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Enzyme replacement therapy prior to haematopoietic stem cell transplantation in Mucopolysaccharidosis Type I: 10 year combined experience of 2 centres

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Abstract

Haematopoietic stem cell transplantation is the treatment of choice for the severe form of Mucopolysaccharidosis Type I, or Hurler syndrome. In many centres standard practice is to deliver enzyme replacement therapy alongside haematopoietic stem cell transplantation to improve the condition of the patient prior to transplant. We report the combined 10 year experience of this approach in two paediatric metabolic and transplant centres. Of 81 patients who underwent a first transplant procedure for Hurler, 88% (71/81) survived and 81% (66/81) were alive and engrafted at a median follow-up of 46 months (range 3–124 months). The incidence of grade II–IV acute and any chronic graft versus host disease was 17% and 11% respectively. Urinary glycosaminoglycans were significantly reduced after a period of enzyme replacement therapy, and

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further reductions were seen at 13–24 months and 25+ months after transplantation. In several individuals with decreased cardiac contractility, an improvement of their condition during enzyme replacement therapy enabled them to undergo transplantation, with one individual receiving full intensity conditioning.

Keywords

Mucopolysaccharidosis Type I; Hurler syndrome; Enzyme replacement therapy; Haematopoietic stem cell transplantation; Outcome

1. Introduction

Mucopolysaccharidosis Type I (MPS I) is a rare, inherited lysosomal storage disorder caused by a deficiency of the enzyme α-L-iduronidase (EC 3.2.1.76). This leads to accumulation of glycosaminoglycans (GAGs) in tissues throughout the body, causing organ dysfunction. In the most severe form of MPS I (Hurler syndrome) presentation is usually early in life with developmental delay, hepatosplenomegaly, musculoskeletal abnormalities, facial dysmorphism and multiple other features.

Intravenous enzyme replacement therapy (ERT) with laronidase has been available for MPS I since 2003 and is routinely used as the mainstay of therapy for patients with attenuated MPS I phenotypes. However, laronidase does not cross the blood-brain barrier and therefore cannot prevent the cognitive decline observed in Hurler syndrome. Haematopoietic stem cell transplantation (HSCT) can preserve intellectual development if performed early in the course of the disease, and is considered to be the standard of care in Hurler syndrome [1].

Many transplantation centres use ERT in combination with HSCT to improve the somatic condition of patients prior to transplantation and in an attempt to reduce transplant related mortality. Standard practice at our centres is to commence ERT at the point of diagnosis and continue through the period of donor selection and pre-transplant conditioning, until effective transplantation can be performed. This is not universal practice and there have been concerns that ERT may sensitize the patient to the enzyme, or stimulate an antibody response that has a negative effect on donor cell engraftment [2, 3].

Here we report the outcome across our two centres of MPS I patients treated with combined ERT and HSCT from 2004 to 2014. Specifically, we analyze overall survival, donor cell-engrafted survival, transplant-related complications and mortality, and change in GAG burden following combination therapy.

2. Patients and methods

MPS I patients who underwent HSCT in combination with ERT between September 2004 and June 2014 were identified from transplantation databases at Royal Manchester Children’s Hospital (RMCH) and University of Minnesota (UMN) (Table 1). The majority of patients had a classical Hurler phenotype, but in three cases HSCT was performed in patients with an intermediate (Hurler-Scheie) phenotype. All patients received weekly

laronidase infusions (0.58 mg/kg) prior to transplantation. RMCH patients discontinued laronidase following documented donor cell engraftment. UMN patients continued laronidase for an average of 8 weeks post-transplant.

Stem cell donor sources varied but the majority were well-matched unrelated cord blood grafts. Fifty-nine (73%) patients received myeloablative busulfan and cyclophosphamide with or without serotherapy and 19 (23%) received myeloablative busulfan and fludarabine with serotherapy. Serotherapy included rabbit *anti*-thymocyte globulin or alemtuzumab. Two patients, both with left ventricular cardiac dysfunction ameliorated (but not corrected) by ERT received non-myeloablative conditioning without busulfan. Patients were followed for a minimum of 3 months after transplantation.

