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Results of allogeneic hematopoietic stem cell transplantation in patients with alpha-mannosidosis – a review of 14 cases

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Introduction

Alpha-mannosidosis and its natural course

Alpha-mannosidosis is a rare lysosomal storage disease with an autosomal recessive inheritance based on a mutation in the MAN2B1 gene coding for the protein alpha-mannosidase. Patients suffer from mental retardation, skeletal and facial abnormalities, hearing impairment and immunodeficiency.

Three clinical forms of the disease have been described: A mild form with only slightly affected patients and very low progression, a moderate form with slow progression and a severe form with rapid progression leading to early death. Still, a clear assignment of a patient to one of the three clinical forms is very difficult. In fact, the clinical presentation is more a spectrum than three sharply distinguishable subgroups. Due to its low incidence and the big inter-individual variation, it is very difficult to exactly predict the long-term course for each individual patient at an early time point.

Therapy

All patients require interdisciplinary supportive care (orthopedically, audiologically e.g.). Allogeneic hematopoietic stem cell transplantation (HSCT) is considered standard-therapy for patients with severe forms. It is the only specific treatment since there is no enzyme replacement- or gene therapy available at this time.

So far, only four follow-up-reports with a total of seven patients with alpha-mannosidosis that underwent HSCT have been published.

Aims of this study

The aim of this study was to summarize the experience of the centers worldwide that perform HSCT for the treatment of alpha-mannosidosis. Primary objective was the investigation of the following data:

- transplant characteristics (donor selection, conditioning, GvHD-prophylaxis)
- transplant complications and survival after HSCT
- evaluation of changes in mannosidosis-specific complications (developmental retardation, hearing impairment)

Patients and methods

A retrospective analysis of 14 cases of alpha-mannosidosis that underwent HSCT in nine different centers.

Twelve patients were identified by personal contact to transplant physicians. Two others were contacted directly via the International Advocate for Glycoprotein Storage Diseases (ISMRD; Dr. Forman). Patients asked their transplant centers for support of our study.

Results

Transplant characteristics

No.	Donor	Stem Cell Source	Year of HSCT	Conditioning	GvHD-prophylaxis
1	MMUD (5/6)	CB	2005	Bu / Cy 200 / ATG	CSA, Pred
2	MMFD	PBSC	2006	Flu 180 / Bu / Mel 140 / ATG // OKT3 + Pred	MMF
	MMFD + MMUD	PBSC + CB	2007	Flu 180 / Treo 42 / TT 10 / ALG	CSA / MMF / MTX
3	MUD (10/10)	PBSC	2008	Flu 180 / Bu / Mel 140 / ATG	none
4	MMUD (8/10)	PBSC	2008	Bu / Cy 200 / ATG	MTX / CSA
5	MRD *	PBSC	2000	Bu / Cy 200	OKT3 - Pred
6	MMFD	PBSC	2005	Flu 30 / Bu / Mel 140 / ATG	-
7	MRD	BM	1997	Bu / Cy 200	MTX / CSA
8	MMUD	NA	1997	BU / Cy / TBI / ATG	CSA, MPred, Elutriate
9	MUD	BM	1997	Bu / Cy / TBI / ATG	CSA, MPred, Elutriate
10	UCB	CB	2002	Bu / Cy / TLI	CSA, MPred
11	NA	NA	1999	Bu / Cy / TBI	NA
12	MMUD (4/6)	CB	1999	Bu / Cy 200 / ATG	
13	MUD	BM	2001	Bu / Flu 40 / ATG	MTX / CSA
	MUD	BM	2002	TBI 1200cGy / Cy 60 / ATG	CSA / MMF
14	MUD	BM	2004	Bu / Cy 200	Alemuzumab

