Hematopoietic Stem Cell Transplantation for Pediatric Bone Marrow Failures

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Curitiba- Brazil

Goteborg, Sweden, EBMT 2009
Background

- BMF syndromes include a broad group of diseases in which hematopoiesis is abnormal or completely arrested in one or more cell lines

  - Acquired: SAA

  - Congenital: FA, DBA, DC, SDS
Fanconi Anemia

- FA is a very heterogeneous disorder.
  - Progressive bone marrow failure
  - Congenital abnormalities
  - High predisposition to cancer

➢ 25% of pts have no congenital abnormalities
Fanconi Anemia

- The hallmark of this disease is the genomic instability in the presence of clastogenic agents.
- DEB test: increased chromosomal breaks with tri or tetra radial figures.
- 13 complementation groups that interact in the FA pathway (DNA repair mechanism)
Treatment

- Bone Marrow failure*
  - Androgens
  - Growth Factors (BM cytogenetics and morphology)
  - Stem Cell Transplantation is the only curative procedure for the BMF in these pts.
Probability of Overall Survival for Fanconi Anemia, Registered to CIBMTR, 1996-2006

- HLA-identical sibling (N=349)
- URD (N=410)
Cincinnati Experience Modified “Gluckman Regimen”

Matched sibling donor BMT for FA

Overall survival

\[ n = 35 \quad 89\% \]

- Cyclophosphamide 5mg/kg/day x4
- TAI 400cGy single fraction
- ATG pre and post BMT
- GVHD prophylaxis: cyclosporin and steroids

Courtesy Stella Davies
Probability of Overall survival for matched siblings SCT

- 38 pts - OS=97.1% (p=.008)
- 22 pts - OS=72.4%

New protocol: CY+FLU+ATG

Courtesy by Mouhad Ayas
Probability of overall survival with fludarabine and nonfludarabine regimens after adjusting for prior red blood cell transfusions and CMV serostatus.
Comprehensive treatment of pts with Fanconi Anemia


Federal University of Parana
Curitiba – PR - Brazil

Goteborg, EBMT, 2009
Brazil: 190 million inhabitants.
3.2 millions live births/year
- Curitiba: 2.3 millions/inhab.

HC-UFPR - BMT Unit:
- 2000 pts
- 173 SAA (pediatric)
- 200 FA
- 10 DBA
- 6 DC
- 9 other
SCT in Fanconi Anemia

Clinical Characteristics

- Period: 11/83 – 12/2008
- Number of pts: 201
- AGE - years - M (range): 9 (3 - 34)
- Gender: 102F/99M
- DISEASE PHASE
  - aplastic: 194
  - leukemic transf.: 03
  - MDS: 04**
- Previous transfusions: units – M(range): 10 (0 - 400)
# Transplant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RELATED</th>
<th>UNRELATED</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients</td>
<td>126 (17 ORD)</td>
<td>75</td>
</tr>
<tr>
<td><strong>SOURCE OF STEM CELL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bone marrow</td>
<td>124</td>
<td>33</td>
</tr>
<tr>
<td>cord blood</td>
<td>02</td>
<td>40</td>
</tr>
<tr>
<td>peripheral blood</td>
<td>00</td>
<td>02</td>
</tr>
</tbody>
</table>

# Most pts in the related group received BM from their HLA identical siblings while in the URD group most pts received CB from mismatched donors.
Stem Cell Transplantation from related donors in Fanconi Anemia

Period 1983 – 2008

Total number of patients: 126pts

Federal University of Parana/ Fred Hutchinson Cancer Research Center - Seattle
### Overall Results

<table>
<thead>
<tr>
<th>Cyclophosphamide (mg/Kg)</th>
<th>200</th>
<th>140</th>
<th>120</th>
<th>100</th>
<th>80</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients #</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>19</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td># of MTX doses for GVHD</td>
<td>3(2-4)</td>
<td>3(2-4)</td>
<td>3(2-4)</td>
<td>3(2-4)</td>
<td>3.5(3-4)</td>
<td>4(3-4)</td>
</tr>
<tr>
<td>Survival %</td>
<td>33</td>
<td>67</td>
<td>57</td>
<td>79</td>
<td>50</td>
<td>93</td>
</tr>
<tr>
<td>Survival, ys. – M (range)</td>
<td>18+</td>
<td>12.5+</td>
<td>12.5+</td>
<td>11.2+</td>
<td>8.6+</td>
<td>45+</td>
</tr>
<tr>
<td>(15-19)</td>
<td>(10-14)</td>
<td>(12-13)</td>
<td>(9-11.7)</td>
<td>(7-9)</td>
<td>(07-95)</td>
<td></td>
</tr>
<tr>
<td>GVHD- A % II-IV</td>
<td>44</td>
<td>33</td>
<td>17</td>
<td>12</td>
<td>67</td>
<td>12</td>
</tr>
<tr>
<td>GVHD- C % Extensive</td>
<td>83</td>
<td>20</td>
<td>20</td>
<td>12.5</td>
<td>60</td>
<td>22</td>
</tr>
<tr>
<td>Hemorrhagic cystitis %</td>
<td>22</td>
<td>17</td>
<td>29</td>
<td>5</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Mucositis grade IV %</td>
<td>90</td>
<td>70</td>
<td>70</td>
<td>36</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Moderate – severe VOD %</td>
<td>33</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Rejection %</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>

