatched donor predicted for lower event-free survival ($P = .04$). A higher age at HCT was a predictor for both aGVHD ($P = .001$) and chronic GVHD ($P = .01$). The use of a mismatched donor was a predictor for aGVHD ($P = .01$). Higher rates of full-donor chimerism were achieved in successfully transplanted UCB recipients compared with MSD/MUD ($P = .002$). If complying with the international HCT guidelines, HCT in MPS patients results in high safety and efficacy. This allows extension of HCT to more attenuated MPS types. Because a younger age at HCT is associated with reduction of HCT-related toxicity, newborn screening may further increase safety.

INTRODUCTION

The mucopolysaccharidoses (MPS) comprise a group of inborn errors of metabolism caused by a deficiency of a lysosomal enzyme resulting in progressive multisystem morbidity [1]. Allogeneic hematopoietic cell transplantation (HCT) is the only treatment option able to prevent progressive neurodegenerative disease in a selected group of MPS disorders [2]. However, its use is limited by a high risk of graft failure and transplantation-related morbidity and mortality [3].

In 2005, the European group for Blood and Marrow Transplantation developed transplantation guidelines for HCT in MPS patients based on a European predictor analysis study [3]. In 2012, the busulfan-based conditioning regimen was slightly modified by replacing cyclophosphamide with fludarabine, because studies demonstrated similar efficacy

Financial disclosure: See Acknowledgments on page 1109.

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http://dx.doi.org/10.1016/j.bbmt.2015.02.011
1083-8791/

with reduced toxicity using fludarabine [4]. In this study we evaluated the survival and graft outcomes of HCT in MPS patients, complying with the international guidelines, in 2 centers performing the highest numbers of HCTs in MPS patients in Europe.

METHODS

Patients

MPS patients consecutively treated at the University Medical Center Utrecht (UMCU) or the Royal Manchester Children's Hospital (RMCH) according to the European group for Blood and Marrow Transplantation guidelines for HCT in MPS patients (www.ebmt.org) were included in the study. The study was approved by the institutional review boards of the 2 centers. Written informed consent was obtained from the parents or legal guardians of the patients.

Conditioning Regimens and Donor Hierarchy

Busulfan + cyclophosphamide (BuCy) was the conditioning regimen used from December 2004 to January 2009. Busulfan was administered intravenously for 4 consecutive days using dose targeting based on therapeutic drug monitoring, as previously described [4]. Cyclophosphamide was dosed at 50 mg/kg for 4 days and administered at least 24 hours after busulfan. At UMCU, Thymoglobulin (Sanofi, Cambridge, MA) 10 mg/kg (cumulative dose over 4 days) was administered over 4 days to all recipients of unrelated donor grafts. At RMCH, Thymoglobulin 10 mg/kg (cumulative dose over 4 days) was used in all unrelated cord blood (UCB) transplants, whereas alemtuzumab was given as serotherapy to recipients of both unrelated (1 mg/kg over 5 days) and related (0.3 mg/kg over 3 days) bone marrow (BM) or peripheral blood stem cell (PBSC) donor grafts.

Fludarabine + busulfan (FluBu) was the conditioning regimen used from January 2009 to March 2014. Fludarabine 40 mg/m^2 was administered intravenously during 4 consecutive days, 1 hour before busulfan infusion. Busulfan was administered intravenously for 4 days, using dose targeting based on therapeutic drug monitoring, as previously described [4]. Serotherapy was similar to the previous period.

For donor hierarchy, a noncarrier matched sibling donor, identical UCB (6/6 on intermediate resolution), or identical matched unrelated donor (10/10 on high-resolution typing) was used. If these donors were not available, preferably a mismatched UCB donor was used.

Supportive Care

Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A in all patients. At UMCU, methotrexate was added on days +1, +3, and +6 after HCT in recipients of a BM transplant. In recipients of a UCB donor, prednisolone (1 mg/kg/day until day +28) was added after HCT. Antimicrobial prophylaxis was standard for all patients and consisted of ciprofloxacin, fluconazole/itraconazole, and acyclovir. All MPS type I–Hurler patients received enzyme replacement therapy peritransplant, 100 U/kg weekly, typically beginning at least 6 weeks before transplant and continuing until either conditioning (UMCU) or engraftment was established (RMCH).

Primary and Secondary Endpoints and Definitions

Overall survival (OS) was defined as survival from HCT to last contact or death. Event-free survival (EFS) was defined as survival from HCT to last contact, death, autologous reconstitution (<10% donor-derived engraftment), or graft-failure (lack of neutrophil recovery or transient engraftment of donor cells after HCT and/or requirement for a second HCT).

