Hematopoietic Cell Transplantation in Lysosomal Storage Diseases; Optimizing Safety and Efficacy

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Research Program
Hematopoietic Cell Transplantation

A. U-DANCE-project
(Utrecht Dendritic Cells against Cancer)

1) Individualized Conditioning: Predictable IR
2) Development of Adjuvant Immunotherapies
   (cord blood-derived)

   4PostDocs, 3PhDs, 2 Technicians
   Co-PI: Stefan Nierkens

B. HCT in Rare Diseases
(Focus on Lysosomal Storage Diseases)

1) Identifying Predictors for Outcome
   (Short and Long Term)
2) Future Strategies

   2PhDs, International Network
Unrelated Cord Blood Central Theme in Research Program
How to Increase Safety and Efficacy?

Project A+B
Standard CBT

Project A
Intervention:
“CB derived DC-vaccines”

Vaccination 1, 2 and 3 from 8-12 wks post-CBT (biweekly)
Challenges in HCT

1. Reducing the toxicity of HCT:
   1. Short term toxicity
   2. Long term toxicity

2. Better disease control

Balancing Optimal disease control and reduced toxicity
How to make HCT more efficient and safer?

1. Cord blood transplantation (CBT)
   1. Lower relapse (Eapen 2007, Brunstein 2010, Milano 2015)
   2. Prompt availability
   3. Mismatch OK

2. Individualized conditioning (PKPD): predictable Immune-Reconstitution

3. 1 + CB-derived DC vaccination

4. Advanced immunomonitoring
Post-HCT exposure of active ATG is associated with IR but not with prop. on aGvHD

Collaboration:
Ped. BMT Program in Leiden
-Robbert Bredius
-Arjan Lankester
-Wouter Kollen
-Dorien Bresters
-Frans Smiers, Lynn Ball

Prof Catherijne Knibbe
Prof Meindert Danhof
Pre-HCT ATG-exposure (< > 40 AU*day/mL) is associated with Prop. on aGvHD and Graft-Failure
Prop on Relapse is associated with CD4+ Reconstitution in Myeloid Malignancies
3. Pre-Clinical to Clinical Protocol (Phase 2)
Draft “AML protocol” >>> move to clinic in 2015

- Standard CBT
  - FluBu
  - CBT = day 0

- Intervention:
  - “3 Full-length WT1 mRNA electroporated CB derived DC-vaccines”
  - Cell Therapy Facility (GMP):
    - Production DC-WT1 vaccine: 2-3 weeks

- Vaccination 1, 2 and 3
  - From 8-12 wks post-CBT (biweekly)

- Immuno- and MRD-monitoring (biweekly)

- +7 days
- +1 month
- +months
- +years
Stefan Nierkens
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Nina Blokland
Ester Dünnebach
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Coco de Koning
Charlotte van Kesteren (PKPD)
Max van Noesel (PMC)
DCOG.GOSH.GPOH

Section Applied LTI
Theme: Tumor Immunology
Allogeneic Transplants for Inborn Errors of Metabolism Registered with CIBMTR, 1980-2013

>2000 HCTs since early 80s
1. Hurler syndrome: MPS-1

IDUA deficiency $\rightarrow$ GAG accumulation

MPS type I

‘Mild’

Scheie
9 years old

‘Severe’

Hurler
6 years old

- Mental retardation
- Orthopedic complications
- Blindness and deafness
- Cardio-respiratory failure
- Premature Death
Hurler syndrome:
No HCT - No survival
Treatment options

Since 2003
Enzyme replacement therapy

Since 1980
Hematopoietic cell transplantation

Peripheral tissues | Central nervous system
---|---
Peripheral tissues | Central nervous system

No CNS involvement: Scheie
CNS involvement: Hurler

Aldenhoven et al. BBMT. 2008
Successful HCT influences long term survival of Hurler Syndrome patients

UK patients 1981-2003

TRM/GF

N=67

N=129

Moore et al 2008
How to optimize the outcomes?
Studies on SCT in Hurler’s Syndrome since 2004

   - *Predictors graft-failure*: T-cell depletion, RIC
   - *Predictor higher EFS*: Busulfan with “therapeutic drug monitoring”

2. HCT in combination with Enzyme Replacement Therapy in patients with Hurler syndrome: *BMT 2006*
   - *No impact, but poor performing patients became eligible for BMT*

   - *Predictor higher EFS*: BuCy, interval Dx-CBT < 4.5mths, 6/6 CBU
4. Survival & graft outcome – predictors
Duke University, Minnesota, CIBMTR, EUROCORD, EBMT