Zanis-Neto et al Br J Hematology 2005
Bonfim C et al BBMT 2007
BMT in FA using CY 60mg/kg : 52pts

- **Period**: 11/83 – 12/2008
- **Gender**: 24F/28M
- **AGE - years - M (range)**: 9 (5 - 34)
  - 21pts>10ys
  - 5pts> 20ys
- **DISEASE PHASE**
  - aplastic: 50
  - MDS: 02**
- **Previous transfusions: units – M(range)**: 6 (0 - 101)
Transplant Characteristics

- **Preparatory Regimen:**
  
  Cyclophosphamide 60mg/kg (15mg/kg/day x 4 days)

- **GVHD Immune prophylaxis:**

  Cyclosporine + Methotrexate:

- **All pts received BM from HLA identical related donors**

  Siblings: 44pts

  Other related: 8pts

- **TNC infused:** $1,71 - 8,6 \times 10^8/kg$ (Median: $4,2 \times 10^8/kg$)
Neutrophil Engraftment

Median 19 days (range 10-42)

98% ± 2

All but one pt engrafted.
Platelet Engraftment

Median 21 days (range 15-33)

98%±2
CY 60 and Rejection: 7 pts

PGF : 1pt : alive

LGF : 6pts( 2pts MDS) 138 - 450 days (M: 202)

No significant # Donors/ cytogenetics/transfusions

14%±5
Acute GVHD grade II-IV (D+100)
Chronic GVHD – limited and extensive

Median FU 62 months (range 7-117)

41%±11
Overall Survival

Median FU 62 months (range 7-117)

89% ± 5

No # OS – type of donor/ transfusions/ cytogenetics
Unrelated Stem cell Transplantation
in Fanconi Anemia

PERIOD: 05/96 – 12/2008

TOTAL NUMBER OF PATIENTS: 75pts
### Unrelated SCT in Fanconi Anemia

**CY + Flu + ATG: 49 pts**

<table>
<thead>
<tr>
<th>Age - years - M (range)</th>
<th>8 (4-18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M/F</td>
<td>14/24</td>
</tr>
<tr>
<td>Previous transf – U - M (range)</td>
<td>12 (1-101)</td>
</tr>
<tr>
<td>CMV positive</td>
<td>41pts</td>
</tr>
<tr>
<td>Source of stem cell</td>
<td></td>
</tr>
<tr>
<td>BM</td>
<td>22</td>
</tr>
<tr>
<td>CB</td>
<td>27</td>
</tr>
<tr>
<td>HLA disparities</td>
<td></td>
</tr>
<tr>
<td>- BM</td>
<td>8/8: 16pts - other:6pts</td>
</tr>
<tr>
<td>- CB</td>
<td>6/6:3pts 5/6:7pts 4/6:17pts</td>
</tr>
<tr>
<td>Immun prophylaxis</td>
<td></td>
</tr>
<tr>
<td>mtx+csa</td>
<td>28</td>
</tr>
<tr>
<td>ctc+csa</td>
<td>21</td>
</tr>
</tbody>
</table>
**CY + FLUDARABINE + ATG Protocol**

- **Prep regimen:**
  - Cyclophosphamide 60mg/kg (15mg/kg/day/4 days)
  - Fludarabine 125mg/m2 (25mg/m2/day/5 days)
  - Rabbit ATG 4m/kg

- **GVHD prophylaxis (no IV MMF available):**
  - Cyclosporine and steroids : CB
  - Cyclosporine + Methotrexate : bone marrow + CB
  - TNC infused
    - CB: 2,19 - 19,2 x 10^7/kg (M: 5,5)
    - BM: 2,0 - 10,7 x 10^8/kg (M: 5,3)
Overall Survival

Median FU 50 months (range 7-72)

24pts 49%±7
Overall Survival vs. Donor

$P = 0.07$

BM 64%±10 (n=22)

CB 37%±9 (n=27)
Patients with good compatibility have a better survival univariate analysis.

