Bone Marrow Transplantation (2003) 31, 1105–1117

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Hurler Syndrome

Outcome of 27 patients with Hurler's syndrome transplanted from either related or unrelated haematopoietic stem cell sources

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Summary:

Over the last 15 years, we have performed a total of 30 haematopoietic stem cell transplants on 27 children suffering from Hurler's syndrome. These children were of median age 11 months at the time of diagnosis and 25 months at the time of transplantation. The phenotype was severe in 21 cases (78%). The donor was familial in 13 cases: nine genotypically identical, one phenotypically identical father and three HLA-mismatched donors. Unrelated donors were selected in 17 cases: four phenotypically identical and 13 with 1–4 HLA mismatches. The conditioning regimen generally consisted of busulphan 600 mg/m^2 plus cyclophosphamide (Endoxan®) 260 mg/kg and cyclosporin with methotrexate for GvHD prophylaxis. Rabbit anti-thymocyte globulin (Thymoglobuline®) was given for all unrelated or familial mismatched transplantations. The median nucleated cell dose infused was 6.00×10^8 TNC/kg. No bone marrow (apart from one) was T cell depleted. For first transplants, engraftment was observed in 23/27 patients (pts) (85%). Primary graft failure was observed in 4/27 patients (16%), two were retransplanted from an unrelated donor, one with success. Four patients have died. The primary cause of death was infection in three cases (TRM : 11%) and disease progression in one case, after primary graft failure. Of the 23 living patients, two have disease progression after graft failure and 21 (78%) have functional grafts with a favourable long-term outcome after a median follow-up of 4.7 years, having either full or mixed chimaerism. Among surviving patients with functional grafts, 13 (62%) were transplanted from unrelated donors of whom 10 (77 %) had HLA disparities. There was a remarkably low incidence of GvHD. In our experience, haematopoietic stem cell transplantation using an HLA-matched familial donor or an HLA-matched or -mismatched unrelated donor without T cell depletion or irradiation can achieve a favourable outcome in Hurler's syndrome, with improved cognitive function, but with a limited effect on the corneas and skeleton.

Bone Marrow Transplantation (2003) **31,** 1105–1117. doi:10.1038/sj.bmt.1704105

Keywords: Hurler's syndrome; mucopolysaccharidosis; unrelated donor; related donor; haematopoietic stem cell transplantation; HLA; thymoglobuline

Hurler's syndrome (MPS IH) is a mucopolysaccharidosis due to a deficiency of lysosomal enzyme activity of α-L-iduronidase, which is needed to degrade glycosaminoglycans (GAGS). The consequent accumulation of heparan sulphate and dermatan sulphate substrates leads to the characteristic facial features, hepatosplenomegaly, cardiac and pulmonary disease, progressive mental retardation and skeletal abnormalities, which become evident by 1 year of age in the severe form. The consequence of this progressive autosomal recessive inborn error is premature death by 8 years of age. Since 1980, bone marrow transplantation (BMT) has been used for the treatment of patients with lysosomal storage diseases with the objective of correcting the inborn storage error by replacing the patient's defective macrophages by marrow-derived donor macrophages. Hobbs *et al*[1] and Krivit *et al*[2] showed clearly that BMT could provide metabolic components and cells that can rapidly correct the enzyme deficiency. Since this first report, selected children with Hurler's syndrome have been transplanted worldwide with a favourable outcome in terms of improvement of neuropsychological functions and long-term survival,[3,4] but with progression of skeletal and corneal abnormalities. The encouraging results obtained with genotypically identical donors[5] prompted some teams to extend to other related donors or to unrelated donors.[6] In a previous study,[7] we reported our experience in 13 patients with Hurler's syndrome, which included three unrelated bone marrow transplants.

Here we report 15 years of cumulative experience for 27 patients suffering from Hurler's syndrome who received 30

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Received 28 May 2002; accepted 13 January 2003

haematopoietic cell transplants: 13 from related donors (including two cord blood transplants), and 17 from unrelated bone marrow donors (UBMDs). In our centre, the first transplant from an UBMD for Hurler's disease was carried out in 1990 from an HLA-mismatched donor with promising results which encouraged us to proceed with such a transplant when an HLA-identical UBMD was not identified right away. This option was proposed in order not to delay BMT. In cases of UBMDs, Thymoglobuline® was added to the standard chemotherapy conditioning regimen, which did not include donor T-cell depletion or irradiation. The purpose of this publication is to update our results for the treatment of Hurler's syndrome[7] using related and unrelated haematopoietic cell sources, and to focus on the beneficial effects and the limitations of the procedure, particularly in patients with a follow-up longer than 3 years post transplantation.

Materials and methods

Patient characteristics

From January 1986 to December 2001, we performed 30 consecutive transplants on 27 patients with Hurler's syndrome: 15 girls and 12 boys aged 11 months (m) (median) at the time of diagnosis (range: 2–87 m) and 25 months (median) at the time of transplantation (range: 14–96 m). In three cases, patients were transplanted twice; from the same identical sibling donor after graft rejection in one case, and from a UBMD after graft failure from the father as donor in two cases. Patient characteristics are shown in Table 1. Patients no. 10, 16 and patients no. 18, 20 are siblings; in the former family, despite the disease in one of their children, the parents were opposed to prenatal diagnosis and patient no. 16 was diagnosed at birth. In the latter family, the diagnosis was made in the older child at the time of birth of the second who also suffered from the disease.

Clinical diagnosis was confirmed by increased excretion of dermatan and heparan sulphates in the urine[8] and deficiency of α-L-iduronidase in leucocytes.[9,10] The three common mutations in France (Q70X, P533R, W402X) were sought in all patients and a few patients had complete gene sequencing carried out. The phenotypes, evaluated by the same clinicians in all patients are classified as follows: 21 patients (78%) had a severe phenotype characterised by early diagnosis at a median age of 10 months (range: 2–40 m) and/or signs of severe dysostosis and dysmorphia; five patients had an intermediate phenotype with late diagnosis (median 38 m), moderate dysmorphia and dysostosis and multiple hyperdense areas in the white matter on MRI examination. One patient (no. 4) had a moderate phenotype with a diagnosis made at 7 years 3 months with only macrocrania, short stature, very mild dysostosis,