Chimerism monitoring was performed on whole blood (RMCH) or on the myeloid fraction of peripheral blood (UMN) at defined time points after transplantation by short tandem repeats (STR) analysis or variable number tandem repeats (VNTR) analysis. Chimerism results at the time of most recent follow-up are reported. Chimerism was grouped into full, mixed or autologous categories (see Table 2 for definitions).

Urinary GAG content (in mg/mmol creatinine) was determined by the dimethylmethylene blue assay [4] in RMCH patients pre-ERT, pre-HSCT, and following transplant at variable time points. Post-HSCT samples were grouped into 12 month bins (1–12 months post-HSCT, 13–24 months post-HSCT and 25+ months post-HSCT) to compensate for missing data, and only patients with at least one pre, and one post sample were included for analysis ($n = 31$). Patients who underwent second transplants were excluded from urinary GAG analysis. Where more than one sample was measured within a bin the values for that patient bin were averaged, resulting in $n = 20–30$ patient values for each bin. Multivariate analysis of variance in JMP software (SAS) was used to compare longitudinal changes in intra-patient urinary GAG excretion between pre-ERT, pre-HSCT, 1–12 months post-HSCT, 13–24 months post-HSCT and 25+ months post-HSCT. p values represent the significance of the F-statistic, using downstream repeated measures tests in univariate analysis to determine individual differences.

The occurrence of acute and chronic graft-versus-host disease (GvHD) and the severity of acute GvHD were prospectively recorded in the institutional transplantation databases and retrospectively reviewed for frequency. The Kaplan-Meier method was used to determine the probability of overall survival (OS) and event-free survival (EFS) (with competing risk graft failure or autologous haematopoietic recovery; see Table 2 for definitions). Survival analysis was performed using IBM SPSS Statistics v22.0.

3. Results

Between September 2004 and June 2014, 81 patients (38 males, 43 females) with MPS I underwent HSCT combined with weekly laronidase infusions. The mean age at first transplantation was 14 months. Patients received a median of 13 doses (range 3–57, $n = 77$) of laronidase prior to transplantation. In four patients the exact number of doses of

laronidase received was not known. The majority of patients (64%) received unrelated cord blood.

Overall 71/81 (88%) of patients survive and 66/81 (81%) demonstrate allo-engrafted survival at a median follow-up of 46 months (range 3–124 months). Of the engrafted survivors, 49/66 (74%) were fully engrafted and 17/66 (26%) had mixed chimerism. Kaplan-Meier estimates of OS and EFS at 5 years were 86% and 80% respectively (Fig. 1). Deaths were from idiopathic pneumonia (4), GvHD (2), veno-occlusive disease (1), adenovirus (1) and sepsis (1) and in one individual cause of death was unknown (presumed cardiac event), giving a transplant related mortality incidence of 12%. Six deaths occurred within 100 days of HSCT. There were seven graft failures, all following unrelated cord blood grafts (Table 3). Six patients received a second HSCT, of whom five survive with full engraftment at last follow-up.

Acute GvHD (grades II–IV) occurred in 14/81 (17%) of patients. Grade III–IV acute GvHD occurred in 3/81 (4%) of patients. Nine patients (11%) developed chronic GvHD. One patient died of acute GvHD and one patient died of chronic GvHD. No surviving patients have ongoing chronic graft versus host disease, and those patients who required treatment have all discontinued immunosuppressive therapy.

Longitudinal urinary GAG data was available for 31 RMCH patients (Fig. 2). Compared to beginning ERT, urine GAG was significantly reduced prior to HSCT ($p = 0.006$). Urine GAG at 1–12 months post-HSCT was not significantly different than pre-HSCT ($p = 0.055$), but a significant reduction was seen from pre-HSCT to 13–24 months post-HSCT ($p = 0.0007$) and 25+ months post-HSCT ($p = 0.0001$) Urinary GAG also significantly reduced from 1–12 months post-HSCT to 13–24 months post-HSCT ($p = 0.0005$) and 25+ months post-HSCT ($p = 0.0001$); and a further significant reduction was seen from 13–24 months post-HSCT to 25+ months post-HSCT ($p = 0.025$).

