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ORIGINAL ARTICLE

Allogeneic hematopoietic SCT for alpha-mannosidosis: an analysis of 17 patients

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Alpha-mannosidosis is a rare lysosomal storage disease. Hematopoietic SCT (HSCT) is usually recommended as a therapeutic option though reports are anecdotal to date. This retrospective multi institutional analysis describes 17 patients that were diagnosed at a median of 2.5 (1.1–23) years and underwent HSCT at a median of 3.6 (1.3–23.1) years. In all, 15 patients are alive (88%) after a median follow-up of 5.5 (2.1–12.6) years. Two patients died within the first 5 months after HSCT. Of the survivors, two developed severe acute GvHD (>=grade II) and six developed chronic GvHD. Three patients required re-transplantation because of graft failure. All 15 showed stable engraftment. The extent of the patients' developmental delay before HSCT varied over a wide range. After HSCT, patients made developmental progress, although normal development was not achieved. Hearing ability improved in some, but not in all patients. We conclude that HSCT is a feasible therapeutic option that may promote mental development in alpha-mannosidosis.
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Introduction

Alpha-mannosidosis (MIM 248500) is a rare lysosomal storage disorder with an autosomal recessive inheritance. It is caused by mutations in the *MAN2B1* gene (MIM 609458) located on chromosome 19 (19p13.2-q12), coding for the intracellular enzyme alpha-mannosidase. Deficient alpha-mannosidase activity leads to lysosomal accumulation of mannose-rich oligosaccharides.[1,2] Though its incidence is not precisely known, it is estimated that about one in 500 000 live births suffer from alpha-mannosidosis.[3]

Patients usually appear healthy at birth, but develop progressive mental retardation, skeletal changes, hearing loss, hydrocephalus, hepatomegaly and recurrent infections.[3] Traditionally, alpha-mannosidosis has been classified into two groups: severe ('early onset', 'infantile', 'type II') and mild ('late onset', 'type I').

Lately, three clinical subtypes have been suggested:

Type 1: A mild form with slow progression of mental retardation and usually without skeletal abnormalities. It is diagnosed at $\geqslant$10 years of age unless other factors—for example, an affected sibling—lead to an earlier diagnosis.

Type 2: A moderate form, clinically diagnosed before 10 years of age. Type 2 patients show skeletal abnormalities and a slow progression of mental retardation. These patients usually develop ataxia at the age of 20–30 years.

Type 3: A severe form with skeletal abnormalities and a rapid and obvious progression that is diagnosed at an early age. This form usually leads to an early death.[3]

The three clinical phenotypes of alpha-mannosidosis are not clearly distinguishable; they form a continuum of varying severity.

The prediction of the clinical course for an individual patient is difficult. Lyons *et al*.[4] reported three Hispanic males with alpha-mannosidosis that, despite early clinical signs, showed relatively benign long-term outcomes. Normal development leading to an independent life seems to be achieved only occasionally.[5] Unfortunately, long-term studies with higher patient numbers have not been published. Many mutations in MAN2B1 have been described,[6] but due to the low number of cases, it was not possible to identify a correlation between genotype and phenotype.[3]

Therapeutic options have been rare up to now. Early attempts to treat patients with alpha-mannosidosis with zinc did not lead to clinical and developmental improvements.[7] Enzyme replacement therapy has only been studied in animal models,[8,9] and clinical studies in humans are in preparation. More recently, enzyme replacement using gene therapy has been studied in a cat model. Using direct intracerebral injection of an adenoviral vector, expression of alpha-mannosidase was achieved in neurons leading to milder symptoms and longer survival in the treated cats.[10]

Thus, hematopoietic SCT (HSCT) is currently the only clinically available approach to enzyme replacement. It has been shown to have effects both in a cat model[11] and in humans, but only a few cases in humans have been published.[12–16] The largest experience with HSCT for lysosomal storage diseases exists in Hurler's disease, in which good long-term neurodevelopmental outcomes can be demonstrated (reviewed by Aldenhofen *et al*.[17]).

