

Stem cell transplantation in Hurler Syndrome: *What is the best cure and how do we care?*

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On behalf of the Working Party Inborn Errors EBMT in collaboration with the MPS society



What is Hurler syndrome?

- It is a devastating progressive and lethal disorder
- Almost all organs are involved
- It is caused by a defect in a single enzyme (α -iduronidase)
- The enzymatic defect leads to accumulation of mucopolysaccharides in body tissues
- The accumulation causes cell dysfunction and cell death
- This leads to progressive invalidation and handicaps

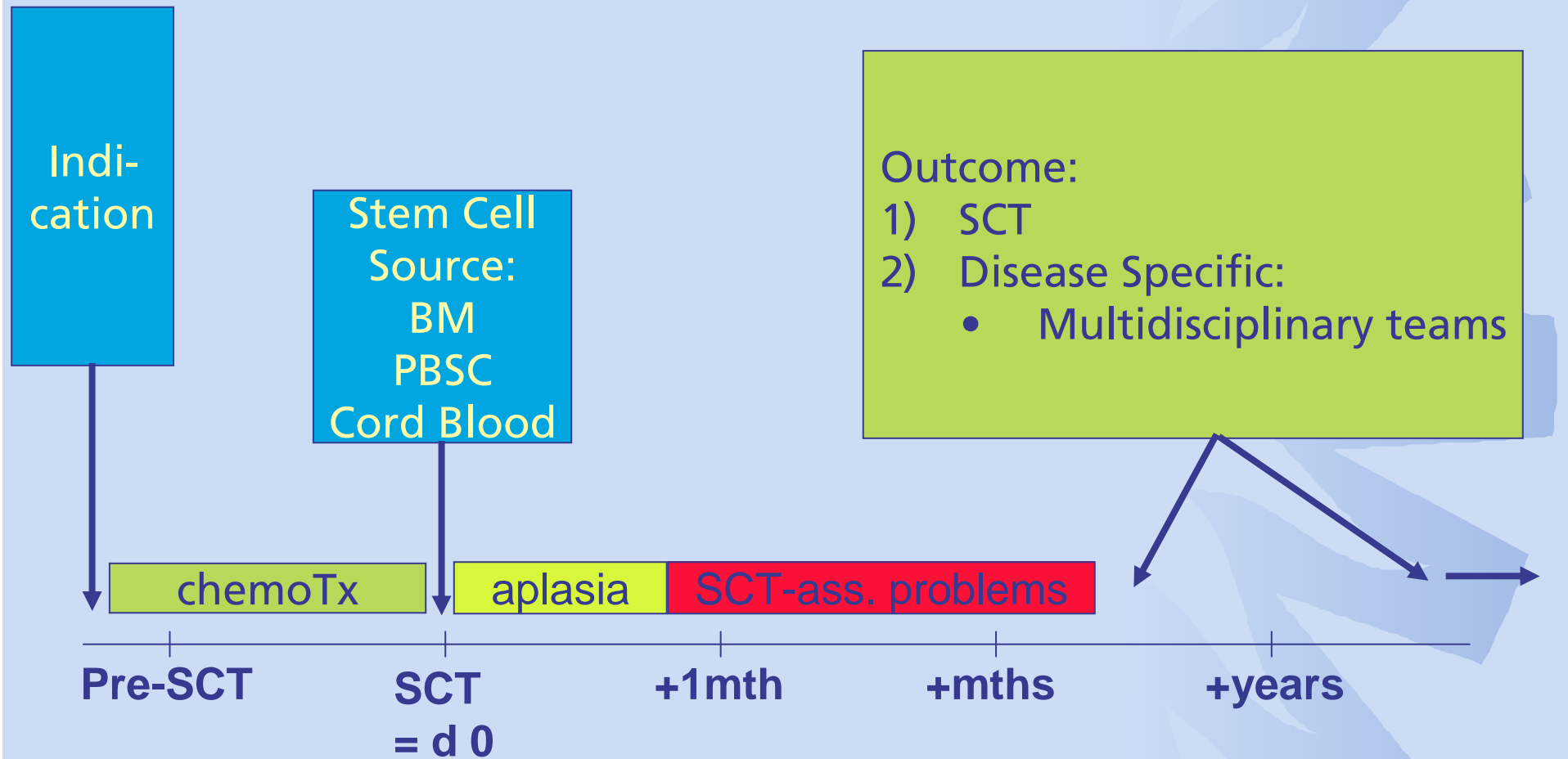


Why stem cell transplantation for Hurler syndrome?