Table 1 Patient's characteristics

Patients no	*Ethnic origin*	*Age at diagnosis*	*Age at transplant*	*Date of BMT*	*Phenotype*	*Genotype*	*Current age*
1	French	7 m	14 m	31/01/86	Severe	W402X/Q70X	17 y 1 m
2	French	2 y 3 m	4 y 10 m	27/02/87	Severe	Q70X/ ?	19 y 8 m
3	French	2 y 3 m	3 y	23/01/90	Severe	W402X/134del12	14 y 11 m
4	French	7 y 3 m	8 y	05/09/91	Mild	P533R/P533R	18 y 2 m
5	North African	4 y 8 m	5 y 7 m	18/02/92	Intermediate	S633L/S633L	
5•			6 y 8 m (2e)	03/03/93			15 y
6	North African	3 y 2 m	6 y 5 m	15/12/92	Intermediate	L209R/L209R	15 y 5 m
7	French	5 m	20 m	27/01/93	Severe	W402X/W402X	
7•			2 y 10 m (2e)	24/03/94			Deceased
8	French	7 m	14 m	09/03/93	Severe	W402X/W402X	10 y
9	North African	4 y 8 m	7 y 3 m	29/01/94	Intermediate	P533R/Y581X	Deceased
10	North African	3 y	4 y 3 m	04/11/94	Intermediate	P533R/P533R	11 y 6 m
11	French	11 m	4 y 1 m	14/02/95	Severe	W402X/ ?	11 y
12	French	13 m	23 m	12/01/96	Severe	W402X/1124delC	7 y 10 m
13	French	7 m	14 m	20/09/96	Severe	W402X/Q70X	6 y 5 m
14	French	8 m	14 m	17/01/97	Severe	W402X/W402X	
14•			26 m (2e)	23/01/98			6 y 1 m
15	French	9 m	21 m	07/03/97	Severe	W402X/134del 12	6 y 7 m
16	North African	2 m	16 m	02/04/97	Intermediate	P533R/P533R	6 y 3 m
17	French	15 m	2 y 1 m	13/06/97	Severe	W402X/W402X	6 y 7 m
18	French	3 y 4 m	3 y 10 m	03/04/98	Severe	W402X/Q70 X	Deceased
19	French	6 m	2 y 9 m	03/11/98	Severe	W402X/ ?	Deceased
20	French	2 m	17 m	06/11/98	Severe	W402X/Q70X	4 y 6 m
21	French	12 m	20 m	20/11/98	Severe	W402X/Q70X	4 y 9 m
22	French	11 m	26 m	16/04/99	Severe	W402X/?	4 y 10 m
23	French	26 m	35 m	01/10/99	Severe	Q70X/?	5 y 1 m
24	French	9 m	25 m	04/11/99	Severe	W402X/W402X	4 y 3 m
25	North African	15 m	23 m	16/06/00	Severe	P533R/?	3 y 6 m
26	N. African/French	10 m	22 m	23/02/01	Severe	W402X/ ?	2 y 8 m
27	French	8 m	19 m	13/04/01	Severe	W402X/W402X	2 y 3 m

• = second BMT; ? = allele mutation have not yet been characterised; m = months; y = years.

corneal clouding, a normal MRI and an intelligence quotient (IQ) of 103.

Eligibility for BMT

The decision about eligibility of a patient for BMT results from a detailed multidisciplinary evaluation including developmental scales, ID/IQ testing, CNS function (including peripheral nerves and brain), neuroradiology and metabolic and genetic studies to assess and correlate phenotypic and genotypic severity. The decision to include a patient in a BMT programme is made before it is known whether or not a suitable family donor exists. In the absence of a genotypically identical sibling donor, UBMD searches are rapidly initiated with the purpose of obtaining a suitable donor before irreversible cerebral damage has occurred. Patients were included in a BMT programme after local consensus that they had the required intelligence quotient/development quotient (IQ/DQ) and good clinical status. For all patients with the severe phenotype, the IQ/DQ required for graft eligibility is $\geqslant 70$.

Patients who did not have HLA-identical siblings were enrolled in an unrelated BMT procedure. Searches for an HLA-A, -B, -DR-identical donor were started simultaneously on every registry and were often extended to donors having one or more HLA class I mismatches.

Donor characteristics and HLA data

Patients who received transplants from relatives were genotyped at the time of the familial investigation for a related donor. Their HLA typing was determined serologically by standard two-stage complement-dependent microlymphocytotoxicity testing.[11] For unrelated donors, HLA typing was also initially performed by serology. At the end of 1991, patients and donors were typed by serology for class I and molecular biology for class II. In 1996, DNA typing for HLA class I alleles was introduced. Currently, we perform DNA typing of alleles at nine polymorphic loci: alleles at the HLA-A*, -B*, -Cw*, -DRB1*, -B3*, -B4*, -B5*, -DQB1* and -DPB1* identified with the use of the polymerase chain reaction (PCR) with sequence-specific oligonucleotide probes[12,13] or PCR-sequence-specific primers. High-resolution typing for class I and/or class II alleles were retrospectively completed for recipient and donor pairs who had been transplanted between 1990 and 1996.

The donor was related in 13 cases: nine were genotypically identical, of whom one was a cord blood transplant, one was a phenotypically identical father and three were HLA-mismatched donors (father in two cases and cord blood in one).

Unrelated donors were selected in 17 cases: four were phenotypically identical donors and 13 had between one and four HLA mismatches (DPB1* mismatches not taken into account). Donor origin, characteristics and HLA data are detailed in Table 2.

Supportive care

All patients had autologous bone marrow harvesting during anaesthesia for insertion of indwelling central venous catheters. Patients were placed under sterile isolator or laminar air flow and received sterile care and oral and gut decontamination. All received polyvalent intravenous immunoglobulins, usually for 6 m, and oral prophylaxis of infection with penicillin, acyclovir and trimethoprim/sulphamethoxazole until 15 m post transplantation. All blood products were irradiated and selected from CMV-negative donors.

Conditioning regimen

The preparative regimen was initially based on the Hobbs protocol[14] consisting of chemotherapy alone with the combination of busulphan (BU) and cyclophosphamide (CY) plus a donor buffy coat infusion ($n = 10$) for related transplants. BU dosage was increased at the time of the first unrelated transplant : BU from 500 to 600 mg/m^2 and CY from 200 to 260 mg/kg was administered without irradiation except in one case of second related BMT after graft rejection (no. 5). This patient received CY 200 mg/kg combined with fractionated total body irradiation (TBI) (8 Gy). Donor marrow was not T cell depleted before infusion except in one patient (no. 4) who received a BMT depleted by the use of rabbit complement and anti-CD2, -CD5, -CD7 monoclonal antibodies.

Thymoglobuline®[15] was initially introduced for unrelated mismatched BMT because of its antirejection and anti-GvHD effect. It was given prior to transplantation, to obtain a partial *in vivo* T cell depletion, at a total dose of 20 mg/kg (5 mg/kg at day −7, −5, −3, −1) and this protocol was subsequently extended to all unrelated transplants, whether mismatched or not.

Pharmacokinetics of BU

In January 1998, we initiated a prospective study to monitor BU plasma concentrations during the conditioning regimen. BU plasma concentrations were determined by liquid chromatography. For 10 patients transplanted from UBMD, pharmacokinetic parameters were estimated by using the USCPACK software program, a Bayesian method that allows the use of only two or three blood samples. The target area under the curve per dose (AUC) was about 4–6 $\mu g \cdot h^{-1} \cdot ml^{-1}$. During the conditioning regimen, four doses were given per day over four consecutive days. Daily pharmacokinetic studies were performed for each patient with adaptation of the dosage regimen for the remaining doses.[16]

GvHD prophylaxis

In both related and unrelated donor transplants, patients received a combination of intravenous cyclosporin (CsA), 5 mg/kg/day beginning on day −2 for 5 days followed by intravenous CsA at 3 mg/kg/day and converted to 12.5 mg/kg/day orally when oral medication could be tolerated. CsA was continued for 9 months and tapered off over 3 months. Intravenous methotrexate (MTX) was adminis-