Objective

Although HSCT is considered the standard therapeutic option in alpha-mannosidosis,[18] this recommendation is based on the very limited safety and efficacy data in humans that are available to date.

To get a more complete view of the outcome, we performed a retrospective multicenter analysis of patients with alpha-mannosidosis who were treated with HSCT.

Patients and methods

Patients were identified via physicians who had treated patients with inherited errors of metabolism by HSCT and via the International Advocate for Glycoprotein Storage Diseases (ISMRD, Mr J Forman, Petone, New Zealand). Mr Forman and his co-workers were asked to forward a letter to those who may have undergone HSCT. In this letter, patients and their families were asked to contact their transplant physicians in support of this study.

Data were collected using a questionnaire that was filled out by the transplant physicians. This questionnaire contained questions on:

- Pre-HSCT status: reason for first presentation, alpha-mannosidase activity, mutation analysis of the MAN2B1 gene, neurodevelopmental status, hearing status, skeletal status, psychiatric status, infectious history of the patient.
- HSCT data: Lansky or Karnofsky index, known pre-transplant risk factors, conditioning, GvHD-prophylaxis, donor type, stem cell source, number of transfused nucleated cells, CD34 positive cells and CD3 positive cells, engraftment (WBC $>1000/\mu L$, thrombocytes $>20.000/\mu L$ and $>50.000/\mu L$), time course of chimerism, acute regimen-related toxicity, grade of GvHD.
- Post-HSCT data: infections, neurodevelopmental status, results of audiometry, psychiatric status, skeletal status, alpha-mannosidase activity in WBC after HSCT, evidence of late therapy-related complications. If there was no systematic neurodevelopmental testing, physicians were asked to give a clinical impression of the current status of their patients.

Statistical analysis

Kaplan–Meier analysis was performed for OS and EFS. Graft failure (with or without second transplantation) and death were defined as events.

Results

Recruitment

A total of 17 patient questionnaires were returned by 11 transplant centers. Of those, 14 were sent by physicians with a special interest in HSCT for lysosomal storage diseases. Of those patients, six had been published before (Patient #1, #2, #5, #10;[14] #7;[12] #9).[19] In three cases, the parents contacted us directly after having received the letter via the ISMRD.

Pre-HSCT data

Patients were diagnosed at a median age of 2.5 years (range 1.1–23 years). In all, 12 were male and five female. Before confirmation by enzymatic testing, mucopolysaccharidosis was suspected due to skeletal malformation ($n=13$) developmental delay ($n=8$), hearing loss ($n=5$), recurrent otitis ($n=5$), recurrent infections ($n=5$), speech delay ($n=2$) and hepato(spleno)megaly ($n=2$; data available in 16 of 17 patients). For all patients, data on mannosidase activity were available, confirming reduced or lacking activity in either peripheral blood leukocytes or serum.

Before HSCT, an assessment of major mannosidosis-related problems was performed in most patients. Hearing was impaired to varying extents in all nine patients in whom those data were available. A hearing aid was necessary in six patients. Moreover, neurodevelopmental testing revealed at least mild developmental delay in 12 of the 13 patients with data available.

Transplantation and side effects

Allogeneic HSCT was performed at a median age of 3.6 years (range 1.3–23.1 years). Median time from diagnosis to transplantation was 7 months (range 1–95 months, mean 15 months).

All but one first-line conditioning regimen contained BU, most commonly combined with CY or fludarabine. Nine patients received BU orally, three intravenously, and in the

