

ORIGINAL ARTICLE

Allogeneic hematopoietic cell transplantation (HCT) in Hurler's syndrome using a reduced intensity preparative regimen

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Allogeneic hematopoietic cell transplantation (HCT) in patients with Hurler's syndrome can improve survival and ameliorate many aspects of Hurler's syndrome including neurologic decline and cardiac compromise. Unfortunately, the toxicity of traditional preparative regimens to organs affected by the syndrome may have deleterious effects. Additionally, despite the intensity of these regimens, achieving stable donor chimerism can be difficult. We report transplant outcomes following a reduced intensity, highly immunosuppressive preparative regimen consisting of alemtuzumab, fludarabine and melphalan prior to HCT in seven patients with Hurler's syndrome treated at two centers. Six patients received grafts from unrelated donors and one received a sibling donor graft. The preparative regimen was well tolerated. All patients had initial donor engraftment at 100 days; one patient had delayed loss of donor chimerism. There was no severe acute GVHD (no GI GVHD of grade II or more, no grade IV skin GVHD). Six of the seven children are surviving at a median of 1014 (726–2222) days post transplant. This reduced intensity preparative regimen has the potential to support engraftment and improve survival and outcome in patients with Hurler's syndrome undergoing HCT.

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Introduction

Hurler's syndrome is a lysosomal storage disease resulting from α -L-iduronidase deficiency.^{1,2} Symptoms are a consequence of deposition of non-degraded heparan sulfate and dermatan sulfate in specific organs. The most

debilitating effect of Hurler's syndrome is neurocognitive decline, the pathophysiology of which is unclear, but which may occur as a consequence of cerebral deposition of substrate, long-term effects of sleep apnea, frequent ear infections, airway compromise, general health issues and so on. Hydrocephalus can develop as CSF absorption is impaired. Hurler's patients also develop cardiomyopathy, airway compromise, hepatosplenomegaly and dysostosis multiplex characterized by skeletal deformities. The condition is eventually fatal due to complications from cardiac, respiratory or neurologic deterioration. Therapy for Hurler's syndrome includes enzyme supplementation, but the enzyme is unable to cross the blood brain barrier.

Survival in children with Hurler's syndrome can be improved with hematopoietic cell transplantation (HCT) when performed before severe neurologic decline. Improvement in bone disease and cardiac valve abnormalities is less notable post transplant than resolution of substrate deposition in well-vascularized organs such as the liver, spleen, myocardium and brain.^{3,4}

Nevertheless, the risks associated with transplant in these patients could be increased as the deposition of mucopolysaccharide in tissues that commonly sustain damage during HCT may compound toxicity from the conditioning regimen. Mucopolysaccharide deposition in the airway of Hurler's patients increases the risk of airway compromise resulting from mucositis, and can make intubation difficult.⁵ Fatal cardiac events have been reported in HCT recipients with Hurler's syndrome.^{6–8} This may be due in part to deposition of mucopolysaccharide in the myocardium and/or the coronary arteries and may add to the increased risk from inflammation associated with radiation and chemotherapy. Mucopolysaccharide deposition in the liver could increase the risk of either veno-occlusive disease (VOD) or GVHD as both of these processes have been associated with previous or ongoing tissue injury.^{9,10} Neurological decline is a dominant feature of Hurler's syndrome and the chief impetus for early transplantation.^{11,12} However, subtle neurological deficits and behavioral changes have also been associated with HCT and are related to factors, such as recipient age, conditioning therapy and medication-related toxicity.^{13,14} Although transplantation ultimately leads to improvement in neurological outcome for many patients, the deposition of

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mucopolysaccharide in the brain may increase vulnerability to neurologic toxicity associated with HCT.

A further problem encountered with HCT in Hurler's syndrome patients is that despite the use of standard conditioning regimens utilizing high-dose chemotherapy and sometimes radiotherapy with their attendant toxicities, achieving stable donor chimerism can be challenging.⁷ Hemolytic anemia, infections and pulmonary hemorrhage can also complicate HCT in these patients.¹⁵

New HCT preparative regimens aim to reduce toxicity while facilitating engraftment using intense immunosuppression rather than myeloablation.^{16,17} In this study, we describe a series of patients with Hurler's syndrome receiving HCT using an immunosuppressive reduced intensity conditioning regimen that incorporates the use of the anti-CD52 monoclonal antibody alemtuzumab.