Table 2 Donor origin, characteristics, HLA data and patients' follow-up

No	*Donors*	*Number of mismatches*			*Class II*	*Sex R/D*	*Post graft follow up(31/12/2001)*
		HLA class I					
	Related						
1	Sibling					F/M	16 y
2	Sibling					M/M	14 y 11 m
5	Sibling					F/F	Rejection, 2nd BMT
5•	Same donor						8 y 10 m
6	Sibling					M/F	9 y 2 m
7	Father	A	B			F/M	Autologous reconstitution
8	Father					F/M	8 y 10 m
9	Cord blood					F/F	✠
10	Sibling					F/M	7 y 2 m
11	Cord blood	A				F/M	Autologous reconstitution
13	Sibling					M/F	5 y 3 m
14	Father	A		Cw*		F/M	Autologous reconstitution
23	Sibling					F/M	2 y 2 m
	Unrelated						
3	France	A				F/F	11 y 11 m
4	France		B*		DQB1	M/F	Autograft rescue
7•	USA					F/F	Autologous reconstitution, ✠ 7.5 y post BMT
12	France		B	2 Cw		M/F	6 y
14•	France	A		Cw		F/F	4 y
15	Germany					M/F	4 y 10 m
16	Italy	A*		Cw	DRB3	M/F	4 y 9 m
17	USA	A		2 Cw		F/M	4 y 7 m
18	France	A				M/F	✠
19	France	A			DRB3	M/F	✠
20	France					F/F	3 y 2 m
21	USA	A		2 Cw*		M/M	3 y 2 m
22	USA	A	B*	Cw		F/M	2 y 9 m
24	USA	A	B*		DRB4	F/F	2 y
25	USA		B	Cw	DQB1	F/M	18 m
26	USA	A + A*	B*	Cw		M/M	10 m
27	**France**					**M/M**	8 m

• Second BMT after graft rejection (pt 5), after graft failure from father (pt 7, 14). HLA mismatches are indicated as allelic (*) or antigenic (without *). *y* = years; m = months. ✠deceased

trered at 15 mg/m^2 on day 1 and at 10 mg/m^2 on days 3, 6, 11. GvHD was graded according to Glucksberg *et al*[17] and confirmed by appropriate histological studies.

Cell dose

Our policy was to increase the graft cell dose above 3.5×10^8 TNC/kg recipient body weight for related transplants, and to try to obtain at least 8×10^8 TNC/kg for unrelated transplants. Bone marrow was always preferred to other haematopoietic cell sources. T cell replete bone marrow was transfused on day 0. All patients received nonfiltered bone marrow. See conditioning regimen details in Table 3.

Psychological support for patient and family

The psychologist saw parents and children as soon as possible after the diagnosis as the parents were very much in need of support. This is when parents were made aware of the disease progression and life expectancy of their child. All patients were psychologically assessed using different tests according to their developmental level and age. Under the age of 3 years, we use the Brunet–Lezine locomotor and performance scale for babies (BLR-E), which gives a DQ. From 3 to 6 years old, we use the Terman–Merril test (T.N.M.L-F), which gives a mental age and a general IQ. After the age of 6, we use the Wechsler Intelligence Scale for children (WISCR-R), which gives a verbal IQ, performance IQ and an overall general IQ.

Assessment of BMT outcome and patient follow-up

Myeloid engraftment was defined as the first of three consecutive days when the absolute neutrophil count (ANC) exceeded 0.5×10^9/l. The functionality of the graft was assessed by measuring leucocyte α-L-iduronidase enzyme activity, urinary GAG excretion, fingerprint studies,[18] cytogenetic studies when applicable and HLA typing in mismatched pairs. Complete donor engraftment was determined by fingerprint analysis and defined as $\geqslant$95% donor cells at 1 month.

Patients were monitored 1 month, 3 months, 6 months and 1 year after BMT and then yearly. The biological follow-up included fingerprint studies for evaluating the donor/recipient origin of peripheral leucocytes, enzyme

Table 3 Graft conditions and outcome

Patients no.	*Stem cell source*	*T Busulphan*	*CY (mg/kg)*	*Thymoglobulin*	*Donor buffy coat*	*Cell dose TNC* $\times 10^8$	*ANC* >500 $\times mm^3(day)$	*GCSF*	*% of donor cells*	
									at 1 m	*Current*
1	Id sibling	16 mg/kg	200		X	1.3	19		100	100
2	Id sibling	16 mg/kg	200		X	3.2	17		95	50
3	MM UBMD	20 mg/kg	240		X	4.7	38		100	100
4	MM UBMD +	20 mg/kg	240		X	0.5		X	0	Auto rescue
5	Id sibling	500 mg/m^2	260		X	3.8	35		70	Rejection
5•	Same donor	**	200			3.8	26	X	85	60
6	Id sibling	600 mg/m^2	260		X	6.6	22	X	>95	50
7	MM father	600 mg/m^2	260	+	X	4.6	29	X	0	SAR
7•	Id UBMD	480 mg/m^2	260			6.2	48	X	0	SAR/deceased
8	Id father	600 mg/m^2	260		X	9.2	20		100	90
9	Id CB	600 mg/m^2	260			0.4	24	X	>95	deceased
10	Id sibling	600 mg/m^2	260			3.2	17		100	100
11	MM CB	600 mg/m^2	260			0.4		X	0	SAR
12	MM UBMD	600 mg/m^2	260	+		9.1	17		80	10
13	Id sibling	600 mg/m^2	260		X	4.0	31		100	100
14	MM father	600 mg/m^2	260	+	X	7.6	26		0	SAR
14•	MM UBMD	547 mg/m^2 ■	260	+		5.0	23		100	100
15	Id UBMD	600 mg/m^2	260	+		8.0	22		100	100
16	MM UBMD	600 mg/m^2	260	+		11.7	24		>95	100
17	MM UBMD	600 mg/m^2	260	+		5.3	24		80	40
18	MM UBMD	600 mg/m^2	260	+		6.0	14	X	100	Deceased
19	MM UBMD	524 mg/m^2 ■	260	+		5.6	16	X	100	Deceased
20	Id UBMD	481 mg/m^2 ■	260	+		6.0	17	X	100	100
21	MM UBMD	569 mg/m^2 ■	260	+		8.4	21	X	100	40
22	MM UBMD	600 mg/m^2 ■	260	+		5.9	17	X	100	50
23	Id sibling	457 mg/m^2 ■	260	+		4.5	24	X	*	50
24	MM UBMD	688 mg/m^2 ■	260	+		10.6	15	X	100	100
25	MM UBMD	612 mg/m^2 ■	260	+		7.3	13	X	100	>90
26	MM UBMD	558 mg/m^2 ■	200	+		9.7	27	X	100	>90
27	Id UBMD	457 mg/m^2 ■	200	+		9.1	19	X	75	75

* = mixed (PCR) nonquantifiable; • = second BMT; Id = HLA identical; MM = HLA mismatch; UBMD = unrelated bone marrow donor; CB = cord blood; ■ = busulphan dosage based on pharmacokinetics; ** = fractionated total body irradiation (2 Gy × 2 fractions in 2 days; 6.2 Gy CNS, 7.5 Gy liver, 2.5 Gy lung); SAR = spontaneous autologous recovery; GCSF = granulocyte colony stimulating factor. m = month.

activity measurements in leucocytes and serum, and quantitative and qualitative studies of excreted urinary GAGS.

A complete multidisciplinary evaluation was performed yearly including: DQ or IQ determination, cerebral and cervical (for the most recently transplanted patients) MRI, audiological examinations including examination of the external auditory canal and tympanic membrane, audiogram, orthophonic evaluation and auditory evoked potentials; ophthalmologic examinations with visual acuity evaluation, slit-lamp examination, intraocular pressure measurement and visual evoked potentials; nerve conduction velocity of the median nerve for carpal tunnel syndrome if not corrected by surgery, skeletal X-rays and joint mobility evaluation, echocardiography and pulmonary X-ray, orthopaedic and neurological evaluation.

Informed consent

The risks of the BMT procedure and the expected benefits and limitations of the transplant were fully explained to the family. Parents of all patients provided informed consent for transplantation.