Table 1 First-line transplant regimens

Patient no.	*Severe form*[1]	*Date of Tx*	*Stem cell donor (HLA matches)*	*Stem cell source*	*Conditioning*	*GvHD-prophylaxis*	*Comments*
1	NA	1997	MMUD[2]	BM	Bu 320 mg/m^2-Cy 120-TBI 750 cGy-ATG 60	CSA, Mpred, T-cell depletion	
2	NA	1997	MUD (8/8)	BM	Bu 320 mg/m^2-Cy 120-TBI 750cGy-ATG 60	CSA, Mpred, T-cell depletion	
3	N	1997	MRD (sister)	BM	Bu 16-Cy 200	MTX, CSA	
4	NA	1999	MMUD (4/6)	CB	Bu 40 mg/m^2-Cy 200-ATG 90	None	G-CSF
5	NA	1999	MUD (7/8)	NA	TBI 1400-Cy 120	NA	
6	NA	2000	MRD (brother)	BM	Bu 12,8-Cy 200	MTX, CSA	
7	Y	2000	MRD[3]	PBSC	Bu 20-Cy 200	CD34-selection, Pred, OKT3	
8	Y	2001	MUD (9/10)	BM	Bu-Flu 40-ATG (rabbit) 2.5 mg/kg	CSA, MTX	G-CSF, secondary graft failure
9	Y	2001	MUD (NA)	CB	Bu 600 mg/m^2-Cy 200-ATG 10	Tacrolimus	Primary graft failure
10	NA	2002	MMUD (4/6)	CB	Bu 12,8-Cy 200-TLI 500cGy-ATG 90	CSA, Mpred	G-CSF
11	NA	2004	MUD (NA)	BM	Bu 16-Cy 200-alemtuzumab	CSA, alemtuzumab	
12	Y	2005	MMUD (5/6)	CB	Bu-targeted-Cy 200-ATG 10	CSA, Pred	
13	Y	2005	MRD[4]	PBSC	Bu 6,4-Flu 150-ATG 160	MMF, CSA	
14	Y	2005	MMFD[5]	PBSC	Bu 16-Flu 180-Mel 140-ATG 30	CD34 selection	
15	Y	2006	MMUD (8/10)	PBSC	Bu 16-Cy 200-ATG 60	MTX 2 × 10, CSA	G-CSF
16	Y	2006	MMFD[5]	PBSC	Bu 15,2-Flu 180-Mel 140-ATG 30	CD34 selection	Primary graft failure
17	Y	2008	MUD (10/10)	PBSC	Bu 16-Flu 180-Mel 140-ATG 30	CD34 selection	

Abbreviations: ATG = anti-thymocyte globulin; CB: cordblood; Flu = fludarabine; Mel = melphalan; MMF = mycophenolate mofetil; MMFD = mismatched family donor (haploidentical donor); Mpred = methylprednisolone; MMUD = mismatched unrelated donor; MRD = matched related donor; MUD = matched unrelated donor; NA = not available; Pred = prednisolone; Tx = transplantation; Y = yes.
Annotations: 1 = classification according to traditional classification; 2 = contains DRB1-mismatch; 3 = HLA-identical mother; 4 = other matched non-sibling family donor; 5 = maternal haploidentical donor.
Total conditioning doses are given for Flu and Mel in mg/m^2, Cy in mg/kg, Treo in g/m^2. Bu in mg/kg unless indicated differently.

Table 2 Second line transplant regimens

Patient no.	*Date*	*Donor*	*Stem cell source*	*Conditioning*	*GvHD-prophylaxis*	*Comments*
8	2002	MUD (9/10)	BM	TBI 1200 cGy-Cy 60-ATG (horse) 30	CSA, MMF	
9	2002	MMFD[5]	BM	Bu 600 mg/m^2-Cy 200-ATG 10	MTX, Tacrolimus, MMF	G-CSF
16	2006	MMFD[5]	PBSC	OKT3–Pred	MMF, CD34-selection/ CD3-/CD19-depletion	Secondary graft failure
16	2006	MUD (5/6) + MMFD[5]	CB + PBSC	Flu 180-Treo 42-TT 10-ALG 60	ALG, CSA, MMF, MTX 5 mg/m^2	

Abbreviations: MMFD = mismatched family donor (haploidentical donor); MUD: matched unrelated donor; CB = cordblood; Flu = fludarabine; ATG = anti-thymocyte globulin; MMF = mycophenolate mofetil; Pred = prednisolone.
Annotations: 5 = maternal haploidentical donor.
Total conditioning doses are given for Flu and Mel in mg/m^2, TT and Cy in mg/kg, Treo in g/m^2. Bu in mg/kg unless indicated differently.

others, data were unavailable. Six patients had targeted BU, and two non-targeted. Data on the others were unavailable.