4. Discussion

This is the first large multi-institutional report of outcomes in patients with Hurler syndrome receiving enzyme replacement in the peri-transplant period. The overall and donor engrafted survival rates in this cohort were very encouraging, and are favourable in comparison to outcomes reported in recent international cohorts of Hurler syndrome patients [5, 6]. Overall survival and EFS in our cohort were 86% and 80% respectively, compared to 74% and 63% respectively in a recently reported international cohort [5]. In the latter cohort, 19% received combined ERT and HSCT and these included many of the patients in this report. Rates of acute GvHD (Grades II–IV) and chronic GvHD (any grade) were low in our cohort (17% and 11% respectively), compared to 25% and 16% respectively in the international cohort [5]. A further outcome study, using exposure-targeted busulfan based conditioning regimens, reported OS and EFS of 95% and 90% respectively, with aGvHD (Grades II–IV) and cGvHD (any grade) of 13% and 15% respectively [6]. The median follow-up period (36 months) in this study was shorter than in this report (46 months), and a number of those patients are also included here.

These positive outcomes may be attributed to the increasing experience of HSCT in MPS I in the last decade in centres with appropriate metabolic and transplantation expertise. This has led to the development of standardised protocols for transplantation [5, 6] including full intensity conditioning with high dose busulfan and pharmacokinetic targeting. In this analysis, there is no evidence that the administration of ERT in combination with HSCT has a deleterious effect on engraftment or GvHD. Direct comparison with patients transplanted without ERT was not possible as only one patient underwent HSCT without ERT since 2004. In theory, ERT prior to transplantation may improve donor engraftment by altering the bone marrow microenvironment [7]. However, previous reports have not identified ERT as a statistically positive predictor of survival after HSCT [2, 5, 8] or of long term outcomes [9]. One small study appears to show that combined ERT and HSCT may be associated with improved cognitive outcomes after transplant [10].

Administration of ERT led to a significant reduction in urinary GAG in our cohort, and further reduction was seen from pre-HSCT levels to 13–24 months post-HSCT and from 13–24 months post-HSCT to 25+ months post-HSCT, suggesting that substrate reduction continues after transplantation (Fig. 2). Previous observations have shown that substrate reduction in the long term is greater in HSCT treated individuals than in ERT treated patients [11].

A clear clinical improvement was seen in certain patients during ERT. This led in some cases to patients who otherwise may not have tolerated full intensity conditioning receiving a fully myeloablative regimen. Full intensity conditioning regimens with targeted busulfan have been shown to be associated with improved rates of engrafted survival [12], and a recent study in MPS I mice suggested that reduced intensity conditioning led to decreased haematopoietic stem cell engraftment in the bone marrow due to GAG mediated blockade of the CXCL12/CXCR4 migration axis [13].

One patient who had significant upper airway obstruction requiring non-invasive ventilation at the point of commencing ERT was subsequently able to discontinue ventilation prior to transplantation, and went on to receive a successful transplant with full intensity conditioning. Three patients had severely impaired cardiac function at the point of diagnosis. One patient with severe left ventricular dysfunction (LVEF 25% at diagnosis) received 3–4 months of ERT prior to transplantation in order to improve myocardial function. She underwent HSCT while receiving a continuous infusion of milrinone in association with a non-myeloablative conditioning regimen for a post-ERT LVEF of 39%. After autologous reconstitution a second non-myeloablative transplant was performed and the patient is alive and remains fully engrafted to date. A second patient had severe dilated cardiomyopathy at the point of referral for transplantation, with fractional shortening of <10%. A reduced intensity conditioning regimen was initially considered. However, he showed evidence of improving cardiac function during ERT and therefore continued laronidase for 36 weeks. Prior to transplant fractional shortening was 26%. He underwent successful HSCT with full intensity conditioning and remains alive and fully engrafted at most recent follow-up. A third patient with LVEF of 25% at diagnosis received three months of ERT, resulting in a post-ERT LVEF of 45%. However, left ventricular end-diastolic diameter remained large, and due to concerns about lack of cardiac reserve he underwent non-myeloablative

transplant and a continuous milrinone infusion. He subsequently died of overwhelming adenoviral infection.