Statistical analysis

All 27 patients who received BMT for the treatment of Hurler's disease were included in this study. The reported outcomes are as of 31 December 2001. The overall survival (including following the second graft) was evaluated by the Kaplan–Meier method, and the log-rank test was used to compare the probability of survival and graft functionality for the whole group, as well as for related or unrelated recipient–donor pairs, and by degree of HLA matching. All statistical analyses were performed using SPSS for Windows (version 9.0, SPSS, Chicago, IL, USA).

Results

BU dose adjustment at time of conditioning regimen

For seven out of the 10 patients included in this clinical trial, BU dosage regimens were decreased from 7 to 24% with regards to our previous dosage (600 mg/m^2) (Table 3). Dosage was increased for two patients who needed a total dose of 688 and 612 mg/m^2. For the final patient, the dose was unchanged. We observed an intraindividual variability of BU clearance for two-thirds of the children during the

4 days of therapy. All these patients had successful engraftment and no cases of veno-occlusive disease were observed during the post transplant period. In our institution, BU clearance disposition for these 10 patients with Hurler's disease is $0.327 \pm 0.164\,l/h^{-1}\,kg^{-1}$, which is higher than that observed in other patients ($n=35$) suffering from other diseases: $0.232 \pm 0.066\,l/h^{-1}\,kg^{-1}$ ($P=0.025$) (Bleyzac, personal communication).

Immediate tolerability of Thymoglobuline®

As expected, all patients experienced fever at least once during the first infusion of Thymoglobuline® and the majority developed a rash and hypotension. Some patients developed hypertension.

Engraftment

The median total nucleated cell dose infused per kg was 6.00×10^8 (range: 1.3–13.3); this calculation excludes the patients who received T-cell depleted marrow ($n=1$) or cord blood cells ($n=2$).

Engraftment was evaluable for all patients and initially observed in 23 out of 27 patients (85%). The median time to neutrophil engraftment was 21 days (range 16–48 days). Four patients had primary graft failure (16%): the patient (no. 4) who received T cell depleted marrow from an HLA-mismatched UBMD, two patients transplanted from two class I HLA antigen-mismatched fathers (no. 7, 14) and one patient who received an HLA-A-mismatched related cord blood transplant (no. 11). The first (no. 4) received autologous transplant rescue. The others demonstrated autologous reconstitution. Among them, two (no. 7, 14) were retransplanted from UBMD, successfully in one patient (no. 14).

Patient no. 5 had secondary graft rejection 6 months after full engraftment from an HLA geno-identical sibling. A second BMT from the same donor was performed successfully, before the introduction of Thymoglobuline® into our strategy, with intensification of the conditioning regimen (irradiation).

Complications and GvHD

One patient (no. 26) had a severe episode of arterial hypertension. Another patient (no. 4) had intracranial hypertension, which resolved after shunting. Three patients (no. 16, 21, 22) suffered severe haemolytic anaemia that resolved with corticosteroid treatment after tapering CsA, and, for one patient, after the use of the anti-CD20 antibody rituximab (Mabthera®).

Acute GvHD occurred in five patients (22%) following their first transplant, of grade I ($n=3$) and grade II ($n=2$). The three patients who underwent a second BMT did not develop acute GvHD. None had chronic GvHD.

Transplant-related mortality

Four patients have died (15%). Three died of infection after full engraftment; invasive aspergillosis in one patient (no. 9) at day 26, one case of interstitial pneumonia (RSV) at day 28 (no. 18) and one case of septicaemia (*Escherichia cali*) at day 89 (no. 19). The transplant-related mortality (TRM) rate is equal to 11%. One patient (no. 7) died of disease progression 7.5 years after failure of two transplants (from a mismatched father and from an identical UBMD without Thymoglobuline® for the second BMT) at the age of 9 years and 2 months.

Survival

Overall, 23 (85%) patients survived. In all, 21 had a functional graft (78%) 8 months to 15 years post BMT; in two cases this was following a second transplant (no. 5, no. 14). Two patients are alive with disease progression. The overall actuarial survival at 3 years is 85% with no difference according to donor origin (familial 90%; unrelated 82.35, log rank 0.39) or HLA identity (HLA match 85.71%, HLA mismatch 84.62%, log rank 0.77) (Figure 1a–c).

Post transplant outcome

Biological outcome

For all patients with durable engraftment ($n=21$), full ($n=11$) or mixed ($n=10$) chimaerism was obtained with a functional graft. Enzyme activity measurements in recipient leucocytes were in agreement with the fingerprint results and homozygous or heterozygous donor status. Table 4 reports the biological data in patients successfully engrafted for more than 3 years. GAG urinary excretion (Table 4) was elevated before grafting and consisted mainly of heparan and dermatan sulphate. After successful engraftment, excretion decreased to the upper limit of age-matched control values, but a low amount of dermatan sulphate and a hardly detectable fraction of heparan sulphate were observed on electrophoresis. No difference could be observed on GAG excretion between patients engrafted with a homozygous or heterozygous donor and between fully engrafted or chimeric patients.

Clinical outcome

For all engrafted patients, we observed the resolution of hepatosplenomegaly during the first 3 months. Within 3–6 months, persistent rhinorrhoea, obstruction of upper airways and hearing dramatically improved. Coarse facial features resolved progressively. Cardiac murmurs or valve dysplasia remained stable and no myocardiopathy occurred. No pulmonary insufficiency was observed. The effect of BMT on skeletal and neuropsychological development is reported on the 15 patients (11 with severe phenotype) who had stable engraftment with more than 3 years of follow-up, with full ($n=8$) or mixed ($n=7$) chimaerism. Seven of these patients were transplanted from genotypically identical siblings and eight from unrelated donors; all after the age of 14 months.