In four of the 10 cases that received transplantation before 2002, the preparative regimens contained irradiation (TBI in three cases, TLI in one case). The patient that did not receive BU received a TBI-based conditioning. Donor types were as diverse as conditioning regimens. First transplants were performed from a matched related donor in four cases (of which two were an HLA-identical sibling, one an HLA-identical mother and one an HLA-identical other family member), matched unrelated BM or PBSC donor in five cases, a mismatched unrelated donor in two cases and a haploidentical family donor in two cases. Four patients received an unrelated cord blood graft: two of those with 4/6 HLA-matches, one with 5/6 HLA-match and one classified as 'matched', the number of HLA-matches was not stated (Table 1).

Primary engraftment was reached in 15 of 17 patients. The two patients with primary graft failure received re-conditioning (one immunosuppressive and one myeloablative) and a secondary transplantation from a haploidentical donor. Both patients engrafted after the second transplantation. Two secondary graft failures occurred, one in a patient after primary graft failure. Both were re-conditioned with myeloablative chemotherapy and showed stable engraftment with the second or third graft (Table 2).

Graft failure occurred in two of five cases (40%) that received BU–fludarabine-based conditioning, but only in one of 11 cases (9%) with BU–CY-based conditioning (statistically NS).

OS after HSCT was 88% within this cohort: one patient died 76 days after HSCT due to sepsis, GvHD and pulmonary hemorrhage. The other patient died on day 135 after HSCT due to multiple viral infections followed by multi-organ failure. All others are alive and engrafted

with a median follow-up of 5.5 years (range 2.1–12.6 years) after first HSCT (Figure 1). The most commonly reported complications following HSCT were:

- Severe sepsis that required ventilatory support in four cases (patients #6, #8, #12 and #16), in two cases leading to death.
- acute GVHD (⩾grade II) in patients #6 and #8, one of whom died.
- chronic GVHD in six cases. In all five cases with data available, the skin was affected. In three cases this was reportedly 'mild' (Patients #4, #9 and #15), sclerosis was described in two cases (Patients #13 and #14). In two cases, the gut was affected, in patient #13 leading to esophageal stricture that required dilatation, in patient #14 resolving without complications. All patients were in remission from GvHD at last follow-up. Three of five patients with data available are off immunosuppression, one requires topical steroids and one is receiving systemic immunosuppression.
- bronchiolitis obliterans was seen in patients #1 and #15.

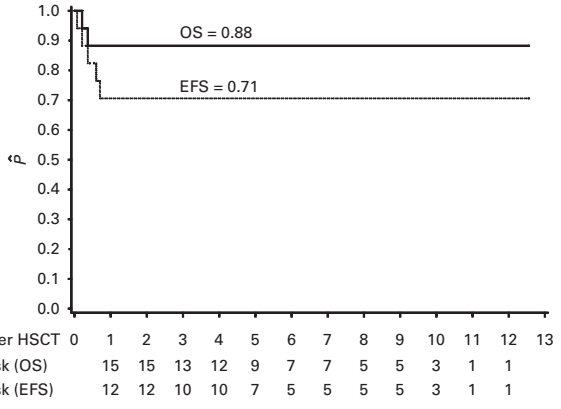

Figure 1 EFS and OS of patients with alpha-mannosidosis after HSCT.

Alpha-mannosidase activity post transplant

Post-transplant mannosidase activity was within normal limits in all eight patients tested.

Hearing

Post-HSCT audiometry results were available in 13 of 15 surviving patients. In only one of them (#13), hearing was within normal limits (see Table 3). The other 12 showed mild to severe hearing loss, eight patients required a hearing aid. In three patients (#1, #14 and #17) the hearing aid was discontinued due to improved hearing after HSCT. In patient #14, progressive hearing impairment led to placement of hearing aids 5 years after HSCT. Three other patients who did not require a hearing aid pre-transplant required placement later.