Patients and methods

Seven children with Hurler's syndrome underwent HCT at two pediatric stem cell transplant centers (five at Cincinnati Children's Hospital Medical Center; two at St Louis Children's Hospital and Washington University in St Louis). The two patients reported here from St Louis were included in a previous paper.¹⁸ The HCTs were performed consecutively at each center. Permission for the review of these patients was obtained from the IRBs of both institutions. Patient characteristics are shown in Table 1. Median age at transplant was 18 months (range 12–36 months). Three patients had known cardiac valve abnormalities and one additional patient (patient no. 5) had decreased cardiac function as demonstrated by a left ventricular shortening fraction (LVSF) of 26%. This had decreased from a shortening fraction of 30% 1 month before. None had liver dysfunction at the time of transplantation. Enzyme replacement therapy (ERT) with Aldurazyme was given weekly for patient number 2 for 5 months prior to transplant and for 2 months prior to transplant for patient number 7. Patient numbers 3 and 5 were given Aldurazyme every 2 weeks for 5 and 4 months, respectively, prior to transplant. Patient number 1 was given Aldurazyme every 2 weeks for 5 months prior to her first transplant, but then did not receive additional therapy prior to her second transplant reported here. Patient numbers 4 and 6 did not receive any ERT prior to

transplant. None of the patients received ERT during conditioning, and only patient number 7 received Aldurazyme after transplant, being treated weekly from day +7 to day +60.

Six patients received 8/8 HLA matched grafts (matched at A, B, C and DRB1 alleles by high-resolution typing) and one received a 7/8 matched graft mismatched at the A locus (patient number 3). Six donors were unrelated to the patient, and one was a sibling. Five patients received grafts obtained from a bone marrow harvest, one received stem cells harvested by peripheral blood leukapheresis after G-CSF mobilization of a sibling donor, and one patient received a cord blood graft. One patient (patient no. 1) received a previous bone marrow allograft with a conditioning regimen of busulfan, cyclophosphamide and rabbit ATG 288 days prior to the HCT reported here and had secondary graft failure. Subsequently, she did not exhibit serious neurologic decline and continued to have good cardiac function with no other organ dysfunction noted.

All patients received a preparative regimen consisting of alemtuzumab, fludarabine and melphalan as previously described.¹⁸ Alemtuzumab was given over 4 days from day –22 to day –19; dosing was 3 mg on day –22, 10 mg on day –21, 15 mg on day –20 and 20 mg on day –19. Fludarabine was given at a dose of 30 mg/m² per day for 5 days on days –8 to –4 (total dose = 150 mg/m²). Finally, melphalan was given on day –3 at a dose of 140 mg/m². GVHD prophylaxis consisted of cyclosporine, methotrexate (10 mg/m² day +1, 7.5 mg/m² days +3 and +6), and methylprednisolone. Cyclosporine commenced on day –3 at a dose of 2.5 mg/kg per dose (3.5 mg/kg per dose for patients under 25 kg body weight) every 12 h aiming for a serum trough of 250–350 ng/ml. Cyclosporine was administered orally as tolerated and was gradually tapered after day +100 in the absence of GVHD. Methylprednisolone was started on day +7 at a dose of 1 mg/kg per day and tapered between day +28 and day +56 as allowed by clinical circumstance. All patients received G-CSF starting on day +1 for patient number 4, who received a cord blood transplant, and on day +7 for everyone else. G-CSF was continued until the ANC was >1.5 × 10⁹ per liter for at least 3 days. Patients were kept in positive pressure isolation rooms with high-efficiency particulate air filtration. All received antifungal prophylaxis with fluconazole, voriconazole, weekly intravenous ambisome or daily

Table 1 Details in HCT recipient demographics

Patient	Sex/age (mo)	Graft	Cardiac abnormalities	LVSF baseline (%)	Cell dose (CD34 per kg × 10 ⁶)
1	F/36	8/8 unrelated marrow	No	47	4.0
2	F/17	8/8 unrelated marrow	No	33	7.2
3	M/14	7/8 unrelated marrow	Trivial mitral and tricuspid insufficiency, small ASD, L–R shunting	31	9.4
4	F/15	8/8 unrelated cord	Small PFO, L–R shunting, mild thickening of aortic valves	37	3.7
5	M/17	8/8 unrelated marrow	Thickened valves, LV enlargement	26	6.0
6	F/14	8/8 unrelated marrow	Mild mitral insufficiency	35	2.4
7	M/12	8/8 related PB	No	35.9	13

Abbreviations: ASD = atrial septal defect; HCT = hematopoietic cell transplantation; L = left; LV = left ventricular; LVSF = left ventricular shortening fraction; PB = peripheral blood; PFO = patent foramen ovale; R = right.

casprofungin. *Pneumocystis carinii* pneumonia prophylaxis was given using pentamidine or bactrim. Acyclovir was administered during transplantation to patients positive for HSV by serology. Patients with fevers were placed on broad-spectrum antibiotics which were continued until engraftment. Blood products given during transplant were leukocyte depleted and irradiated. Hemoglobin was maintained above 7 g/dl and platelets above 20×10^9 liter on all patients until engraftment.