A potential concern of combined ERT and HSCT is that delivering ERT could delay transplant in a disease where earlier transplantation is known to be associated with improved outcome [14]. Patients in this cohort commenced ERT at diagnosis and continued during the period of donor selection and conditioning, and HSCT was performed within standard time scales for transplantation at both centres. Though several patients received over 20 weeks of ERT this was most often due to delays in referral, transfer from international centres or based on the choice of the families. One pair of syngeneic twins had their transplants staggered for logistical purposes leading to a longer course of ERT in one twin. HSCT was delayed in one patient due to septic arthritis. In three cases HSCT was delayed in order to deliver a prolonged course of ERT. Two patients received ERT to improve cardiac function as described and one patient who was diagnosed antenatally received prolonged course ERT and was transplanted at 6 months of age.

Antibodies to laronidase are known to develop in the majority of patients with Hurler syndrome treated with ERT. Antibodies were not measured in all patients in this cohort. However, *anti*-laronidase IgG titres were analysed in a subset of eight RMCH patients. These were reported in a previously published longitudinal study, in which 7/8 patients developed high titre antibodies during ERT [15]. Development of antibodies appeared to precede an arrest in substrate reduction. The antibody response was abrogated following HSCT, with a median time to immune tolerance of 101 days [15]. Though it is likely that many patients in the cohort described here developed antibodies, ERT can be seen to have a clear biochemical and clinical effect, evidenced by the reduction in urine GAG prior to HSCT as well as marked clinical improvement during ERT in certain cases.

Engraftment rates in this analysis were very encouraging, with 54/71 (76%) surviving patients fully engrafted after one or more transplants. Where graft failures did occur the majority were managed successfully with a second HSCT. This suggests that despite the likelihood that most patients developed antibodies, engraftment was not impaired. Stem cell gene therapy is an approach that has been investigated in patients with metachromatic leukodystrophy [16] and in MPS IIIA mice [17], and could be a potential strategy for MPS I. In this situation, the potential effect of antibodies to ERT on the function or engraftment of gene modified autologous cells should be considered.

Combined ERT and HSCT remains the standard of care for patients with Hurler syndrome at many centres. The outcomes of this cohort suggest that this practice is safe. Previous reports have not identified combined ERT and HSCT as a statistically significant predictor of improved survival. As transplant outcomes have improved for Hurler syndrome patients, a large number of patients would likely be required to demonstrate significance. However, in this report there is clear evidence of clinical improvement during ERT in certain patients. Pre-transplant risk factors affecting tolerability of HSCT have been identified [18], predominantly respiratory disease, which could potentially be modified by ERT. An analysis that concentrated on such higher risk patients may be able to better demonstrate any beneficial effect of peri-transplant ERT.

Abbreviations

EFS	event-free survival
ERT	enzyme replacement therapy
GAG	glycosaminoglycan
GvHD	graft versus host disease
HSCT	haematopoietic stem cell transplantation
LVEF	left ventricular ejection fraction
MPS I	Mucopolysaccharidosis Type I
OS	overall survival
STR	short tandem repeats
VNTR	variable number tandem repeats

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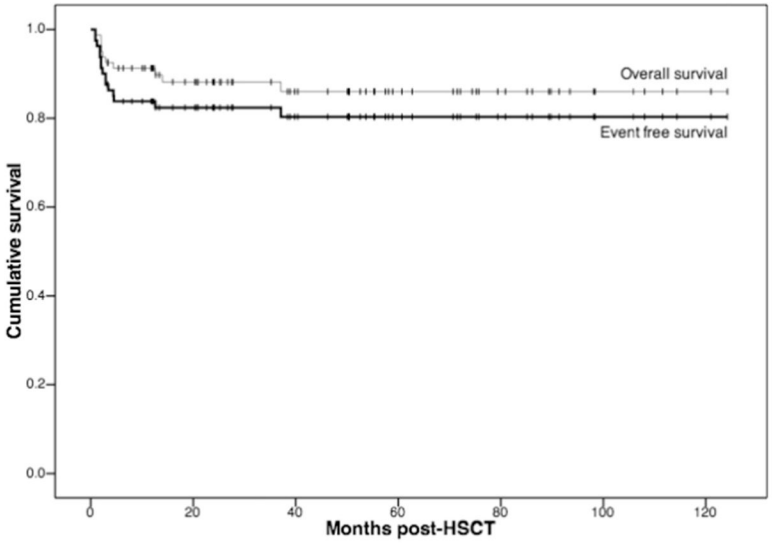

Fig. 1.
Overall and event free survival in MPS I patients post-HSCT.