Neurodevelopment

Neurodevelopmental follow-up data were available in 13 of the 15 surviving patients, including some more recent follow-up-data for the previously published patients #1, #2, #5 and #10. For most patients, formal post-HSCT neurodevelopmental evaluation or a description of their every-day life functioning was available. These data are summarized in Tables 4 and 5.

All patients showed below average skills for their age group. Still, all made developmental progress. None of the pediatric patients was able to attend regular school without special education, although all patients were able to participate in every-day life and were described as being very social. Of the two adult patients, one was able to live

Table 3 Hearing before and after HSCT

Patient no.	*Before HSCT*		*After HSCT*		
	Audiometric findings	*Hearing aid*	*Audiometric findings*	*Hearing aid*	*Time after HSCT (years)*
1	NA	Y	−20 dB (500 Hz–4kHz) −60 dB (8kHz)	N	10.8
2	Mild hearing loss	N	Mild hearing loss in low frequencies, high grade hearing loss in high frequencies	N	5.2
3	−60 dB to −80 dB	Y	−50 to −60 dB	Y	4.5
4	Mild to moderate hearing loss	Y	Mild sensoneurinal hearing loss	Y	10.8
5	NA	NA	Mild low-frequency hearing loss	N	2.9
6	NA	N	*Died day 76 after HSCT*		
7	−60 dB	N	Mild high fequency hearing loss	Y	9.2
8	−70 dB both ears	Y	−15 dB with hearing aids placed	Y	8.0
9	NA	N	NA	N	NA
10	Mild to moderate hearing loss	N	NA	Y	4.0
11	NA	NA	Sensoneurinal hearing loss	Y	NA
12	−40 dB	N	*Died day 135 after HSCT*		
13	Not possible to perform	N	Within normal limits	N	2.6
14	−50 dB	Y	−40 dB to −50 dB	Y	3.8
15	NA	N	−30 dB	N	2.4
16	NA	N	−110 dB	Y	3.8
17	−50 dB	Y	−30 dB	N	0.8

Abbreviations: dB = decibel; HSCT = hematopoietic SCT; N = no, NA = not available; Y = yes.

Table 4 Neurodevelopmental status before and after HSCT

Patient no.	*Before HSCT*			*After HSCT*			
	Age at test (years)	*Result*	*Test method*	*Age at test (years)*	*Result*	*Test method*	*Time after HSCT (years)*
1		NA		16.9	Reading 69, fine motor skills 65	WJ-III PP	10.4
2		NA		8.3	Verbal IQ 91, performance IQ 91	NA	5.0
3	7.0	ITPA 4–5 years WISC-R 83	ITPA WISC-R	11.7	7 to 8 years	WISC-R	1.5
4	3.0	Normal mental development, slightly delayed adaptive skills, global language delay	NA	12.0	Overall IQ 55	DAS-II	8.7
5		NA			NA		
6	1.3	Developmental quotient 73 cognition 83 social skills 1.25 yrs gross motor skills 1.25 yrs	CAT/CLAMS		Died day 76 after HSCT		
7	2.0	Mild delay in fine motor skills and speech development	NS	4.3	Non-verbal overall-IQ 94, speech development 3 years	SON	2.3
8	5.1	Communication skills 58 (2.1 years), daily living 45 (1.4–2 years), socialization 66 (2–3 years), motor skills 37 (1–5 years)	VABS	12.8	Adaptive behaviour 48–53 (90–109), mathematics 40, oral language 45	ABAS-II WIAT-II	7.7
9	NA	Within normal limits (1–3 years)	Tsumori/Inage method	9.6	Verbal IQ 52, performance IQ 46, full scale IQ 43	WISC-III	7.4
10	3.5	Fine motor skills 61, communication 66, socialization 91, motor skills 56	PP VABS	5.8	Overall IQ 81 (84–116), fine motor skills (both hands) 71, communication 78, socialization 88, motor skills 51	SBIS4 PP VABS	1.7
11	NA	Speech delay	NA	7.2	Mild learning difficulties, immuraties in speech, dyspraxia	WISC-IV	3.6
12	NA	Developmental quotient 85, loss of milestones	WISC-3		*Died day 135 after HSCT*		
13		NA		4.6	Verbal tasks 2.5–3.5 years, daily living skills 1–2 years, socialization 2–2.5 years, motor skills not addressed, school readiness 3.6 years	VABS-II	3.1
14	3.4	Developmental age 2–6 years	SPT	7.6	Speech development 2.5–2.75 years, fine motor skills 2.5–3 years	HA-WIVA-III	4.0
15	3.0	Running 1.9–2.5 years, fine motor skills 2–2.6 years, speech 1.4–1.9 years, understanding 1.2–1.6 yrs, social skills 1.9–2.6 years	MFED		NA		
16	3.3	Speech 1.25–1.3 years, social contact 1.6–2.1 years, fine motor skills 1.9–2.8 years, gross motor skills 1.5–2.3 years	DS	7.6	Speech 2.5 years, gross motor skills 5–6 years, fine motor skills 5–6 years	DS	3.8
17	2.4	Social skills 1.75 years, fine motor skills 1.5 years, speech 1.2–1.25 years, gross motor skills 0.75 years	DS	3.0	Speech 1.25–1.7 years, fine motor skills 1.25–1.7 years, social skills 1.25–1.7 years, gross motor skills 1.7–2 years	DS	0.5