Chimerism was determined using a FISH study for the Y chromosome in the case of sex mismatched donor/recipient pairs, and STR analysis in the case of same sex donor/recipient pairs.

Results

Hematopoietic recovery

Patient outcomes are described in Table 2. All patients had an ANC $>0.5 \times 10^9$ per liter within 21 days of transplantation (median 13 days, range 11–21 days) and platelet recovery ($>20 \times 10^9$ per liter) at a median of 16 days (range 11–82 days). All patients initially had complete donor engraftment at 1 month (defined as greater than 90% donor cells), but two patients subsequently developed mixed chimerism. Patient number 5 had 100% donor chimerism on day 100 which decreased to 52% donor cells 1 day prior to his death on day 157 post-HCT. Patient number 7 had recovery of host hematopoiesis by day 200 post transplant (10% residual donor cells). Immunosuppression was withdrawn and lymphocyte engraftment was retained but neutrophil engraftment was lost. No donor leukocyte infusions were given. This patient subsequently underwent a successful myeloablative peripheral blood stem cell transplant with busulfan and cyclophosphamide conditioning from the same sibling donor at 24 months of age with achievement of full donor chimerism that has been sustained for 12 months.

GVHD

One patient developed moderate acute GVHD (grade III skin and grade I GI). Four of the remaining six patients had mild GVHD (grades I–II skin). All GVHD responded

to treatment and resolved. Five of six patients have discontinued all immunosuppression.

Regimen-related toxicity and infections

Patient number 5 was intubated for respiratory distress shortly before his death at day +147 from sterile interstitial pneumonitis. No pulmonary toxicity was noted in other recipients. Four of the seven patients had elevations of their liver enzymes in the first 20 days after transplant (ALT 311–572 U/l), but only one patient (patient no. 1) had VOD, which resolved spontaneously. Patient number 5 had an asymptomatic decrease in his LVSF by echocardiography from 26% prior to transplant to 18% at 100 days post-HCT. An echocardiogram obtained at day +136 showed a stable LVSF of 21% and a further one obtained in the pediatric intensive care unit on day +142 after intubation for respiratory distress showed no change in his LVSF at that time. Besides chlorothiazide and enalapril given to treat hypertension, and dopamine, epinephrine and milrinone given in the intensive care unit for hypotension 2 days prior to his death, no medical treatment was given for decreased left ventricular function. No pericardial effusion was seen on any of his echocardiograms. No other patients exhibited cardiac toxicity or a decline in cardiac function. No episodes suggesting CNS toxicity were seen. All patients had Lansky scores of at least 80 or above at day +100 post transplant. Patient number 1 had a positive serology for CMV before transplant. All other patients and all donors were CMV serology negative. Patients were screened weekly for CMV and EBV by blood PCR until day 100. There was no CMV viremia observed in any of the patients.

Survival

Six out of the seven patients are currently surviving at a median of 870 days post-HCT (range 583–2079 days). One patient died 147 days post-HCT of interstitial pneumonitis with no infectious agent identified by culture or bronchoscopy. No autopsy was performed.

Quality of life outcomes

All surviving patients are fully ambulatory after transplant with the exception of patient number 1 who was

Table 2 Outcomes following HCT

Patient	Days post BMT	Engraftment (days to ANC per liter)	LVSF at 100 days (%)	VOD	GVH (location/grade)	Lansky score at 100 days	Donor chimerism		
							100 days (%)	1 year (%)	Most recent (day post-HCT)
1	Alive 866	17/73	35	Yes	No	80	100	100	100% (761)
2	Alive 1012	11/13	47	No	Skin/III GI/I	90	99.6	100	100% (715)
3	Alive 1014	13/16	36	No	Skin/II	100	100	100	100% (948)
4	Alive 726	21/82	39	No	Skin/I	90	100	100	100% (639)
5	Died 147	17/21	18	No	Skin/I	80	97.2	NA	52% (146)
6	Alive 2222	12/13	34.9	No	No	90	>99	>99	>95% (2005)
7 ^a	Alive 1394	12/11	26	No	Skin/I	100	74 ^b	0 ^b	NA

Abbreviations: LVSF = left ventricular shortening fraction; HCT = hematopoietic cell transplantation; NA = not applicable; VOD = veno-occlusive disease. ^aPatient subsequently lost graft and was successfully retransplanted 13 months after first transplant using a preparative regimen that included busulfan and cyclophosphamide. See text.