* MRD is a 10/10 HLA-identical mother

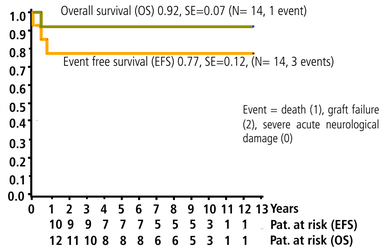
Complications

Infectious complications	Severe sepsis	4 (Pat. 1., 2, 12 and 13)
	- with respiratory failure	3 (Pat. 1, 2 and 13)
	- leading to death	1 (Pat. 1)
	CMV-Pneumonia	1 (Pat. 9)
	CMV-Retinitis	1 (Pat. 11)
Engraftment/GvHD	Graft failure	
	- requiring DLI	1 (Pat. 5)
	- requiring Re-Transplantation	2 (Pat. 2 [twice], Pat. 13)
	Relevant GvHD	
	- chronic	3 (Pat. 6, 11 and 12)
	- acute (≥II°)	2 (Pat. 12 and 13)
Other	BOOP	2 (Pat 4 and 8)
	Hemolytic anemia	1 (Pat. 6)

General abbreviations:
NA = not available; ND = not done; mo = months; Pts = points; StdSc = standard-score; yr = years; ** results have been published elsewhere

Abbreviations (Transplant characteristics and complications):
MMUD = mismatched unrelated donor; MMFD = mismatched family donor; MUD = matched unrelated donor; MRD = matched related donor; PBSC = peripheral blood stem cells; BM = bone marrow; UCB = umbilical cord blood
Bu = Busulphan; Cy = Cyclophosphamide; Flu = Fludarabine; Mel = Melphalan; ATG = anti-thymocyte globulin; TBI = total body irradiation; TLI = total lymph node irradiation; CSA = Ciclosporin A; MMF = Mycophenolate Mofetil; Pred = Prednisolone; Mpred = Methylprednisolone; BOOP = Bronchiolitis obliterans organizing pneumonia; DLI = Donor lymphocyte infusion; GvHD = Graft versus host disease

Event free survival and overall survival after HSCT



Hearing after HSCT

No.	Before HSCT		After HSCT		
	Test result	Hearing aid	Test result	Hearing aid	Time after HSCT
1	ND	NA	Died 135 days after HSCT		
2	Reduced	no	High grade hearing loss	yes	1 7/12 (2 7/12)
3	-50dB	yes	-30dB	no	1 1/12
4	ND	no	Mild hearing loss	no	2 4/12
5	-60dB	no	-35dB**	no	3
6	-50dB	yes	-35 to -40dB***	yes	2 7/12
7	-60 to -80dB	yes	-50 to -70dB	yes	5
8	NA	yes	High frequency loss	no	7 5/12
9	Mild hearing loss	no	Mild hearing loss in low frequencies Moderate in high freqencies	no	5 6/12
10	Mild to moderate hearing loss	no		yes	
11			Mild low-frequencies hearing loss	no	2 10/12
12	Mild to moderate hearing loss	yes	-30 to -40dB (L), -10 to -30dB (R)	yes	10 1/12
13	-50dB (L) -70dB (R)	yes	-10 to -20dB (aided)	yes	9/12 (1 6/12)
14	Hearing loss	NA	Sensory neural and conductive deafness	yes	NA

Neurological development after HSCT

No.	Before HSCT			After HSCT			
	Findings	Test method	Age	Findings	Test method	Age	Time after HSCT
1	IQ 85, loss of milestones	WISC-III		Died 135 days after HSCT			
2	Speech 15-16 mo Social contact 19-25 mo Fine motor skills 23-34 mo Gross motor skills 18-28 mo	DS	40 mo	Speech 15 mo Social contact 4,5 yr Fine motor skills 3 yr Gross motor skills 3,5-4 yr	DS	6,5 yr (=55 mo)	1,6 yr (2,6 yr after 2nd HSCT)
3	Speech 14-15 mo Social contact 21 mo Fine motor skills 18 mo Gross motor skills 24 mo	MFED	31 mo	Speech 20-24 mo Social contact 24-29 mo Fine motor skills 24-29 mo Gross motor skills 30 mo	DS	3,7 yr (=43 mo)	1,1 yr
4	Speech 14-23 mo Social contact 23-31 mo Fine motor skills 24-31 mo Gross motor skills 23-30 mo	MFED	35 mo	ND			
5	Delayed speech development Delayed fine motor skills**	NS		Non-verbal IQ 94(SON) Speech development 3 yr**	SON	4,25 yr (=51 mo)	2,25 yr
6	Developmental age 31 mo SON 52 Pts	SPT SON	41 mo	Cognitive age 2 1/2 - 3 yr Speech development 2,5 -2,75 yr	HWIT	6,5 yr (=78 mo)	2,75 yr
7	Developmental age 4 - 5 yr	ITPA and WISC-R	7 yr	Developmental age 7-8 yr	WISC-R	12 yr	2 yr
8	**			**			
9	**			**			
10	**			**			
11	**			**			
12	Normal mental development Slightly delayed adaptive skills Global language delay Growth delay		3 yr	Visits 6th grade			10 yr
13	Communication skills 25 mo (StdSc 58) Daily living 17-24 mo. (StdSc 45) Socialisation 28 mo (StdSc 66) Motor skills 18 mo (StdSc 37)	VABS	5 yr	Adaptive Behaviour StdSc 48-53 Mathematics StdSc 40 Oral language StdSc 45	ABAS-II WIAT-II	12,8 yr	7,8 yr
14	Speech delay			NA		7,25 yr	3,6 yr

