Allogeneic Hematopoietic Stem Cell Transplantation in Thirty-Four Pediatric Cases of Mucopolysaccharidosis—A Ten-Year Report from the China Children Transplant Group

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A B S T R A C T

We investigated the efficacy of allogeneic hematopoietic stem cell transplantation (alloHSCT) in pediatric patients with mucopolysaccharidosis (MPS). A retrospective analysis of transplantation data from 34 cases of MPS from the China Children Transplant Group, treated between December 2004 and September 2015, was conducted. Among the 34 cases, 12 cases were type I, 12 were type II, 4 were type IV, 4 were type VI, and 2 were of an unknown type. The median age at transplantation was 3.75 years (range, 1 to 7 years); the median follow-up time was 14 months (range, 2 to 119 months). Eleven patients underwent unrelated cord blood transplantation and 23 underwent peripheral blood stem cell transplantation (4 cases with an HLA-matched sibling donor, 2 cases with an HLA-mismatched related donor, and 17 cases with an unrelated donor). A busulfan-based myeloablative regimen was used as a conditioning regimen. The estimated overall survival at 3 years was 84.8% ± 6.3% and 91.2% of the patients (31 of 34) achieved full donor chimerism. Twenty-seven children were evaluable and all but 1 (carrier sibling donor; enzyme level improved but failed to reach normal) achieved normal enzyme level after transplantation. The incidence of grades II to IV acute graft-versus-host disease (aGVHD) was 41.1% (14 of 34), wherein the incidence of grades III and IV aGVHD was 11.8% (4 of 34). The incidence of moderate-to-severe chronic graft-versus-host disease was 5.9% (2 of 34). There was a significant difference in the survival rate between children who received transplantation before 2009 and those after 2009 (55.6% versus 95.7%, $P = .002$); the survival rate was lower in patients with pneumonia before transplantation than in those with no active infection before transplantation (66.7% versus 95.5%, $P = .019$), and no significant differences in survival rates were observed among children with different disease types, ages at transplantation, donor/graft source, and conditioning regimens. After transplantation, upper-airway obstruction, hepatosplenomegaly, and corneal clouding were significantly improved; hearing and motor function were improved to a certain extent; valvular heart disease was improved in some patients but progressed in others; and short stature and speech skills showed little improvement. AlloHSCT may save the lives of patients with MPS I, II, IV or VI and could improve quality of life. Pretransplantation pneumonia affects transplantation outcomes. Advances in transplantation protocols and techniques help to improve patient prognosis. Well-matched unrelated donors can also be an ideal donor source. Standardized follow-up and a multidisciplinary team contribute to accurate evaluation of long-term post-transplantation outcome and further improve the quality of life of MPS patients.

INTRODUCTION

Mucopolysaccharidosis (MPS) is a heterogeneous group of diseases characterized by deficiency of lysosomal enzymes responsible for the normal degradation of glycosaminoglycans (GAGs). The enzyme deficiency results in progressive lysosomal accumulation of GAGs followed by the development of various somatic and neurologic symptoms. MPS is classified according to 7 types: types I, II, III, IV, VI, VII, and IX. All but type II (an X-linked inherited disease) are autosomal recessive inherited diseases. Although the severity of clinical manifestations varies, most patients present disability and often die at a young age. Severe MPS I (MPS IH; Hurler syndrome) exhibits early onset, rapid progression, and profound mental retardation. Such patients usually die within the first decade of life from respiratory and/or cardiac failure, making MPS IH the most severe form of MPS.

Currently, enzyme replacement therapy (ERT) and allogeneic (allo) hematopoietic stem cell transplantation (HSCT) are the main treatments for MPS. ERT products, which have been approved to treat MPS I, II, and VI, can effectively improve the clinical symptoms of MPS patients while reducing treatment-related complications. However, ERT cannot cross the blood-brain barrier and, thus, cannot improve neurological symptoms; moreover, ERT is a long-term treatment, which increases its cost. AlloHSCT replaces endogenous hematopoietic lineage cells with exogenous cells transplanted from a healthy donor, which can migrate across the blood-brain barrier, differentiate into microglia, and express lysosomal enzymes to improve neurological symptoms, making alloHSCT

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advantageous over ERT [1]. As a consequence, alloHSCT is presently the first-line treatment for MPS IH in children under 2.5 years of age [2]. However, the potential benefits and possibility of treatment-related mortality and morbidity from HSCT in MPS IH children over 2.5 years and those with other types of MPS are unclear.

The China Children Transplant Group includes nearly all the major children's HSCT centers in China; thus, their data reflect the overall condition of HSCT in children throughout China. In this paper, we report multicenter results from the group of alloHSCT for MPS.

MATERIALS AND METHODS

Patients

Data on all MPS cases in the China Children Transplant Group were collected. The group included 29 children's HSCT centers, of which 6 performed HSCT for patients with MPS. The first transplantation for MPS was performed in December 2004. As of September 2015, a total of 34 patients had undergone transplantation for MPS. Among them, 12 cases were type I, 12 were type II, 4 were type IV, 4 were type VI, and 2 were of an unknown type. Twenty-four were boys and 10 were girls. The median age at transplantation was 3.75 years (range, 1 to 7 years); specifically, the median age at transplantation was 2.96 years (range, 1.5 to 6.67 years) for type I, 4.6 years (range, 2 to 6.75 years) for type II, 2.9 years (range, 1 to 7 years) for type IV, and 3.25 years (range, 1 to 6 years) for type VI MPS. Nine patients had pneumonia before transplantation.