^bValues shown for patient number 7 were obtained from bone marrow. All other chimerism values shown here are from peripheral blood.

ambulatory until placed in a spica cast following a recent surgery on her right hip. All surviving patients are conversant and speaking in sentences, except patient number 3 who has a limited vocabulary (approximately 15 words). Hearing aids are required for patient number 1 for mild sensorineural hearing loss and patient number 3 for mild to moderate sensorineural hearing loss.

Discussion

HCT can improve many clinical manifestations of Hurler's syndrome if performed early in the course of the disease.^{2,3} However, deaths from regimen-related toxicity (RRT) and difficulty in achieving stable donor chimerism have been important limitations to success.^{7,8,19,20}

Our experience demonstrates that a hematopoietic cell transplant can be performed in Hurler's syndrome patients using a reduced intensity preparative regimen with acceptable RRT and achievement of stable donor chimerism in the majority of cases. There was no prolonged aplasia or primary graft failure in this small study, although there was one patient with secondary graft failure (Patient number 7) and another whose percent donor chimerism had been decreasing at the time of his death (Patient number 5). This is encouraging when compared to a primary graft failure rate of 38% and an overall graft failure rate of 48% in a series of 40 patients receiving unrelated grafts reported by Peters *et al.*⁷, although this difference could also be explained in part by the better HLA matching reported in this study. Other studies have subsequently also reported a high frequency of graft failure. Souillet *et al.*²¹ reported a series of 27 children with a primary graft failure rate of 16% and an overall graft failure rate of 22% employing a preparative regimen using busulfan and cyclophosphamide. In agreement with our report, Grigull *et al.*²² showed no graft failure in a series of five patients transplanted using a preparative regimen consisting of fludarabine, ATG and busulfan.

Successful early donor engraftment may be related to the use of alemtuzumab in the conditioning. Alemtuzumab is a monoclonal antibody against CD52 that effectively depletes T-cells and dendritic cells that could be expected to mediate graft rejection and GVHD.^{23,24} Alemtuzumab was given 3 weeks prior to HCT to minimize *in vivo* T-depletion of the donor graft, as alemtuzumab has a half-life of approximately 2 weeks.²⁵ Fludarabine is also a potent lympholytic agent, and may have been synergistic for host immunosuppression.

Two of the seven children went on to develop mixed donor chimerism (<80% donor cells) after day 100. One of these patients died before the stability of mixed donor chimerism could be established, and may have lost engraftment following an infectious complication.²⁶ The second child gradually lost an allograft from a sibling who was heterozygous for the disease. He successfully underwent a second transplant using a myeloablative preparative regimen of busulfan and cyclophosphamide 1 year later which he tolerated without major toxicities.

Since Hurler's syndrome involves organs known to be susceptible to RRT in HCT, including the brain, liver, heart

and lungs, these patients might be expected to manifest a higher degree of vulnerability to toxicity from classical conditioning regimens such as those using busulfan, high-dose cyclophosphamide and total body irradiation. In particular, a high incidence of diffuse alveolar hemorrhage has been described following myeloablative HCT in Hurler's patients.²⁷ The reduced intensity regimen used in our patients was well tolerated and had a low incidence of RRT. No patient developed upper airway complications or pulmonary alveolar hemorrhage as have been described in other studies and mucositis was modest.^{15,28,29}

Although six of seven HCT recipients received unrelated donor allografts, only one patient had moderate acute GVHD (grade I GI and grade III skin). As GVHD may be related to tissue damage, there is a possibility that a reduced intensity preparative regimen with adequate GVHD prophylaxis may be associated with less GVHD than the use of more intense preparative regimens. Additionally, alemtuzumab eliminates antigen presenting dendritic cells implicated in the development of GVHD.²⁴ Furthermore, it is a potent lympholytic agent even at very low levels, below the sensitivity of detection. It is possible that this afforded some lymphocyte depletion of the allograft, despite early administration, also contributing to the low incidence of severe acute GVHD. Our experience may corroborate early evidence that the incidence and severity of GVHD are reduced when alemtuzumab is used in preparative regimens.³⁰⁻³²

Although it was only done in patient number 7, consideration may be given to ERT immediately following HCT.³³ As the correction of neurological defects from HCT may be delayed after transplant, continuation of ERT may potentially ameliorate progression of the disease during this time period. Additionally, it may provide some protection from progression of the disease in the case of graft failure. The effects of ERT on engraftment if any will need to be studied in greater detail in that setting.

In summary, our data suggest that the use of a preparative regimen containing alemtuzumab, fludarabine and melphalan can be used for successful HCT in Hurler's syndrome with at least equivalent rates of engraftment, RRT and GVHD to those reported in other studies. Our experience suggests that the approach described here warrants further evaluation in HCT for children with Hurler's syndrome. A larger trial would be needed to confirm the initial promising results reported here.

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