Abbreviations (Neurological development after HSCT):
ABAS-II = Adaptive Behavior Assessment System II; DS = Denver Scale; HWIT = Hannover-Wechsler Intelligenztest für Vorschulalter; ITPA = Illinois Test of Psycholinguistic Abilities; NS = no systematic testing performed; SON = non-verbal Snijders-Ooen IQ-testing; SPT = Symbolic Play Test; VABS= Vineland Adaptive Behavior Scales; WIAT = Wechsler Individual Achievement Test; WISC-III/-R = Wechsler Intelligence Scale for Children-III/-Revised

Abbreviations (Hearing after HSCT):
(L) = left; (R) = right; dB = decibel; ***hearing aid had been discontinued until 5 years after HSCT

Discussion

Transplantation and side effects

The conditioning regimens used showed big variations. Regimens used in early transplantations that included TBI or TLI have been replaced by chemotherapy-based regimens like Bu/Cy or Flu/Bu(+Mel) in first-line-conditioning. New treosulfan-based conditioning regimens have only been used in one patient for conditioning after graft failure.

Patients experienced transplant-associated side effects to an expected level. One of 14 patients did not survive HSCT, two more experienced graft failure and underwent re-transplantation. At a median follow-up of 6,9 years [0,4 to 12,9] the 13 other patients are alive and showed stable donor-derived chimerism.

Hearing

Hearing impairment is a well-described feature of all alpha-mannosidosis patients. At diagnosis most of the patients suffered from hearing impairment to different extents. Six of eleven patients of whom data were available required hearing aids. After HSCT, hearing aids could be discontinued in three cases. One patient required a hearing aid before transplantation, and did not need it directly after transplantation, but progressive hearing impairment let to placement of a hearing aid at last follow-up 5 years after HSCT.

Neurological development after HSCT

Developmental data at HSCT were available for ten patients. Data of five patients (Pat. 5 and 8 to 11) have already been published[1, 2] and showed developmental progress after HSCT. The other patients also showed developmental progress after HSCT. None of the patients showed normal development, however.

Speech development, even after HSCT, appeared to be most affected by mannosidosis. Patients have learned to talk and to communicate. One patient (Pat. 7) even learned to speak a foreign language. In general, motor skill development was faster than speech development.

So far there is no way to predict the developmental trajectory of a patient at the time of HSCT. All patients in this series had developmental delay at the time of HSCT and belonged to the more severely affected patient group, so complete neurodevelopmental recovery was not expected.

Conclusion

The patients tolerated conditioning and HSCT without unusual or unexpected complications. The final survival rate with engraftment was 92% making HSCT a feasible therapeutic option which may promote mental development.

However, the natural history of alpha-mannosidosis without transplantation is so far not well characterized. Therefore, it is difficult to predict before HSCT how severely the affection of an individual patient would become if he or she was not transplanted. That is why the quantification of the developmental benefit of HSCT for patients with alpha-mannosidosis remains difficult.

Still, patients that underwent HSCT showed clear developmental progress afterwards, even though a normal development was not achieved.

To answer the question whether or not patients with alpha-mannosidosis benefit from HSCT, careful evaluation of neurodevelopmental outcome of transplanted and non-transplanted patients is an important task for the future.

Literature:
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