Diagnostic Criteria and Organ Evaluation

The diagnostic criteria included a significant decrease in the level of 1 of the following lysosomal enzymes: serum α-L-iduronidase, iduronate sulfatase, galactose-6-sulfatase, β-galactosidase, or arylsulfatase B; positive urine GAGs; and the exclusion of multiple sulfatase deficiency and GM1 ganglioside disease. Twelve patients had undergone genetic testing. Pretransplantation history, physical examination, routine laboratory tests, and imaging data were collected, and the functions of organs were evaluated.

Transplantation

For the alloHSCT donor/graft source, 11 patients received 4/6 to 6/6 HLA–matched unrelated cord blood and 23 received peripheral blood stem cell, including 4 from identical sibling donors (1 donor was a MPS carrier), 2 from mismatched related donors (7/10 and 5/10 HLA-matched, 1 of which was a CD34-purified manipulated graft and the other had added cord blood to minimize the risk of graft-versus-host disease [GVHD]), and 18 from unrelated donors (8/10 to 10/10 HLA-matched). A busulfan-based myeloablative regimen, which contained busulfan 16 mg/kg to 20 mg/kg and cyclophosphamide 200 mg/kg ± fludarabine 150 mg/m^2 to 200 mg/m^2 ± rabbit antihuman thymocyte globulin 7.5 mg/kg to 10 mg/kg, was used as a conditioning regimen. Cyclosporine, methotrexate, mycophenolate mofetil, and methylprednisolone were administered to prevent GVHD.

Follow-Up

Post-transplantation follow-up data, including symptoms, signs, routine laboratory tests, and imaging data, were collected. Moreover, information about post-transplantation chimerism and enzyme levels was collected, and the post-transplantation functions of organs were evaluated using the same methods as for pretransplantation evaluation. Donor chimerism was determined by fluorescein in situ hybridization in sex-mismatched transplantations or PCR-based assessments in same-sex transplantations. *Full-donor chimerism* was defined as >95% donor-derived hematopoietic cells and *mixed chimerism* was defined as 10% to 94% donor-derived hematopoietic cells. The functional outcome of organs were determined as follows: *complete remission*, the resolution of clinical signs and symptoms, with normal imaging findings and laboratory tests; *partial remission*, the patient's condition was not completely normal but was improved after transplantation; *no remission*, no significant change after transplantation; and *progressive disease*, the condition worsened after transplantation. Complete remission and partial remission were considered *effective*, and no remission and progressive disease were considered *not effective*. Post-transplantation data were from the latest follow-up. For the 34 patients, the mean follow-up time was 24 months, and the median follow-up time was 14 months (range, 2 to 119 months).

Statistical Methods

A chi-square test was performed for between-group comparisons, the Kaplan-Meier method was used for survival analysis, a log-rank test was performed to compare survival rates, and SPSS 13 software (SPSS Inc., Chicago, IL) was used for the statistical analysis.

RESULTS

Chimerism, Enzyme Levels, and Transplantation-Related Complications

A total of 31 patients (91.2%, 31 of 34) achieved full donor chimerism, 2 achieved stable mixed chimerism, and 1 died early (thus, the status of chimerism was not assessed). After transplantation, enzyme levels reached normal in 26 patients and failed to reach normal in 1 patient (with a carrier sibling donor), although the level was higher than before transplantation in the latter patient. Enzyme level data were missing in 6 patients because of serious conditions or loss to follow-up (Table 1). No significant differences in full donor chimerism or normal enzyme levels were observed between patients who received umbilical cord blood and those who received other graft sources ($P = .606$ and $P = .627$, respectively).

The incidence of grades II to IV acute GVHD (aGVHD) was 41.1% (14 of 34), and the incidence of grades III and IV aGVHD was 11.8% (4 of 34). The incidence of moderate-to-severe chronic GVHD was 5.9% (2 of 34). Five patients died; the median time of death was 3 months (range, 2 to 6 months) after transplantation. Three patients died of severe pneumonia and respiratory failure (1 case of cytomegalovirus interstitial pneumonia and 2 cases of severe pneumonia and grades III and IV GVHD); 1 patient died of septicemia, pneumonia, hepatic veno-occlusive disease, and multiorgan failure; and 1 patient died of fulminant myocarditis at a local hospital 6 months after transplantation. One patient was in a vegetative state, a severe neurological sequelae caused by

Table 1
Chimerism, Enzyme Activity, and Transplantation-Related Complications

Outcome	n	%
Full donor chimerism	31	91.2
Normal enzyme level	25	80.6
Enzyme level < LLN ("low")	1	3.2
Unknown	5	16.1
Mixed chimerism	2	5.9
Normal enzyme level	1	50
Enzyme level < LLN ("low")	0	0
Unknown	1	50
Unknown status of chimerism	1	2.9
aGVHD		
Grade I	10	29.4
Grade II	10	29.4
Grade III	3	8.8
Grade IV	1	2.9
cGVHD		
Mild	2	5.9
Moderate	1	2.9
Severe	1	2.9
Other transplantation-related complications		
Pneumonia	11	32.3
Respiratory failure	6	17.6
Septicemia	4	11.8
Heart failure	1	2.9
Intracranial hemorrhage	1	2.9
VOD	1	2.9
Hemorrhagic cystitis	3	8.8
Immune thrombocytopenia	1	2.9
Hepatitis C infection	1	2.9
Causes of death	5	14.7
CMV interstitial pneumonia	1	20
Grade III and IV GVHD + severe pneumonia	2	40
Infection + VOD + MOF	1	20
Fulminant myocarditis	1	20

LLN indicates lower limit of normal; cGVHD, chronic GVHD; VOD, hepatic veno-occlusive disease; CMV, cytomegalovirus; MOF, multi-organ failure.