Stem cell transplantation is the only treatment available that can save the brain from getting affected and reverse disease symptoms!



Clinical Approach



Supportive care: disease- & HCT-related



SCT for Hurler Syndrome (HS)

3 patients 1.5-2.5 years after SCT



How does it work? (I)

- Replacing defective enzymes by giving blood cells with normal enzyme activity
- Blood cells will distribute in almost all body tissues
- Blood cells will cross the blood-brain barrier and restore enzyme activity in the brain



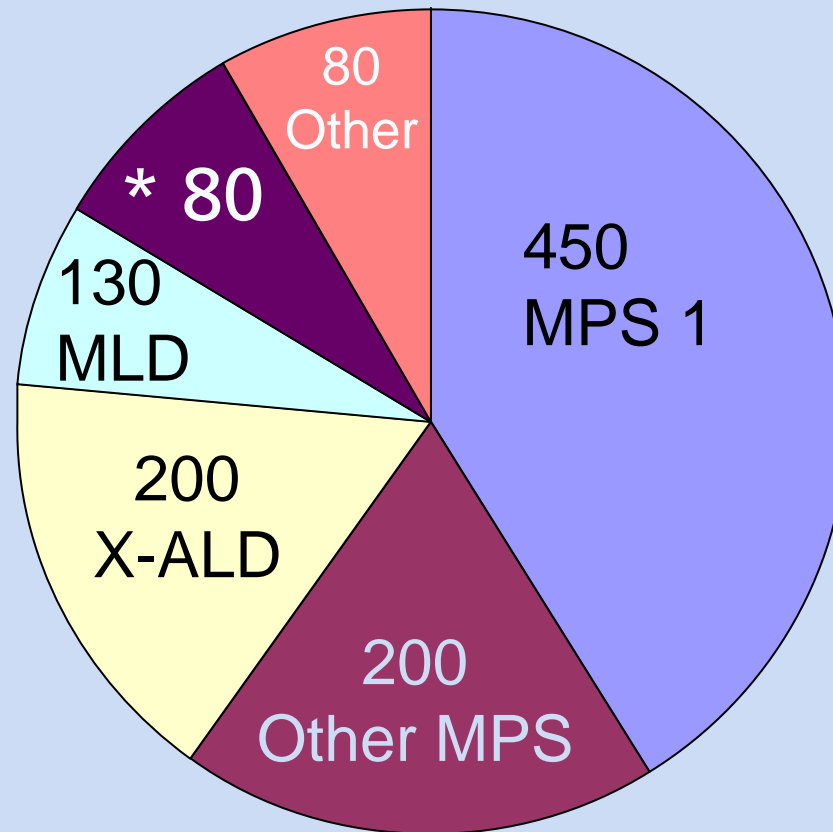
How does it works? (II)

- Source of the donated blood cells can be:
 - Stem cells from peripheral blood
 - Stem cells from bone marrow
 - Stem cells from **umbilical cord blood**



Is it an experimental therapy?

Worldwide: almost 1000 registered patients underwent SCT for an IEM
(registry: EBMT and CIBMTR 2004)



* Other Leucodystrophies / white matter diseases



What do we know about the long term outcome of SCT?

