Hematopoietic Cell Transplantation for Mucopolysaccharidosis: Current status and future perspectives

Carmem Bonfim, Lisandro Ribeiro, Samantha Nichele
Pediatric Blood and Marrow Transplantation Program
Federal University of Parana – Curitiba – Brazil

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Summary of the talk

- IEM comprise a large group of inherited disorders, some of which might be improved following HCT.
  - Current indications for HSCT in Hurler (MPS I) and Hunter (MPS II)
- Disease specific issues
- Transplant outcomes worldwide
- Challenges and transplant outcomes in Brazil
- Future perspectives
Introduction

- These devastating diseases may affect bone integrity, growth and development, cardiopulmonary status, the airway, hearing and vision, neurological and cognitive function.

- Genotype–phenotype correlations: Severe phenotypes with little residual enzyme activity usually have an early onset and rapid deterioration followed by early death.

- Treatment recommendations are based on the diagnosis, phenotype, rate of progression, prior extent of disease, family values and expectations and the risks and benefits associated with all available therapies, including HCT.

Boelens et al; Br J Hematol 2014
What is the rationale?

- Goal is to provide cells that can produce the missing enzyme
- Can halt or stabilize the disease progression
- 6-12 months before effects can be observed clinically
- Balance the risks with the probability of improving disease-related symptoms
- Timely diagnosis and immediate referral to an IEM specialist/dedicated transplant center as well as collaboration (between specialists, centers and countries) are essential steps for optimal management and better outcome.

_Boelens 2007; Chiesa 2016; Wynn- EBMT oral presentation 2016_
How does it REALLY work?

The effectiveness will depend on the migration, homing, and engraftment of donor derived cells to affected organs.

Microglia turnover may take 4-6m

CROSS –CORRECTION

- The effectiveness will depend on the migration, homing, and engraftment of donor derived cells to affected organs.

Aldenhoven et al BBMT 2008
Hurler Syndrome

- Autosomal recessive disorder caused by alpha iduronidase deficiency.
- Intracellular accumulation of GAGs disrupts normal cell function and results in progressive multiorgan dysfunction (neurocognitive delay, dysostosis multiplex, cardiopulmonary complications and early death.

UK patients 1981-2003
196 pts with Hurler
67 transplants (65 hurlers)

Moore et al 2008

Manchester/Utrecht
data: 62 pts with MPS

Aldenhoven BBMT 2015
Outcomes of HSCT using various stem cell sources in children with Hurler syndrome after MAC conditioning

N=258 Hurler syndrome after myeloablative HCT 1995-2007: all sources

Duke University, Minnesota, CIBMTR, EUROCORD, EBMT

Age at HCT

Source / HLA matching

- MSD, 81±6% (n=37)
- 6/6 CB, 81±9% (n=22)
- 5/6 CB, 68±6% (n=66)
- MUD, 66±7% (n=47)
- 4/6 CB, 57±10% (n=28)
- MMUD, 41±6% (n=58)

Boelens et al Blood 2013
How well does transplant work for Hurlers?

- Rapid improvement: hepatoesplenomegaly and obstructive symptoms
- Normalizes enzyme levels (lifelong), GAG excretion is reduced.
- Myocardial function is preserved, no progressive coronary involvement. Valve deformities persist.
- Neurocognitive function improved. Prevention of hydrocephalus.
- Improvement in vision and hearing. Retinal degeneration may occur.
- Skeletal abnormalities persist (HSCT in young pts < 6m???)
- Improvement in joint mobility

- **Outcome will depend on genotype, age of HSCT, mental status at HSCT, donor chimerism and enzyme level**

_Aldenhoven et al BBMT 2008_
Risk Factors before transplant

- Pulmonary problems before HSCT
  - Sleep apnea; history of snoring
  - Previous difficulties to extubation
  - History of pneumonia
  - Reactive lower airway disease

**Role of ERT!!!**

- Patients in a very poor clinical condition, especially those with cardiac dysfunction, may improve significantly on ERT, making them eligible for HCT.

*(Wiseman et al 2013)*
Use of ERT is becoming less controversial

- Single and multicenter studies.
- ERT prior to HSCT could improve somatic performance and decrease the probability of HSCT complications due to accumulation of GAGs.
- ERT is well tolerated but the combination of ERT and HSCT did not significantly affect rates of survival, engrafted survival or TRM when compared with HSCT alone.
- Currently, many centers are administering ERT prior to HSCT and continuing it until either start of the conditioning or achievement of engraftment.