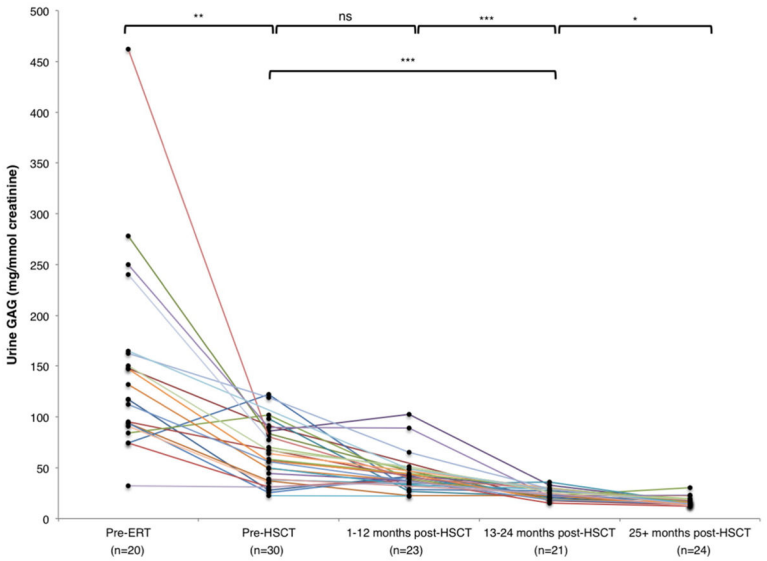

Fig. 2.

Urinary GAG pre- and post-HSCT. Longitudinal analysis of total urinary GAGs measured in MPSI patients pre-, and post-HSCT. Samples were grouped into 12 month sample bins and figures averaged within bins where several samples were present. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ns = not significant ($p \geq 0.05$).

Table 1

Patient, donor and transplantation characteristics.

	n	%	Missing	Median	Range
Patient characteristics					
Overall	81				
RMCH/UMN	46/35	57/43			
Gender (male/female)	43/38	53/47			
ERT doses before HSCT			4	13	3–57
Age at HSCT (months)				13.1	3.9–34.5
Donor characteristics					
Related (14 BM/5 PBSC/1 CB)	20	25			
Unrelated donor (7 BM/2 PBSC)	9	11			
10/10	7	78			
9/10	1	11			
8/10	1	11			
Unrelated CB	52	64			
UCB HLA matching			3		
6/6	34	65			
5/6	15	29			
Transplant characteristics					
Conditioning					
Bu/Cy	7	9			
Bu/Cy/ATG	19	23			
Bu/Cy/Alem	33	41			
Bu/Flu/ATG	11	14			
Bu/Flu/Alem	8	10			
Bu/Flu/Thiotepa	1	1			
Non-Bu	2	2			

Bu, busulfan; Cy, cyclophosphamide; ATG, *anti*-thymocyte globulin; Alem, alemtuzumab; Flu, fludarabine.

Table 2

Definitions of transplant outcomes.

Term	Definition
Primary graft failure	Failure to achieve ANC N 500 cells/μL on or before day +42
Delayed primary graft failure	Persistent ANC b 500 cells/μL after day +42
Fully engrafted	≥95% donor-derived haematopoietic cells
Mixed chimerism	20–94% donor-derived haematopoietic cells
Autologous reconstitution	b20% donor-derived haematopoietic cells

ANC, absolute neutrophil count.

Table 3

Graft failures.

Pattern	Days post-HSCT	Management	Outcome
Primary	36	2nd HSCT	Alive & fully engrafted
	56	2nd HSCT	Died
Delayed primary	87	2nd HSCT	Alive & fully engrafted
	103	2nd HSCT	Alive & fully engrafted
	137	2nd HSCT	Alive & fully engrafted
Autologous reconstitution	27	2nd HSCT	Alive & fully engrafted
	54	–	Died (day +65)