Abbreviations: ABAS-II = Adaptive Behavior Assessment System II; CAT/CLAMS = Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale; DAS-II = Differential Ability Scales-II; DS = Denver Scale; HA-WIVA-III = Hannover–Wechsler Intelligenztest für Vorschulalter; ITPA = Illinois Test of Psycholinguistic Abilities; MFED = Münchner Funktionelle Entwickungsdiagnostik; NS = no systematic testing performed; PP = Purdue Pegboard; SBIS4 = Stanford–Binet Intelligence Score 4; SON = non-verbal Snijders–Ooen IQ-testing; SPT = Symbolic Play Test; VABS = Vineland Adaptive Behaviour Scales; VABS-II; Vinneland II Adaptive Behaviour Scale; WIAT = Wechsler Individual Achievement Test; WISC-III/-R = Wechsler Intelligence Scale for Children-III/-Revised; WJ-III = Woocock–Johnson Test for Achievement, Third Edition.

Annotation: Numbers indicate standard scales with a normal range from 85–115, unless indicated differently. Different normal values are given in brackets. If numbers indicate the corresponding developmental age, this is indicated by years.

Table 5 Current clinical status

Patient no.	*Age (years)*	*Time after HSCT (years)*	*Status report*
1	16	10	Receives special education services and attends a mainstream school for non-academic subjects. Has a job washing dishes in a local catering company, is in the process of obtaining a driver′s license and enjoys outdoor activities.
2	8	5	Lives with family and attends first grade with the support of extra tutoring in reading and mathematics. Suffers from a bilateral cataract and received eye surgery on one side.
3	22	12	After BMT, pt. could join the regular class and passed examinations in some topics, including biology. At age 22, pt. works as an apprentice in a kindergarden, lives alone in a flat, lives a relatively normal social life with chatting, going out with friends. Speaks a foreign language. Can also travel by plane or train to other cities in the country independently. Pt. can run (a bit clumsily, but even played tennis), goes skiing and has no problem with ataxia.
5	32	9	After a difficult course post transplantation, pt. still suffers from monocular blindness after CMV–retinitis and a polyneuropathy that is now improving. During the last year, pt's gait worsened and pt. has become more difficult to understand. Underwent repeated phlebothomies due to hemosiderosis. Lives with parents who work from home.
6		Died	After severe acute GvHD and sepsis with Klebsiella and Clostridium difficile pt. died after pulmonary hemorrhage at day 76.
7	11	9.5	Is in 4th grade of a school for children with learning difficulties. Ataxia has improved; does ice- and roller-skating. Unfortunately, pt. had a hip luxation and required orthopedic surgery. Gross and fine motor coordination have improved, but remain below average. Speech and verbal expression improved, pt. is able to form complex sentences.
8	12	7	Visits a special school for children with learning disabilities and is able to recognize about 80 words. Lives with family, is very social and enjoys being with peers.
9			Helps in father′s restaurant and understands what is said, but vocabulary is limited. Receives special education.
10	8	4	Lives with family and attends full-day school. Mother reports problems with a reduced attention span.
12		Died	Experienced multiple viral reactivations (HHV6, EBV, adenovirus and HSV) and had two episodes of respiratory insufficiency. During the second episode, pt. developed renal insufficiency and died of multiorgan failure on day 135 post transplant.
14	8	4.5	Visits a kindergarten, is very social and benefits a lot from the contact with other children. Still suffers from mental retardation. The parents are preparing pt. for first school year. Can form three word sentences.
15	6	2.4	Length and weight increase within the 25th to 50th percentile. Suffered from recurrent otitis. Visits preschool and takes part in physical education classes. Does not talk a lot, but receives bilingual upbringing. Does understand his primary language well.
16	8	4.5	Visits a special kindergarten, is preparing to go to school. Speech and motor skills are improved, but still suffers from problems with coordination.
17	4	1.5	Hearing aids could be discontinued and motor skills are improved, movements are much more fluid. Expressive speech development is still poor and unimproved, receptive speech is good.