Secondary endpoints were neutrophil engraftment (first day of achieving a neutrophil count > .5 × 10^9/L for 3 consecutive days) and platelet engraftment (platelet count > 50 × 10^9/L for 7 consecutive days). Grades II to IV acute GVHD (aGVHD) was graded according to published criteria [5], and both limited and extensive chronic GVHD (cGVHD) were graded according to standard criteria and evaluated in patients who survived at least 100 days with sustained engraftment [6]. Veno-occlusive disease, defined according to Bearman [7], and viral reactivation of cytomegalovirus, adenovirus, and Epstein-Barr virus with a viral load > 1000 cm/mL were recorded. A donor chimerism > 95% was considered as full donor. An enzyme level above the local lower reference limit was considered normal. Urinary glycosaminoglycan excretion below the local upper reference limit was considered normal.

Statistical Analysis

For predictor analysis, we selected patient (gender, diagnosis, age at HCT) and HCT-related (HCT center, conditioning regimen, donor type, HLA disparity, total nucleated cells infused) factors. The association between these factors and the primary and secondary endpoints were analyzed using Cox proportional hazards regression analysis. Univariate predictors of endpoints with $P < .10$ were selected for multivariate analysis. Predictors with $P < .05$ in multivariate analysis were considered statistically significant. Kaplan-Meier curves were used to depict outcome probabilities. Statistical analysis was performed using SPSS version 20.0 (IBM, Armonk, NY).

RESULTS

Patient Characteristics

Sixty-two MPS patients were included: 56 MPS type I–Hurler, 2 MPS type II–Hunter, 2 MPS type III–Sanfilippo, and 2 MPS type VI–Maroteaux-Lamy. Twenty-nine received a BuCy conditioning regimen and 33 a FluBu conditioning regimen. Median age at HCT was 13.5 months (range, 3 to 44). Forty-one patients received a UCB transplant and 21 an unrelated or matched sibling BM or PBSC transplant. Median follow-up was 36 months post-HCT (range, 1 to 93). All baseline characteristics are shown in Table 1.

OS and EFS

The OS rate was 95.2%, whereas EFS was achieved in 90.3% of patients (Table 2, Figure 1). Causes of death were idiopathic pneumonia (n = 2) and cGVHD (n = 1). All 3 patients with graft failure received a second HCT with subsequent achievement of donor engraftment and were alive at latest follow-up time point. A mismatched donor predicted for lower EFS (hazard ratio, .176; $P = .04$; Figure 2).

Secondary Endpoints

Neutrophil and platelet engraftment were achieved after a median of 16.5 (range, 10 to 39) and 31 days (range, 0 to 89), respectively. A higher infused total nucleated cell dose predicted for higher neutrophil ($P = .04$) engraftment rates in BM recipients. The probability of aGVHD grades II to IV was 13.3%, whereas 14.8% of the patients were diagnosed with cGVHD (1.9% extensive). A higher age at HCT was a predictor for both aGVHD ($P = .001$) and cGVHD ($P = .01$). The use of a mismatched donor was a predictor for aGVHD ($P = .01$). The incidences of veno-occlusive disease and viral reactivations

Table 1
Baseline Characteristics

	n (%)	Median (range)
Number of patients	62	
Gender, males	37 (59.7)	
Diagnosis, MPS type I–Hurler*	56 (90.3)	
Age at HCT,† mo		13.5 (3-44)
Follow-up post-HCT, mo		36.0 (1-93)
Conditioning regimen, BuCy	29 (46.8)	
Donor, UCB/UBM or UPBSC/MSD	41/4/17 (66.1/6.5/27.4)	
HLA disparity, matched‡	44 (71.0)	
TNCs infused, ×10^7/kg		
CB		9.8 (1-102)
BM		69.0 (15-218)
PBSCs		109.5 (76-170)
CD34$^+$ cells infused, ×10^5/kg		
CB		4.0 (.5-52)
BM		103.0 (12-564)
PBSCs		122.5 (82-426)

UBM/UPBSC indicates unrelated BM/unrelated PBSCs; MSD, matched sibling donor; TNCs, total nucleated cells; CB, cord blood.

* Other MPS types included MPS type II–Hunter (n = 2), MPS type III–Sanfilippo (n = 2), and MPS type VI–Maroteaux-Lamy (n = 2).

† 12.0 months (range, 3-36) in MPS type I–Hurler patients.

‡ n = 28 UCB, n = 4 UBM/UPBSCs, n = 16 MSD; regarding UCB donors: n = 24 matched (6/6), n = 17 mismatched (n = 11 5/6, n = 6 4/6).