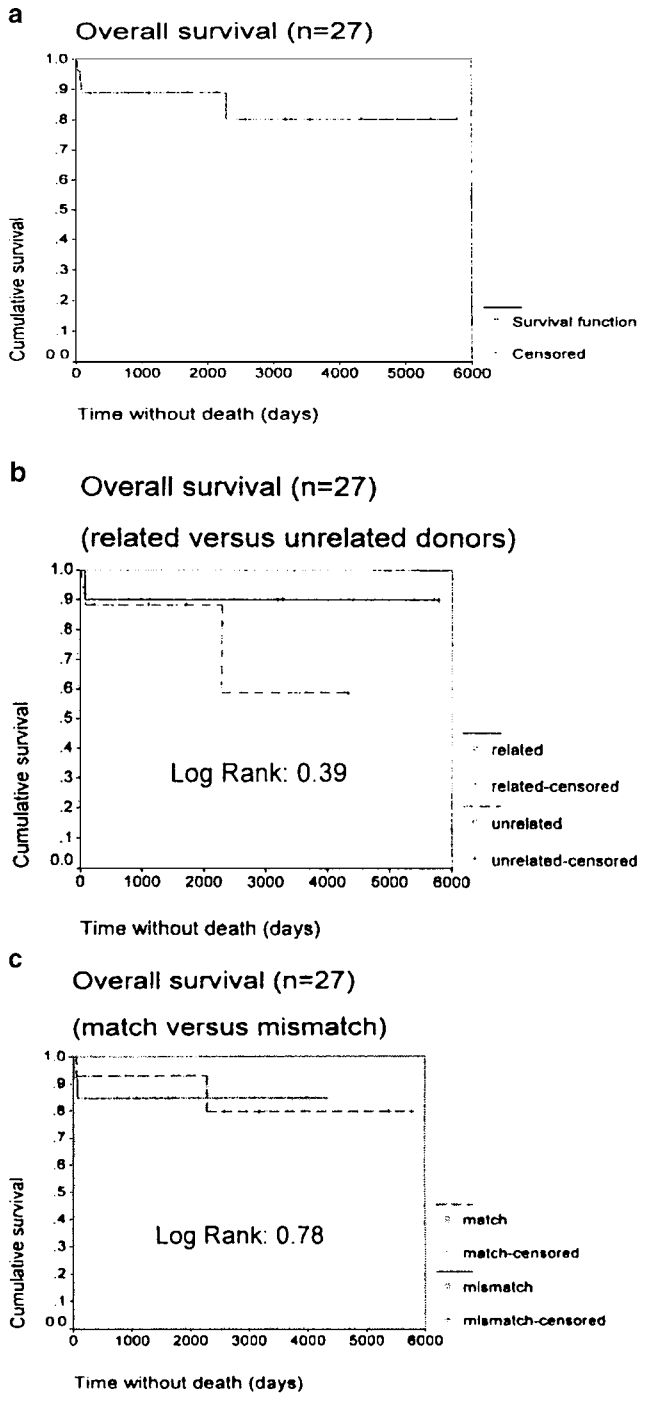

Figure 1 Survival curves: (**a**) overall survival for the whole group; (**b**) overall survival function of donor origin (related/unrelated); (c) overall survival function of HLA identity (match/mismatch).

Joint mobility

In the physiotherapist measurements, the 15 patients were assessed before BMT and yearly. In every patient, there was an improvement in joint mobility. Their improved shoulder movements and knee extension are the most impressive measurements. For shoulder antepulsion, 85% of patients had a regular and analogous progression whatever the time from BMT (Figure 2). For one child, progression is stationary despite a 7-year follow-up and one other patient lost 10° of antepulsion with a 10-year follow-up. The changes are similar for knee extension. All patients, but one improved (Figure 3) including one patient who had a 0° of knee extension at the time of BMT, and only one patient worsened, losing 5° of extension.

Orthopaedic management is shown in Table 5

Linear growth was maintained for some years and then fell to −1 s.d. for most patients ($n = 10$) and lower than −2 s.d. for six patients. Growth remained normal for patient no. 15 and above the normal for patients no. 13, 20, 21. While growth was generally maintained or increased at the time of BMT, it became evident that growth worsened with time, independent of the presence (nos. 3, 8) or absence of kyphosis (nos. 2, 5). Growth velocity curves for boys and girls are shown in Figures 4 and 5.

Dorsolumbar spine kyphosis was present in 10 cases, severe in eight and associated with scoliosis in three cases (no. 1, 12, 21). All except the two patients with slight kyphosis wore an adapted jacket for a prolonged period. Kyphoscoliosis worsened in patients no. 1 and no. 12 and required surgery. Patient no. 1 had posterior spinal fusion and anterior spinal fusion, respectively, 10 and 11 years post BMT; patient no. 12 had posterior spinal fusion 18 months post BMT with improvement in both these cases. Spinal arthrodesis is planned for patients no. 13 and 21. Patient no. 2 (height - 3 s.d.) required a C1-C2 arthrodesis because of a cervical spine dislocation without other vertebral abnormality. In the case of the other patients, thoraco-lumbar kyphosis became stable with brace treatment. Despite the absence of kyphosis, patients no. 6 and no. 10 had poor growth (respectively −1.2 and −1.5 s.d.).

Carpal tunnel syndrome developed in 10 out of these 15 patients (67%), all of whom who underwent decompression surgery before grafting in four cases, post BMT in six cases, with a favourable outcome in all cases.

Genu valgum deformity was noted in 11/15 of our patients (73%) with progressive increasing valgus deformity. Epiphyseal stapling was performed in two cases, 5 and 8 years post BMT, respectively.

Hip dysplasia was present in 10 cases. Nine patients underwent surgical orthopaedic treatment, femoral varus osteotomy in seven cases, femoral varus osteotomy and iliac Salter osteotomy in one case, hip abutment alone in one case. Currently, no patient reports hip pain or has a hip dislocation despite acetabular and femoral capital epiphyseal dysplasia. Patients are stabilised and no hip subluxation has occurred.

Neuropsychological outcome

Psychological outcome is reported for the same 15 patients (Table 6). Long-term follow- up MRIs of the brain did not show progressive cerebral atrophy or hydrocephalus. Before grafting, five children had a normal IQ/DQ ($= 100$). For the others ($n = 10$), IQ/DQ varied from 66 to 99. The follow-up shows that all children made progress initially,

Table 4 Biologic follow-up in 15 patients >3 years post BMT

Pts no.	*Follow-up*	*Enzyme activity (%) of day control at most recent evaluation*			*Urinary GAG (mg of glucoronic acid/g of creatinine)*	
		Fingerprint analysis	*Leucocytes*	*Serum*	*Before transplantation*	*At most recent evaluation*
1	16 y	100	100	40	232±112 CS++DS+++HS+	26 CS±
2	14 y 11 m	50	40	10	184±20 CS++DS+++HS+	**21** **CS++DS++HS±**
3	11 y 11 m	100	100	46	177±58 CS+DS+++HS++	12 CS++DS+HS±
5•	8 y 10 m	60	42	20	91±32 CS++DS+++HS++	**20** **CS++DS+HS±**
6	9 y 2 m	50	34	13	70±8 CS++DS+++HS++	15 CS++DS+HS±
8	8 y 10 m	90	40	12	247±47 CS++DS++++HS++	18 CS+++DS++HS-
10	7 y 2 m	100	47	38	97±42 CS++DS+++HS++	22 CS++DS+HS+
12	6 y	10	**12**	8	136±63 CS+DS+++HS+	**50** **CS++DS++HS-**
13	5 y 3 m	100	54	24	231±37 CS++DS++++HS++	31 CS+DS+HS±
14•	4 y	100	140	21	198±64 CS++DS++++HS++	**14** **CS++DS-HS-**
15	4 y 10 m	100	130	48	117±10 CS+DS++HS+	18 CS++DS±HS±
16	4 y 9 m	100	146	19	302±115 CS++DS+++HS+	**24** **CS++DS+HS±**
17	4 y 7 m	40	33	28	194±15 CS++DS++++HS++	22 CS++DS++HS±
20	3 y 2 m	100	86	53	94±46 CS++DS++++HS++	**19** **CS++DS±HS-**
21	3 y 2 m	40	30	10	121±29 CS++DS++++HS++	37 CS++DS+HS+

• = second BMT after graft rejection (pt 5), after graft failure from father (pt 14); Before BMT = α-L-iduronidase ⩽1% in leucocytes and serum; Underlined rate = heterozygous donor (carrier); ± = just detectable; CS = chondroitin sulphate; DS = dermatan sulphate; HS = heparan sulphate; Urinary GAGs = normal rate 00 = 8 to 29 (1–3 y); 6–23 (3–7 years); 3–16 (7–15 years); Normal electrophortic pattern = CS+ or CS++. α-L-iduronidase activity in leucocytes and serum are given in percentage of mean control values (at the time of assay) which vary for long period follow-up as the quality of commercial substrate lots is not equal, y = years.