Abbreviations: HSCT = hematopoeitic SCT; pt. = patient.

independently in her own apartment, the other lived with parents at the age of 32 years.

Skeletal abnormalities

Signs of skeletal abnormality have been reported in 13 of 15 cases with data available before HSCT.

After HSCT, a skeletal status was reported for twelve of the 15 surviving patients. In three cases, transplant physicians reported no progression of dysostosis multiplex. In four cases, there was evident ongoing dysostosis multiplex, including in one patient who required surgery for a hip subluxation (patient #7) and in one patient (#5) who required knee replacement. One patient underwent correction of pes equinus (patient #17).

In six cases the dysostosis was described as 'mild'. In the other cases, information about musculoskeletal progression was inconclusive or not available after HSCT (Table 6).

Cerebral imaging

Results from cerebral magnetic resonance imaging (MRI) were available in ten patients before HSCT, and in seven patients post-HSCT. Nonspecific 'changes in the white matter' were reported in three cases (patients #4, #12 and #17). In one patient, white matter volume was reportedly decreased (patient #8). One of the patients with white matter changes died shortly after HSCT (patient #12). Patient #4's MRI was normal 10 years after HSCT and #17's MRI was stable 0, 8 years after HSCT. In patient #8 the MRI revealed ongoing decrease of white matter volume 1 year after his second HSCT. Decreased myelination was reported in two cases (patients #7 and #14) with normalization in patient #7, 1 year after HSCT. Patient #14 had no post-HSCT MRI.

Arnold–Chiari malformation with extension of the cerebellar tonsils below the foramen magnum was reported in three cases (patients #2, #11 and #16). In patient #2. Arnold–Chiari malformation was part of the presenting symptoms that lead to the suspicion of a lysosomal storage disease. In patient #11, it was primarily reported after HSCT.

Discussion

In this work, we describe the largest series of patients with alpha-mannosidosis after HSCT that has been published to date. Within the limits of a retrospective multicenter analysis, the data presented suggest a benefit for the patients from the procedure.

Randomized controlled studies are not feasible due to the low incidence of alpha-mannosidosis. Another