- We don't know the natural course of Hurler syndrome after SCT!
- Long term outcome encouraging, however:
 - Success is limited by high rates of graft-failure / (Mixed Chimerism)
 - What exactly is the long term outcome?
 - What is the residual disease burden?
- How can we further optimize SCT for HS?
 - Europe (world) wide studies (EBMT)



Collaborative Studies Performed: SCT for MPS1

On behalf of WP-IE EBMT (and Eurocord)

1. Outcomes of Haemotopoietic Cell Transplantation for MPS-1 in Europe: a risk factor analysis (n=146): **in press**
2. Outcomes of Cord Blood Transplantation for Hurler's Syndrome. An Eurocord-Working Party Inborn Errors EBMT Survey: Manuscript in preparation. Presented on EBMT-Lyon 2007
3. Stem Cell Transplantation in combination with Enzym Replacement Therapy in patients with Hurler Syndrome: **BMT 2006**
4. **Study proposal:** Long Term Outcome of Hurler Syndrome Patients after successful Stem Cell Transplantation



SCT for Hurler Syndrome

Summary Results from Previous studies

- Graft Failure can be reduced by avoiding the following transplantation techniques (**novel EBMT-guidelines**):
 - T-Cell Depletion
 - Reduced Intensity Conditioning
 - Busulfan should be given using TDM (therapeutic drug monitoring)
- Cord Blood might be the preferred cell source
 - Results in full-Donor Chimerism associated with higher enzyme levels
- Low rate of transplantation associated morbidity/mortality
 - like “graft-versus-host disease”



What do we not know about the long term outcome of SCT for Hurler Syndrome?

- We don't know what the optimal SCT source is etc
- We don't know what the optimal in- and out patient care for patients with Hurler syndrome is
- We don't know the natural course after successful SCT
 - Residual Disease Burden



New Study

Study the long term follow-up of successfully transplanted HS patients

Started in November 2006



Aims (I)

1. To study predefined long-term outcome parameters (e.g. neuropsychological, orthopedic) in a European cohort of HS-patients successfully (being “alive and engrafted”) transplanted between 1980 and 2005 with a minimum follow up 36mths.
2. Influence of source, mixed-chimerism, genotype.....on these predefined long term outcome parameters
 - **To optimize selection criteria, transplantation techniques**



Aims (II)

1. Innovation in care for patients with Hurler syndrome post SCT:
 - Analyze the need and processes of medical and nursing care via validated methods
 1. MPOQ
 2. PEDI
 3. Focus Groups
 4. Questionnaires regarding Family Issues
 5. Development of standardized protocols of care
 6. Develop quality control instruments
 7. Develop political instruments to increase awareness and improve hospital policies
 - Standardized protocols health care administration / hospital management



Approach

- Prospective multi-center study using the Hurler Database (190 transplanted patients)
 - 135 more than 3 year follow up (1/2008)



Participating centers

- Primary investigators (JJB, Tom de Koning) and study coordinators in University Children's Hospital Utrecht, The Netherlands
 - Mieke Aldenhoven: PhD-student
 - Manchester: Ed Wraith en Rob Wynn
- EBMT-centers:
 - Manchester
 - Lyon
 - London
 - Dublin
 - Paris
 - Utrecht
 - Monza and others

- In collaboration with:



Future

- Neonatal screening
- More collaboration with CIBMTR: Worldwide registry
- Gene therapy (organ specific)
- ...



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Maureen Cleary, GOS, London



TABEL 2 Resultaten na SCT bij patiënten met het syndroom van Hurler.

	n =	SCT bron	Mediane lft SCT (mnd)	Mediane follow-up (mnd)	Succesvolle SCT ¹ (%)	Volledig donor chimerisme ² (%)	Normale enzymcon ³ (%)	GvHD		
								Acuut ⁴ (%)	Chronisch (%)	
								0-I	II-IV	
Peters 1996 ^{ref 5}	21	BM ⁵			43		56			
	19	BM ⁶	20	34	26	87	67	70	30	30 ⁷
Peters 1998 ^{ref 6}	28	BM ⁸	22	88	75	71	30	68	32	0
	26	BM ⁹	23	55	35	89	0	45	55	41 ¹⁰
Souillet 2003 ^{ref 7}	27	BM	25	72	70	52	53	91	9	0
Staba 2004 ^{ref 13}	20	NSB	16	30	85	100	100	72	28	12 ¹¹
Boelens 2005 ^{ref 14}	146	↔ ¹²	18	44	56	71	60	84	16	7 ¹³