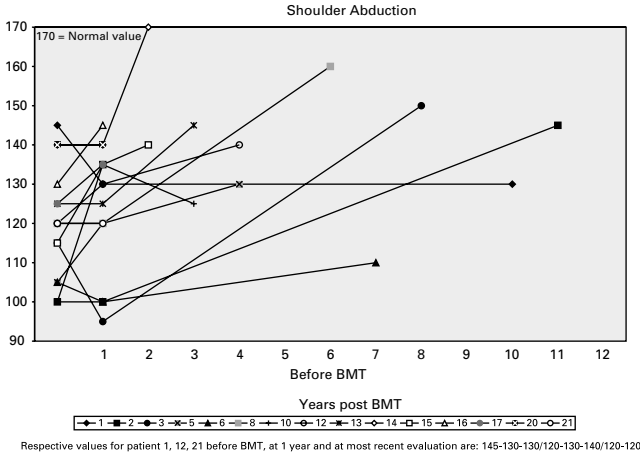

Figure 2 Shoulder abduction.

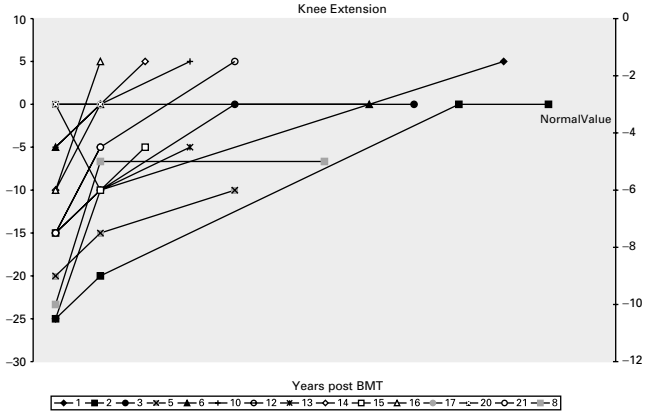

Figure 3 Knee extension.

they then developed difficulties and showed a decline in equivalent age score, and then appeared to stabilize (Figure 6). For five children: IQ/DQ ⩾100, for 10 children, IQ/DQ was between 77 and 99. No patient had severe mental retardation. All the patients are going to school. They all adapted well to nursery school, but learning difficulties began to be obvious on entering elementary school. Owing to their broad hands and stubby digits, some have problems in drawing and writing, but they learn to adapt well with time. The majority of them have language troubles and require speech therapy. Among five patients

Table 5 Orthopaedic management in 15 patients >3 years post BMT

Pts no.	*Follow-up*	*Growth (s.d.)*	*Kyphosis*	*Surgery year*	*Carpal tunnel syndrome*	*Decompression surgery*	*Genu valgum intermalleolar distance*	*Hip displasia*	*Surgery year*	*Femoral osteotomy*
1	16 y	−2.5	Severe	Arthrodesis (96 ; 97)	+	9 y	5 cm	No		
2	14 y 11 m	−3	No C1-C2 instability	Arthrodesis (96)	+	6 y	5 cm	No		
3	11 y 11 m	−4.5	Severe		+	2 y	9 cm Surgery 98 *	+	+ 1998, 2001	+
5•	8 y 10 m	−2.3	No		+	Before BMT	14 cm surgery 97, 99	No		
6	9 y 2 m	−1.2	No		+	Before BMT	No	+	+ 2000	□
8	8 y 10 m	−3.5	Slight		+	2 y	5 cm	+	+ 2000	+
10	7 y 2 m	−1.5	No		+	1 y	No	+		
12	6 y	−3.3	Severe	Arthrodesis (97)	+	Before BMT (left) 2 y (right)	7 cm	+	+ 2000	+
13	5 y 3 m	+0.3	Severe	Planed 2002	No		10 cm	+	+ 2000	■
14•	4 y	−1.8	Severe Jacket		+	1 y	No	+	+ 2001	+
15	4 y 10 m	Mean	Severe Jacket		No		7 cm	+	+ 2001	
16	4 y 9 m	**−1**	No		No		No	No		
17	4 y 7 m	−0.5	Moderate Jacket		+		5 cm	+	+ 2000	+
20	3 y 2 m	+0.5	Slight		No		3 cm	+	+ 2001	+
21	3 y 2 m	+1	Severe Jacket	Planed 2002	+	Before BMT	5 cm	+	+ 2000	+

• = second BMT after graft rejection (pt 5), after graft failure from father (pt 14); decompression surgery for carpal tunnel syndrome = number of years post-BMT; patients 1, 12, 21 had severe associated scoliosis; * = physeal stapling; ■ = femoral osteotomy + innominate osteotomy; □ = hip abutment only.

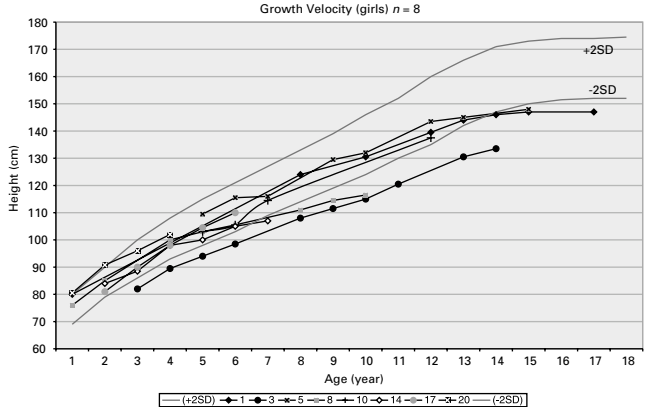

Figure 4 Growth velocity (girls).

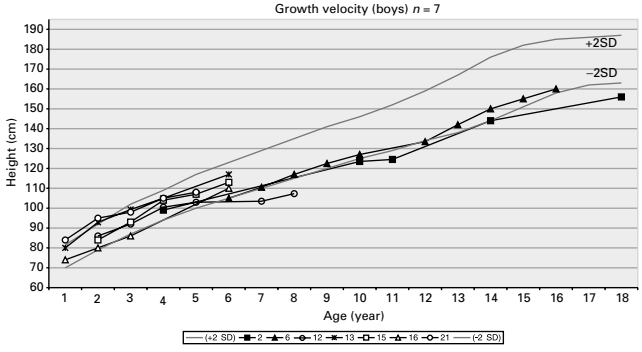

Figure 5 Growth velocity (boys).

currently over 12 years old, only one remains at normal school level (no. 1). The others go to a special school. They have memory and concentration deficits. Three out of five are self-conscious about their physical appearance, the others enjoy their life and they all hope to study for a job in the future. Social life has improved in every patient because of a better physical appearance and the improvement of joint mobility.

Vision

Only three patients had normal vision. Others had impaired vision and glasses were required for the majority of patients. Before BMT, all patients had visible corneal clouding; following BMT improvement was seen in five patients, but one patient needed corneal transplantation. Glaucoma was observed in two patients. No cataracts were observed.