Table 6 Musculoskeletal status before and after HSCT

Patient no.	*Before HSCT*	*After HSCT*	*Time after HSCT (years)*
1	NA	NA	
2	Underwent posterior fossa decompression due to Arnold—Chiari malformation	Mild genu valgum, mild hip dysplasia	5.2
3	Macrocephalus, genu valgum	No progression	NA
4	No signs of dysostosis	No signs of dysostosis, mild heel contractures, osteoporosis due to chronic steroids	10.8
5	NA	Knee replacement, avascular necrosis of femoral condyle	6.2
6	Gibbus, 'thick skull'	*Died day 76 after HSCT*	
7	Compact bone structure of cranium, spine and ribs, clubsy femoral head and metacarpal bones	Progressive dysostosis hip subluxation	9.8
8	Scoliosis requiring surgery	Progressive scoliosis requiring fusion of seven vertebrae	7.3
9	Dysostosis multiplex, mainly vertebrae and iliac bone	Progressive dysostosis multiplex, with collapse of L1	NA
10	Bony spine abnormalities mild dysmorphic features	NA	
11	Scoliosis	Mild features of dysostosis multiplex	5.2
12	Dysostosis multiplex	*Died day 135 after HSCT*	
13	No signs of dysostosis	NA	
14	Coarse metacarpals, biconvex lumbal vertebrae	Scoliosis and kyphosis, genu valgum, unstable gait	3.6
15	Minor dysostosis	No progression	2.4
16	Mild dysostosis	Dysostosis multiplex with thickening of ribs and cranium (mild, not affecting everyday life)	3.8
17	Coarse facial dysplasia	Correction of pes equinus, no signs of dysostosis multiplex in cMRI	0.8

Abbreviations: HSCT = hematopoeitic SCT; NA = not available.

problem is the lack of detailed information on the natural course of patients with alpha-mannosidosis. A natural history study is being performed by a multinational group (NCT00498420; Beck M, Mainz, Germany, personal communication). Comparison of the clinical course of transplanted and non-transplanted patients will become possible once these study results are available. We propose the establishment of a multicenter registry for alpha-mannosidosis patients with and without HSCT, where the natural history of the disease without HSCT can be compared with the course of transplanted patients.

We were able to show that HSCT in patients with alpha-mannosidosis is a feasible therapeutic option. Transplant-related mortality and morbidity was comparable to other nonmalignant diseases. There were no obvious mannosidosis-specific adverse events of the procedure.

The majority of the patients presented in this study showed an intermediate or severe phenotype before transplantation with signs of neurodevelopmental delay. In these patients, an unfavorable natural course could be expected.[3] Developmental improvement after HSCT was observed in all patients. Loss of previously learned skills was not seen in any of our patients. However, none of the patients reached normal development. The capacity to live an independent life has been reported in one patient. One adult patient seems dependent on her parents to help to manage her everyday life.

Improvement of hearing ability could be seen in our patient group. In some patients, hearing aids were discontinued. Total resolution of hearing disability was not found. In the long term, many patients with alpha-mannosidosis required hearing aids even after HSCT.

Stabilization or even improvement of skeletal abnormalities was reported by some of the treating physicians. Still, obtaining hard evidence for this proved to be very difficult, as measurement and quantification of skeletal abnormalities is difficult in the growing skeleton.

Compared with Hurler's disease, the most common mucopolysaccharidosis with a transplant indication, several differences can be noted. First, neurodevelopment in mannosidosis was less impaired at presentation for HSCT, and HSCT was performed in older patients. These patients still seemed to gain a developmental benefit. Also, neuroimaging in mannosidosis was much less abnormal, and improvements after HSCT were much more discrete. Although dysostosis was a problem for all mannosidosis patients, compared with Hurler's disease, it appeared to be milder and to progress more slowly after HSCT.

The most important clinical problem for alpha-mannosidosis patients was their deficiency in hearing and expressive speech. Most patients with Hurler's disease that are transplanted early develop almost normal hearing and speech that is appropriate for their (delayed) developmental stage. It is our impression that expressive speech, and probably functioning of the auditory system, was disproportionately affected in our alpha-mannosidosis patients. HSCT improved auditory functioning in some, but not all patients, suggesting that contribution of sensorineural hearing impairment to neurodevelopmental disability is more prominent in alpha-mannosidosis than in Hurler's patients.

Finally, HSCT-associated side effects and late effects may have a relevant influence on the post-transplant outcome. Patients that experienced few side effects during transplantation seemed to have better neurodevelopmental

outcome and better social integration than those that experienced a complicated transplant course. Therefore, strategies to reduce HSCT-associated side effects are needed.

Conflict of interest

The authors declare no conflict of interest.

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