Long term outcome: 217 pts with MPS-1H, 10 international centers. *Aldenhoven Blood 2015*

- Age at transplant: **16m** (2-47) and age at last follow-up: **9 ys** (3-23)
- Age and baseline clinical status at HSCT as well as IDUA levels post-transplant were important prognostic factors
- Neurodevelopment outcome was negatively influenced by a lower baseline development IQ, higher age at HCT and the use of TBI
- A higher level of IDUA was associated with less complications
Neonatal BMT prevents bone pathology in a mouse model of MPS type I

- BMT increases the life span of patients with MPS IH, musculoskeletal manifestations are only minimally responsive if the timing of BMT delays, suggesting already irreversible bone damage.

- The authors tested the hypothesis that transplanting normal BM into newborn MPS I mice soon after birth could prevent skeletal dysplasia.

- At 37 weeks of age, they observed an almost complete normalization of all bone tissue parameters, using radiographic, microcomputed tomography, biochemical, and histological analyses.

- Overall, the magnitude of improvements correlated with the extent of hematopoietic engraftment. We conclude that BMT at a very early stage reduces signs and symptoms of MPS I before they appear.

Pievani et al Blood 2015
MPS treatment guidelines

- 1\textsuperscript{st}: Non carrier MSD or unrelated CB 6/6
- 2\textsuperscript{nd}: MUD BMT
- 3\textsuperscript{rd}: Unrelated CB 4/6 or mismatched unrelated BMT
- Myeloablative prep regimen
- Drug monitoring (busulfan)
- FU: multidisciplinary team

Figure 2 Treatment algorithm for MPS I patients.

* HSCT might be considered under special circumstances
** In patients with presumed MPS I-H

Ru et al.; 2011
The early progressive form of the X-linked disorder MPS II is characterized by cognitive decline, pulmonary and cardiac complications that often cause death early in life.

Deficiency of iduronate-2-sulfatase results in deposition of the GAGs, dermatan, and heparan sulfate in various tissues.

Enzyme replacement therapy has become the mainstay of treatment, but is ineffective in arresting cognitive decline.

HSCT provides enzyme replacement, and may be effective in stabilizing neurocognitive function if initiated early, although data are limited.

A. Selvanathan et al, 2018
50% of pts affected by progressive central nervous system (CNS) disease and 50% children affected by a milder phenotype and no significant neurological involvement.

Earlier reports did not show any benefit from SCT. This data is outdated and should be revisited.

Correlation between genotype and phenotype in MPS II is not clear but large deletions may be associated with a severe phenotype.

Most centers would offer HSCT in the first 1-2 years of life in case of high risk of developing CNS phenotype (genotype or a previous affected family member).

Chiesa 2016; Boelens 2014
HSCT for pts with MPS III and VI

- **MPS III – Sanfilippo**
  - Duke University: 12 of 19 pts treated with UCBT are alive, 9 showed disease stabilization (little impact in cognitive function). Children transplanted < 2 ys of age showed modest gains in cognitive skills. *Prasad and Kurtzberg 2010*
  - Dutch experience: no benefit in 2 pts transplanted before symptoms. Both had full donor chimerism and biochemical correction of MPSIII. *Welling et al 2015*

- **MPS VI – Maroteaux-Lamy:**
  - Autosomal recessive. Arylsulfatase B deficiency.
  - **121 untreated pts: primary cognitive impairment due to central nervous system GAG storage is not common.**
  - CIBMTR study: 45 MPS VI pts with a median age of 5 ys (range, 1–22 ys) at the time of HCT. CI of aGVHD at 100 days was 36%. OS was 78% at 100 days and 66% at 1 and 3 years. *With the availability of an effective ERT, the future role of HCT in treatment of patients with MPS VI is unclear* *Rosenthal 2016*
Brazilian Experience: 25 pts
HSCT for Mucopolysaccharidosis: 1988 to 2018

- HC-UFPR: 15 pts
- HNSG: 1 pt
- HPP: 1 pt
- Rio de Janeiro: 1pt
- ITACI: 1 pt
- Einstein: 2 pts
- HC- UFRGS: 4 pts
MPS Hurler: 17 pts

- Age: 1 – 4 ys (Median: 2ys)
- Gender: 9 M/8 F
- Type of donor:
  - Matched Sibling: 2 pts
  - Matched related (mother): 2 pts
  - Unrelated: 13 pts (7 CB)
- Bone marrow was the stem cell source in 10 pts while cord blood was used in 7 pts
- Preparatory regimen:
  - All pts received a MAC regimen
    - BU+CY+/- ATG or BU+FLU+ATG
MPS Hurler: 17 pts

• Engraftment:
  • **BM: 5/10** developed PGF or SGF, and 4/5 are alive waiting a second transplant (n=2) or receiving ERT (n=2)
  • **CB: 4/7** pts developed PGF, and 2/4 are alive. One after the 3rd transplant and one with autologous recovery.