Table 6 Neuropsychological outcome in 15 patients >3 years post BMT

Pts no.	*Follow-up*	*IQ at BMT*	*IQ current*	*Scholastic*	*Social adjustment*	*MRI*	*Corneal clouding*	*Visual acuity*	*Hearing impairment*
1	16 y	75	103	Normal	Very good	Normal	Improved	6/24	Normalized
2	14 y 11 m	95	88	Working after apprenticeship	Very good	Normal	+ *	6/30	Normalized
3	11 y 11 m	66	90	Normal	Very good	Normal	+	6/30	Normalized
5•	8 y 10 m	100	85	Especially school	Good	Unchanged	Improved	6/6	No
6	9 y 2 m	79	94	Apprenticeship	Acceptable	Unchanged	+	6/24	No
8	8 y 10 m	100	95	1 y late	Good	Slight atrophy	+	6/24	Improved
10	7 y 2 m	100	100	Normal	Very good	Unchanged	+	6/10	No
12	6 y	80	105	Elementary school	Good	Unchanged	Improved	6/24	Normalized
13	5 y 3 m	100	99	Elementary school	Good	Unchanged	+	6/24	No
14•	4 y	100	100	Nursery school	Very good	Normal	Improved	6/10	Improved
15	4 y 10 m	90	86	Nursery school	Good	Unchanged	+	6/6	Improved
16	4 y 9 m	99	77	Nursery school	Satisfying	Stroke	+	6/6	No
17	4 y 7 m	70	91	Nursery school	Very good	Normal	+	6/6	No
20	3 y 2 m	93	100	Nursery school	Very good	Normal	Improved	Subnormal	Improved
21	3 y 2 m	83	83	Nursery school	Good	Normal	Stable	6/6	No

• = second BMT after graft rejection (pt 5), after graft failure from father (pt 14); * = corneal graft; y = years; m = months.

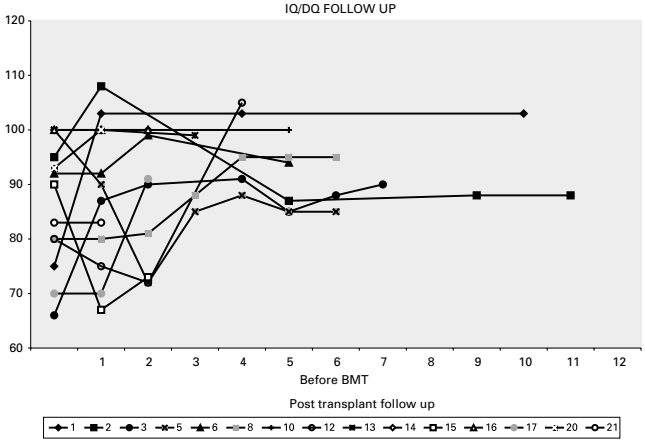

Figure 6 IQ/DQ follow-up.

Hearing

Hearing impairment is still present in eight out of the 15 patients (53 %), has normalised in four and improved and stablised in four patients (62.5 %) after BMT.

Discussion

Allogeneic BMT represents the only method of durably replacing genetically abnormal stem cells with normal donor stem cells. It is thus the treatment of choice for patients with severe Hurler's syndrome for whom death is usually expected in the first decade of life. As most of the children did not have a genotypically identical sibling donor, alternative donors were identified for transplant. In our protocol, UBMDs have been used with increasing frequency. This study reports a 4.7 years median follow-up in 27 patients who underwent transplantation from matched or mismatched donors, either related or unrelated, in a single paediatric centre. There were 13 related and 14 unrelated transplants but a high number of HLA mismatches were present in the unrelated transplant group. Since the beginning of our experience,[7] unrelated transplant outcome has been encouraging[19] despite the absence of the most stringent HLA matching. That is why, currently, if a matched sibling donor is not available, our policy is to look for an UBMD, this being preferred to alternatives such as cord blood transplantation or haplo-identical transplantation. Out of our group of patients, 16 transplants were performed with HLA disparities between recipient and donor; 76% of unrelated transplants and 23% of related transplants being mismatched.

Patient selection was conducted carefully after a full evaluation and consensus regarding disease severity. All but one patient included had an IQ/DQ score $\geqslant 70$, and 67 % of patients with a severe phenotype were under the age of 2 years at the time of BMT. Severe phenotype correlates well with severe genotype and high levels of urinary GAGS. Homozygotes for the nonsense W402X mutation (patients no. 7, 8, 14, 17, 24, 27 – Table 1) or compound heterozygotes for the two nonsense mutations W402X and Q70X (patients no. 1, 13, 18, 20, 21 – Table 1) were all diagnosed very early in life, at 2 and 15 months of age, except patient no. 18, diagnosed at 3 years 4 months, who died. This finding confirms previous reports of a good correlation between genotyping and phenotyping in these cases.[20–22] Genotype–phenotype correlations are more difficult for missense mutations. This difficulty is illustrated by P533R homozygous patients whose phenotype was associated with either mild (patient no. 4) intermediate (sibling no. 10 and no. 16) or severe Hurler's phenotype.[23] Patients with urinary GAGS levels greater than 100 mg of glycuronic acid/g of creatinine had a severe phenotype and genotype. Consequently, these easily and accurately measurable physiological parameters should be assessed after transplants have successfully engrafted (Table 4).

While neuropsychological improvement stabilised after the progress generally observed during the first 2 years following BMT, none of the children deteriorated. These

favourable long-term outcomes support the efficacy of BMT itself, whatever the donor origin, and whatever the disease severity. However, Peters has shown that children transplanted from unrelated donors after 2 years of age demonstrate a different and less favourable trajectory of development than those transplanted before the age of 2.[6] The significant association between age at BMT and the IQ/DQ score was found in his study reporting transplantation results from related donors.[5] Thus, in children with a good initial IQ/DQ who are aged less than or equal to 2.4 years at the time of BMT, the risk for cognitive deterioration appears relatively low, in comparison with historical controls who were not transplanted.[24] The efficacy of related or unrelated BMT to prevent the inevitable dementia associated with the disease is confirmed. These reports suggested that the optimal neuropsychological outcome following BMT would occur when children were less than 2 years of age and had an IQ/DQ greater than 70 which underlines the importance of an early diagnosis and clinical decision-making. In our study, the transplant procedure was not delayed by the necessity of finding UBMDs. The median interval between search initiation and unrelated donor recruitment was 1.7 months.[19] Currently, finding an UBMD is not a challenge, but finding a perfectly HLA-matched donor for certain patients, particularly for non-caucasian children, can be. Given the urgency to proceed to the transplant, we therefore accepted partially compatible donors.[19] Identification of a suitable donor of haematopoietic stem cells includes not only HLA typing and matching when possible but also donor enzyme level estimations. Neuropsychological function is significantly lower when the donor is a carrier, or recipient engraftment is less than complete from a homozygous enzymatically normal donor.[5] Using haematopoietic stem cells from an obligate carrier in haplo-identical grafting[5] from partially mismatched related donors[25] or from genotypically matched sibling carriers gives less favourable outcomes than using a homozygous enzymatically normal sibling or normal unrelated donor. The latter also have the advantage of giving a larger graft cell dose. In our experience, as for other investigators, two or three loci haplo-identical related BMTs have less favourable outcomes than unrelated BMTs.

The major obstacle, using both related or unrelated transplants, is to find the optimal method of obtaining durable engraftment. The transplant procedure must be sufficiently immunosuppressive and myeloablative to give the highest likelihood of donor cell engraftment and the lowest chance of rejection and GvHD while minimizing toxicity to fragile organ systems secondary to pathological accumulation of dermatan sulphate, particularly in liver, lung, heart and brain. A consensus regarding the optimal preparation for Hurler's syndrome is lacking. We opted for the combination BU-CY without irradiation or T cell depletion and with the addition of Thymoglobuline® in unrelated transplants.