Table 2
Primary and Secondary Endpoints

	n (%)		
	Total	CB	BM/PBSCs
Number of patients	62	41	21
Primary endpoints			
OS*	59 (95.2)	39 (95.1)	20 (95.2)
EFS†	56 (90.3)	36 (87.8)	20 (95.2)

	n (%)			Median (range)		
	Total	CB	BM/PBSCs	Total	CB	BM/PBSCs
Secondary endpoints						
Neutrophil engraftment, days post-HCT	60 (96.8)	39 (95.1)	21 (100.0)	16.5 (10-39)	17.0 (11-39)	16.0 (10-22)
Platelet engraftment, days post-HCT	57 (93.4)	36 (90.0)	21 (100.0)	31.0 (0-89)	31.5 (16-89)	25.0 (0-55)
aGVHD (grades II-IV), days post-HCT	8 (13.3)	6 (15.4)	2 (9.5)	40.5 (19-71)	49.0 (19-71)	34.0 (33-35)
cGVHD (all grades), mo post-HCT‡	8 (14.8)	5 (15.2)	3 (14.3)	5.0 (3.3-15.1)	5.9 (3.3-15.1)	5.0 (3.3-7.5)
Veno-occlusive disease	0 (0)	0 (0)	0 (0)			
CMV reactivation, days post-HCT	5 (8.1)	4 (9.8)	1 (4.8)	13.0 (4-59)	13.0 (4-59)	12.0
Adenovirus reactivation, days post-HCT	9 (14.5)	5 (12.2)	4 (19.0)	16.0 (−1-76)	18.0 (6-76)	11.0 (−1-25)
EBV reactivation, days post-HCT	5 (8.1)	3 (7.3)	2 (9.5)	41.0 (−40-130)	21.0 (−40-41)	93.5 (57-130)
Full-donor chimerism	30 (88.2§)	23 (100§)	7 (63.6§)			
Normal enzyme level	39 (95.1§)	26 (96.3§)	13 (92.9§)			
Normal urinary GAG excretion	47 (100§)	29 (100§)	18 (100§)			

CMV indicates cytomegalovirus; EBV, Epstein-Barr virus; GAG, glycosaminoglycan.
* n = 3 death, at 2, 3, and 37 months post-HCT.
† n = 3 graft failure, at .7, .8, and 4.3 months post-HCT, all receiving a second HCT with subsequent donor engraftment.
‡ n = 1 extensive cGVHD.
§ Of alive and engrafted patients with testing ≥ 12 months post-HCT.

were very low (Table 2). Full-donor chimerism, normal enzyme levels, and normalized urinary glycosaminoglycan excretion after a follow-up of at least 12 months were found in 88.2%, 95.1%, and 100%, respectively, of patients with successful donor engraftment. Higher rates of full-donor chimerism were achieved in successfully transplanted UCB recipients, compared with recipients of BM/PBSCs (100% versus 63.6%, $P = .002$).

Significant results of multivariate predictor analysis are shown in Table 3. No differences were found between using a BuCy and FluBu conditioning regimen in any endpoint or between the 2 HCT centers.

DISCUSSION

In this study we clearly showed when complying with the international HCT guidelines, HCT in MPS patients results in remarkably low toxicity and high engrafted survival rates. This is significantly improved compared with the 45 MPS type I–Hurler patients transplanted between 1994 and 2004 in the same 2 HCT centers (OS 77.8%, EFS 40.0%; Supplemental Figure 1). The results of this study hereby confirm the previously reported observations of higher survival and engraftment rates concerning HCT in MPS type I–Hurler patients using a fully ablative conditioning regimen with busulfan therapeutic drug monitoring and strict donor hierarchy [3,8,9].

The incidence of grades II to IV aGVHD was lower compared with that observed in similar patient cohorts [8-10], presumably because of the relatively low number of donor–recipient HLA mismatching in our study population and the use of UCB in most patients. Improved matching possibilities might further improve this endpoint. The overall cGVHD incidence was comparable with or lower than previous studies, with only 1 patient developing extensive cGVHD [8-10]. Because a younger age at HCT is associated with reduced HCT-related toxicity, newborn screening and subsequent timely HCT might increase safety even further. Although extensive results on survival and graft outcome in

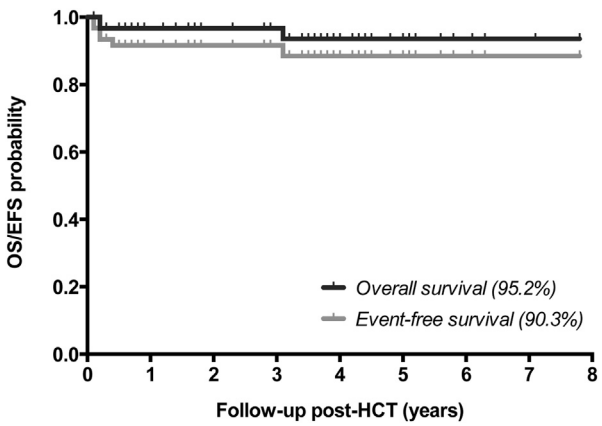

Figure 1. Overall survival and event-free survival.