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

Age at HCT

Age at HCT <16.7m: 71%
Age at HCT >16.7m: 55%

Source / HLA matching

MSD: 81%, 6/6 UCB: 81%
MUD: 66%, 5/6 UCB: 68%, 4/6 UCB: 57%
MMUD: 41%

Boelens et al. Blood. 2013
<table>
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<th>UCB</th>
<th>UD</th>
<th>TCD-UD</th>
<th>idSI B</th>
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<tr>
<td><strong>Full donor chimerism (%)</strong></td>
<td>92</td>
<td>74</td>
<td>47</td>
<td>70</td>
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<tr>
<td>Mixed 50-95% donor</td>
<td>7</td>
<td>17</td>
<td>26</td>
<td>20</td>
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<tr>
<td>Mixed &lt;50% donor</td>
<td>&lt;1</td>
<td>9</td>
<td>26</td>
<td>10</td>
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<tr>
<td><strong>Normal enzyme level (%)</strong></td>
<td>98</td>
<td>66</td>
<td>50</td>
<td>56</td>
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Cord blood significantly associated with higher full donor chimerism & normal enzyme levels (p< 0.01)
New EBMT guidelines - HCT in IEM

• Donor hierarchy
  1. Non-carrier MSD
     Or Identical UCB (6/6 intermediate resolution)
     Or Identical MUD (10/10 high-resolution typing)
  2. Mismatched UCB

• Conditioning regimen
  • Myeloablative: Bu/Cy (2008) or Flu/Bu (2012)
  • Bu drug monitoring recommended
Utrecht / Manchester Data Since 2006 (n=62)
BuCy (29) and FluBu (33)

Med.age @ HCT = 13 mths

42/62 Cord Blood

OS = 95%
EFS = 90%

Note:
Low GvHD
No VOD
<5% cGvHD
Improved safety and efficacy

- N=62 MPS-patients
- HCT EBMT guidelines 2006-2014 (Manchester/Utrecht)

Overall survival

- 1994-2004: 71%
- 2004-2014: 95%
- No HCT: 0%

Event-free survival (after 1st HCT)

- 1994-2004: 53%
- 2006-2014: 90%

Aldenhoven et al. BBMT. 2015
Urinary GAG excretion (DS/CS-ratio)

Influence of treatment

Long term outcome Hurler syndrome post-HCT

High variability between Hurler patients post-HCT

Explanation?
International collaboration
Identifying predictors for Late Outcomes

N=217 Hurler syndrome
Age at HCT 16 (2-47) months
Follow-up age 9 (3-23) years

Aldenhoven et al. Blood. 2015
How to collect these data?

Mieke Aldenhoven:

Visited all (larger) centers in USA and Europe to collect data

PhD: 15th of Jan 2015
Neurodevelopmental outcome: Predictors

**Age at HCT**

- Baseline IQ: \( \beta = -8.58; P = 0.009 \)
- TBI: \( \beta = -9.90; P = 0.03 \)

**Developmental age (years)**

- Age <12 months (IQ 83)
- Age >12 months (IQ 69)

Aldenhoven et al. Blood. 2015
Enzyme level Post-HCT
Predictor for Outcomes

Cord compression
3% vs 30%

Respiratory support
1% vs 12%

Multi-system effect

Aldenhoven et al. Blood. 2015
Outcome of cord blood transplantation for leukodystrophies

JOINT EUROCORD, EBMT and Duke University
(Working Party Inborn Errors)
STUDY 2014

Janna Hol; J.J. Boelens, MD PhD
OS according to Leukodystrophy (n=220) Duke, EBMT, Eurocord

5 yr OS: 61 ±3%

Disease status
Predictor OS
Collecting Late Outcome data
In summary: Hurler and HCT

• No fatal disease

• Improved safety & efficacy: >95% engrafted survival
  – Cord Blood Preferred Cell Source

• Age & enzyme level predictors for late outcomes

• Future:
  – Newborn screening!
  – Genetherapy: increasing the enzyme levels (supranormal)
    • MLD, X-ALD, MPS-3, (MPS-1)
EUROCORD TEAM 2013

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1. Newborn screening

Challenge: phenotype prediction
2. Gene therapy?

‘No enzyme’  ‘Subnormal enzyme’  ‘Normal enzyme’  ‘Supranormal enzyme’

No HCT  HCT  Gene therapy?
In summary

1. With Individualized Conditioning and Adjuvant Immunotherapies: Better Disease Control

2. HCT in Lysosomal Storage Diseases:
   - Improved Safety and Efficacy
   - Newborn Screening and Genetherapy for Further improvement
Quality of Life

Physical health: mean z-score -2.5 (SD 1.5)
Psychosocial health: mean z-score -0.1 (SD 1.3)
-Post-HCT enzymes Predictor