Several studies have shown a wide inter- and intrapatient variability of BU disposition in children[26] depending on age, disease, drug interactions, etc. They all concluded that improvement in BMT results, in terms of optimal efficacy and controlled toxicity, requires a reduction in interpatient variability in systemic exposure.[27] In order to regulate BU pharmocokinetics, specific monitoring was instituted including a first dose and a daily Bayesian forecasting of BU plasma levels.[16] In this study, the rate of full engraftment and veno-occlusive disease (VOD)-free survival was higher than in other studies, while doses were decreased in seven patients, increased in two and unchanged in only one out of 10 patients with Hurler's syndrome (a subset of the study described here). Clearance of BU was increased in comparison to non-Hurler's diseases.[28]

To prevent GvHD in unrelated transplants, we opted for the use of Thymoglobuline®. The use of Thymoglobuline® induces *in vivo* T cell depletion involving both donor T lymphocytes and residual host T lymphocytes resistant to the conditioning regimen. Thymoglobuline® has a potent control effect on immunoactivation of T cells involved both in graft rejection and acute GvHD. In Peters' study[6] of the outcome of unrelated donor BMT in 40 children with Hurler's syndrome, neither T-lymphocyte depletion of the bone marrow nor irradiation appeared to influence the likelihood of engraftment. In all, 25 of the patients initially engrafted, with an estimated 49% of patients being alive at 2 years, 63% alloengrafted and 37% autoengrafted. In total, 10 of 16 patients are alive at 1 year who received a bone marrow cell dose $\geqslant 3.5 \times 10^8$ cells/kg engrafted, while only three of 11 patients receiving a lower bone marrow cell dose engrafted. Peters speculates that in this patient population, insufficient myeloablative and/or immunosuppressive therapy was the main cause of graft rejection (16%). In our experience, engraftment (85%) and rejection are not major problems, nor indeed is GvHD (22%). We observed a low incidence of aGvHD (three grade I, two grade II) and an absence of chronic GvHD despite a high number of HLA mismatches (Table 2). In the 40 transplanted patients, 25 initially engrafted, the probability of grade II to IV aGvHD was 30% and the probability of extensive chronic GvHD was 18%.

Durable engraftment in our patients led to a dramatic reduction of GAGS in urine to the upper limit of age-matched control values with a low amount of dermatan sulphate and a hardly detectable fraction of heparan sulphate. No difference could be observed between patients engrafting from related or unrelated donors, homozygous enzymatically normal donors or carriers, or between fully engrafted *vs* mixed donor/recipient chimaerism. In fully engrafted patients, leucocyte α-L-iduronidase enzyme levels remained within the expected range of their respective donors.

Survival of engrafted patients is radically different from that of patients who do not undergo transplantation or who experienced BMT failure. As hypothesised by Hobbs,[1] donor leucocyte precursors provide a natural source of the missing α-L-iduronidase enzyme able to correct lysosomal engorgement of the cells. BMT dramatically improves the metabolism and clearance of GAGS from highly perfused organs such as adenoids, tonsils, spleen, liver, lung and heart, Virchow-Robin space, but with a limited effect on the corneas and no effect on skeletal tissue.

As in other reports,[3–7,25,29] in all our engrafted patients substantial clinical improvement of somatic disease was

evident with resolution of hepatosplenomegaly, improvement in facial appearance, hearing, maintenance of normal heart and pulmonary function and prevention of hydrocephalus with improvements in Virchow–Robin space abnormalities.

In contrast, dysostosis multiplex progressed with abnormal growth of the skeleton. In the musculoskeletal tissues, growth and cellular maturation is deficient with systemic disturbance of bone modelling and focal failures of ossification particularly at the upper two lumbar vertebral bodies, at the superolateral roof of the acetabulum and the lateral margin of the proximal tibial metaphasis.[30,31] Linear growth by the age of 10 years was retarded with apparent retarded trunk growth. Increasing genu valgum was not prevented. Orthopaedic problems persisted in engrafted patients and orthopaedic surgery was required for genu valgum, kyphoscoliosis, acetabular dysplasia, trigger digits and median nerve release for carpal tunnel syndrome if not performed before grafting. Eight patients had a femoral osteotomy of whom one also had a Salter osteotomy, and one patient required hip abutment only, with an excellent result. Our patients seem to be currently stabilised without pain or hip subluxation. No gradual musculoskeletal deterioration has been observed under orthopaedic management with the help of intensive prolonged physiotherapy. The orthopaedic management of these patients remains a research problem. In Field's experience,[30] 10 of 11 children showed gradual musculoskeletal deterioration. The hip dysplasia was not prevented by proximal femoral osteotomies. In Masterson's experience,[31] bilateral hip-containment surgery was performed in five cases at a mean follow-up of 17 months. Innominate osteotomy would appear to be an essential part of the surgical procedure with improved cover of the femoral head. In the Minneapolis experience, Ogilvie and Peters (Orthopaedic aspects of MPS syndrome, personal communication, ASH meeting 2001) and Pemberton reported an improvement in the patients' orthopaedic outcomes by the use of varus femoral osteotomy. In our experience, we have systematically performed preoperative tridimensional scanner reconstruction of the pelvis and upper femur, which has shown severe acetabular dysplasia with anterior and posterior defects. For that reason, we do not advise innominate pelvis osteotomy combined with varus femoral osteotomy to obtain good hip containment. On the other hand, a Pemberton osteotomy seems to be more logical to obtain an anatomical acetabular hip containment. After a first experience of varus femoral osteotomy alone (combined with hip abutment at the end of skeletal growth), we now plan to start a new surgical procedure combining Pemberton osteotomy and varus femoral osteotomy following Olgivie and Peters recommendations.

The reported neurological outcome is variable and related to the heterogeneous natural course of the disease, IQ/DQ and age before the graft. Quality of life is globally improved despite skeletal problems; joint mobility is improved and clawing of the digits is limited compared to the degree seen in untreated cases; however, the digits remain stubby, and the hands remain abnormally broad in those with the severe phenotype. Family and patients enjoy a better physical appearance, better socialisation and the possibility of a normal scholastic life even with the severe phenotype (no. 1). Nevertheless, we will have to wait until the children in this cohort have reached adulthood before their quality of life and social adjustment can be properly assessed. Undoubtedly, improved quality of life after BMT will occur as a result of earlier diagnosis and early transplantation during the first year of life facilitated by dose-adaptation of BU.

Today, stem cell transplantation remains the only effective intervention in severe Hurler's syndrome, even if preliminary results from human α-L-iduronidase enzyme replacement are encouraging and demonstrate comparable quality of life outcomes in those with the moderate phenotype.[32] Enzyme replacement cannot be applied in severe forms because the substitute enzyme cannot cross the blood–brain barrier.

Ongoing analysis of patients with Hurler's disease who are untreated indicates a median survival of slightly less than 5 years of age and the progressive deterioration leads to a minuscule survival rate after 10 years. Unrelated donor grafts and mismatched procedures are more difficult technically than identical related transplantations but are feasible, and successful with a low transplant-related mortality rate. We would recommend that such transplants be offered to the patients and their families but be carried out only in specialised centres with appropriate paediatric metabolic expertise.

Acknowledgements

We thank the assistant physicians, nurses and medical staff of the Immuno-haematology & Paediatric Bone Marrow Transplant Unit, Debrousse Hospital, for their support and commitment (Prof Philippe, Dr K Kebaili, Dr R Mardini) and the physicians and technicians of Histocompatibility Laboratory in Lyon, for their efforts and efficient collaboration (Dr A Eljaafari, Dr D Rigal, Dr JP Tremisi, JP Bourgeot, Ph Debost, S Rey). All of them have contributed to help the patients. We also address special thanks to Prof C Peters and Dr N Whitaker for their constructive and useful suggestions in reviewing the manuscript.

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