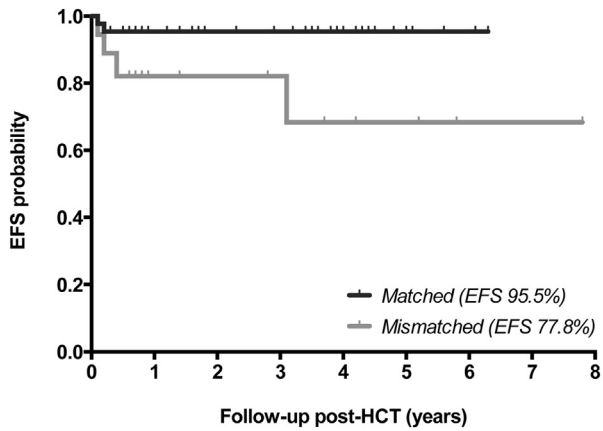

Figure 2. Influence of HLA matching on event-free survival.

Table 3
Multivariate Predictor Analysis: Significant Predictors

	Predictor	HR	95% CI	*P*
Primary endpoint				
EFS	HLA disparity (mismatched)	.18	.03-.97	.04
Secondary endpoints				
Neutrophil engraftment*	TNCs infused ($\times 10^7$/kg)†	1.01	1.00-1.02	.04
aGVHD (grades II-IV)	Age at HCT, mo†	1.13	1.05-1.21	.001
	HLA disparity (mismatched)	9.38	1.70-51.83	.01
cGVHD (all grades)	Age at HCT, mo†	1.08	1.02-1.15	.01
CMV reactivation	Age at HCT, mo†	1.09	1.01-1.18	.02
Full-donor chimerism	Source (UCB)	9.50	2.21-40.86	.002

HR indicates hazard ratio; CI, confidence interval.
* Only in bone marrow recipients.
† Continuous variable.

MPS patients younger than 6 months old receiving HCT are lacking, the results in patients with severe combined immunodeficiency receiving HCT at 3.5 months of age or younger are hopeful [11]. Median age at HCT of the MPS type I–Hurler patients in this study was 12.0 months (range, 3 to 36). This is considerably lower compared with the median age of 16.7 months described in a study concerning HCT performed in similar patients between 1995 and 2007 [9]. A younger age at HCT is also important for the long-term prognosis of MPS type I–Hurler syndrome patients, including their neurodevelopment [12].

To achieve maximal engrafted survival rates, a noncarrier matched sibling, fully matched UCB, or adult unrelated donor remains the highly preferred donor in MPS patients. A mismatched UCB donor is a suitable alternative option, also resulting in high engrafted OS (94.1%). The number of events was too low to analyze the effect of the degree of mismatch on EFS. In line with previous studies, the use of a UCB donor was associated with higher levels of full-donor chimerism compared with BM/PBSCs [9]. Although high rates of normal enzyme levels were achieved in both UCB and BM/PBSC recipients in this study, mixed chimerism remains a risk for lower enzyme levels in the long term, as seen in larger studies [9]. Normal enzyme levels post-HCT appeared to be highly important for the long-term prognosis of MPS type I–Hurler syndrome patients [12]. Furthermore, UCB donor grafts are readily accessible, enabling the reduction of the time from donor search to transplant and thereby the age at HCT, which was another significant predictor for superior long-term outcomes [12]. Taken together, in our view fully matched UCB grafts could therefore be considered the most attractive source for HCT in MPS patients even when a noncarrier matched sibling donor is available.

The observed high engrafted survival rates after HCT with low toxicity in MPS patients will enable the extension of HCT indication to the more “attenuated” MPS (sub)types, for example, MPS type I–Hurler-Scheie. The potential application of HCT to attenuated MPS patients, many of whom are currently treated with enzyme replacement therapy, is further supported by the fact that enzyme replacement therapy may initiate antibody formation, which is not observed after HCT [13]. In addition, it was previously shown that HCT is associated with superior metabolic correction compared with enzyme replacement therapy [14].

ACKNOWLEDGMENTS

Financial disclosure: M. A. was supported by a fellowship from the European group for Blood and Marrow Transplantation and a grant from ZonMw (The Netherlands Organisation for Health Research and Development; project 92003535) while working on this study.

Conflict of interest statement: S.A.J. reports grants from Genzyme and BioMarin, outside the submitted work. There are no conflicts of interest to report.

Authorship statement: R.F.W. and J.J.B. share last authorship.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2015.02.011.

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