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

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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

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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).