• Overall Survival:
  • 11 pts are alive between 10 months and 18 ys,
  • 6 pts have full donor chimerism, one after a 3rd transplant
    • 1 pt has mild C-GvHD)
  • 5 pts have mixed chimerism, none with acute or chronic GvHD
  • NO GOOD DATA ON LTFU
Causes of death - Hurler

- 6 pts died between 22 and 315 days
  - D+ 22 (2018): 20 months old, URD CBT 6/10, VOD
  - D+ 93 (1997): 4 ys old, MUD BMT, GvHD + sepsis
  - D+ 102 (2012): 2 ys old, URD CBT 5/8, GF (2 CB transplants)
  - D+ 151 (1993): 3 ys old, MRD (mother), GvHD + fungal infection
  - D+ 288 (2007): 1 ys old, URD CBT 7/8, GF (3 CB transplants)
  - D+ 315 (2013): 2 ys 11 months, URD BMT, GF, (2 transplants)
Better donor selection, higher enzyme level and full donor chimerism

Wynn RF BMT 2009
All male and all received MAC regimen and unrelated CBT

- 2 months old, unrelated CBT 5/6 in 2009. Alive and well 8 ys after transplant. No GVHD. Mixed chimerism (90%)
- 2 ys-old, unrelated CBT 5/6 in 2011. Died on D+ 104 from disseminated adenovirus. No GvHD. Full donor chimerism
- 1 yr-old, unrelated CBT 5/6 in 2017. Alive and well but progressive loss of donor chimerism. Family denied a 2nd CBT
Can HSCT change the outcome if performed very early and if everyone **works together**?

Porto Alegre: Diagnosed intra uterus : Giugliani’s team

Curitiba: Unrelated 5/6 cord blood transplantation at the age of 2m

Rio de Janeiro: Post transplant care: Dr Dafne Horovitz ’s team + INCA BMT team
MPS type III and type VI

- MPS III: HLA MSD BMT in 1988. 5 ys-old female, asymptomatic. Full donor chimerism, no GvHD but progressive neurological deterioration. Lost to follow up.
- MPS VI: 3 pts
  - 7 ys-old, female, URD mismatched BMT in 1997, died on D+ 37 due to severe acute GvHD and TMA
  - 10 ys-old, male, Matched URD BMT in 2005, died on D+ 48 due to severe acute GvHD
Latin America Activity:
Increasing BUT still VERY LOW

- Curitiba: 44 pts with IEM
  - MPS: 17; ADL: 24; GLD: 1; MLD: 1, Gaucher: 1
- Porto Alegre* (MPS: n=4);
- Sao Paulo* (MPS n=3)
- Rio de Janeiro (MPS n=1)

Latin America: MPS (until 12/2016)
- Chile: MPS I, n=2
- Venezuela: MPS I, n=1
- Colombia: MPS I, n=1
- Argentina: MPS I, n=3; MPS II n=7
- Mexico: MPS I, n=2

600 million inhabitants !!!!!!!
LESS than 40 MPS pts transplanted in South America
Final comments

- Approved indication by the Brazilian public health system since 2018, thanks to the big effort from the Brazilian Genetic Society (Dra Carolina F Moura)

HCT is an effective treatment option for selected patients with MPS I and II. Residual disease burden may be high after HSCT, and patients need to be followed up by a multidisciplinary team.

Early referral leads to much better outcomes. No benefit in advanced diseases, especially in countries with limited resources and few transplant beds.

- Brazilian Pediatric BMT centers : Cure4kids platform : every Tuesday; 7:15 AM (Sao Paulo’s time): Everyone is welcome

NATIONAL AND INTERNATIONAL COLLABORATION IS THE KEY TO A SUCCESSFUL TRANSPLANT
Muito obrigado

Curitiba BMT team

- HC-UFPR: Dr Pasquini, Dra Carmem Bonfim; Samantha Nichele, Gisele Loth; Joanna Trennepohl, Adriana Melo, Adriana Koliski, Rebeca Mousquer, Daniela Marinho, Paula Tacla, Pollianay Pelegrina

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Jaap Boelens
Utrecht Univeristy

Joanne Kurtzberg
Duke Univeristy

carmembonfim@gmail.com
lisandro.ribeiro18@gmail.com