Afkortingen: BM: beenmerg, enzymcon: enzymconcentratie, GvHD: Graft-versus-Host Disease, lft: leeftijd, mnd: maanden, n=: aantal patiënten, NSB: navelstrengbloed, ref: referentie, SCT: stamceltransplantatie, ↔: verschillende stamceltransplantatiebronnen

Superscript: ¹ levend en > 10% donor chimerisme, ² > 95% donor chimerisme, ³ volgens lokale normaalwaarden, ⁴ acute GvHD-gradering: 0-I: geen tot mild, II-IV: matig tot ernstig, ⁵ Hoge dosis BM (≥ 3.5*10⁸ cellen/kg), ⁶ lage dosis BM (< 3.5*10⁸ cellen/kg), ⁷ waarvan 6 patiënten met uitgebreide chronische GvHD, ⁸ HLA genotypisch-identieke broer of zus ⁹ HLA-haploidentieke verwante donor, ¹⁰ waarvan 5 patiënten met uitgebreide chronische GvHD, ¹¹ geen gevallen van uitgebreide chronische GvHD, ¹² beenmerg, perifere bloed of navelstrengbloed, ¹³ waarvan 1 patiënt met uitgebreide chronisch GvHD



TABEL 3 Resultaten na SCT met navelstrengbloed als stamcel donor bij patiënten met een ASZ.

	Ziekte beeld	n=	Mediane lft SCT (mnd)	Mediane follow-up (mnd)	Succesvolle SCT ¹ (%)	Volledig donor chimerisme ² (%)	Normale enzymcon ³ (%)	GvHD		
								Acuut ⁴ (%)	Chronisch (%)	0-I
Staba 2004^{ref 13}	Hurler	20	16	30	85	100	100	72	28	12 ⁵
Escolar 2005^{ref 12}	Krabbe	11 ⁶	0,5	36	100	100 ⁸	100	91	9	18 ⁵
		14 ⁷	8	41	43	100	100	44	56	11 ⁵
Boelens 2007^{ref 15}	Hurler	15 ⁹	18	18	40	100	100	85	15	19 ¹²
		25 ¹⁰			84	93 ¹¹	100			
Martin 2006^{ref 9}	↔ ¹³	31 ¹⁴	22	25	81	96 ¹⁶	100	64	36	19 ¹⁷
		38 ¹⁵			64	100	100			

Afkortingen: enzymcon: enzymconcentratie, GvHD: Graft-versus-Host Disease, lft: leeftijd, mnd: maanden, n=: aantal patiënten, ref: referentie, SCT: stamceltransplantatie, ↔: verschillende ziektebeelden

Superscript: ¹ levend en >10% donor chimerisme, ² >95% donor chimerisme, ³ volgens lokale normaalwaarden, ⁴ acute GvHD-gradering: 0-I: geen tot mild, II-IV: matig tot ernstig, ⁵ geen gevallen van uitgebreide chronische GvHD, ⁶ asymptomatische neonaten, ⁷ symptomatische neonaten, ⁸ 1 neonaat met een gemengd chimerisme, deze neonaat ontving géén antithymocyt globuline (ATG), ⁹ SCTs < 2001, ¹⁰ SCTs > 2001, ¹¹ 2 patiënten met een gemengd chimerisme (86 en 92% nog steeds toenemend), ¹² waarvan 3 patiënten met uitgebreide chronisch GvHD, ¹³ Hurler (21), Hurler-Scheie (2), Hunter (2), Sanfillipo (10), I-cell (1), Krabbe (16), adrenoleukodystrofie (8), metachromatische leukodystrofie (6), Tay-Sachs (3), ¹⁴ SCT 1999-2002, ¹⁵ SCT 2002-2004, ¹⁶ 1 Hunter patiënt met een gemengd chimerisme ¹⁷ waarvan 2 patiënten met uitgebreide chronische GvHD