Adeq. compatibility 27pts: 66.7%

No adeq. Compatibility : 22pts : 27.3%

P: 0.005

BM: 8/8
CB: 6/6 or 5/6
Overall Survival: BM 8/8

81% ± 9.8 (n=16)
# Engraftment

<table>
<thead>
<tr>
<th></th>
<th>CB – 27pts</th>
<th>BM – 22pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGF</td>
<td>6pts</td>
<td>2pts**</td>
</tr>
<tr>
<td></td>
<td>12pts</td>
<td>16pts</td>
</tr>
</tbody>
</table>
Engraftment is extremely important: no late rejection was observed in this group.
Alive and engrafted at 4 months after SCT
## Acute GVHD

<table>
<thead>
<tr>
<th></th>
<th>CB</th>
<th>BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>death or PGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A- GVHD II-IV</td>
<td>6/ 13pts</td>
<td>7/19pts</td>
</tr>
</tbody>
</table>
## Chronic GVHD

<table>
<thead>
<tr>
<th></th>
<th>CB</th>
<th>BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not evaluable</td>
<td>15pts</td>
<td>6pts</td>
</tr>
<tr>
<td>Death&lt;100d or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-GVHD</td>
<td>6/13pts</td>
<td>4/18pts</td>
</tr>
<tr>
<td>Limited:</td>
<td>4pts</td>
<td>3pts</td>
</tr>
<tr>
<td>Extensive:</td>
<td>2pts</td>
<td>1pt</td>
</tr>
</tbody>
</table>
Unrelated SCT: Other complications

- Severe arterial hypertension: 60% pts
- Neurotoxoplasmosis: 4 pts (1 necropsy)
- Pulmonary Toxoplasmosis: 1 pt
- Frequent CMV reactivation
- EBV reactivation: 6 pts (all CB)
  - 2 pts with high grade lymphoma - extensive GVHD – C
- Neurotoxicity: 58%
- Hemolytic Uremic Syndrome: 2 pts
Transplant Related Mortality

25pts between 7-599d (M: 50)

- CB: 17pts (TRM at D+100: 48%)
  - 9 pts: early death related to bacterial infections
  - 6pts: PGF (infections- toxoplasmosis) or bleeding
  - 2pts had extensive GVHD – EBV/ bacterial sepsis

- BM: 8pts (TRM at D+100: 36%)
  - VOD + infection: 2pts
  - PGF + Infections: 1pt
  - Fungal infections: 5pts (* GVHD)
Results of Unrelated Cord Blood Transplant in Fanconi Anemia Patients: Risk Factor Analysis for Engraftment and Survival

Gluckman E, Vanderson Rocha, Irina Ionescu, Marc Bierings, Richard E. Harris, John Wagner, Joanne Kurtzberg, Martin A. Champagne, Carmem Bonfim, Marco Bittencourt, Philip Darbyshire, Manuél-Nicolas Fernandez, Franco Locatelli, Ricardo Pasquini, on behalf of Eurocord-Netcord and EBMT

E. Gluckman et al, BBMT2007

Eurocord - International Registry on Cord Blood Transplantation
Significant factors improving survival
93 pts

Univariate analysis for survival
- HLA match (78% vs 45% vs 21% vs 25% p=0.005)
- Number of cells infused >4.9x10^7/kg (50% vs 26%, p=0.005)
- Use of Fludarabine (52% vs 19%, p=0.002)
- Number of transfusions (73% vs 40% vs 10% p=0.0005)
- CMV serology (neg 60% vs pos 26% p=0.0008)
- Median age 9y (< 47% vs > 31% p=0.02)

Multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cord blood cells &gt; 4.9</td>
<td>2.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of Fludarabine</td>
<td>2.04</td>
<td>0.012</td>
</tr>
<tr>
<td>CMV negative serology</td>
<td>2.78</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Malignancies

- Tongue carcinoma: 7pts (104pts > 2ys)
  - Age of diagnosis: 11, 12*, 12*, 14, 18, 18 and 26y.
  - All pts had grade IIIb or IV mucositis (CY200; CY100; CY60*).
  - 4pts had extensive C-GVHD involving oral mucosa. They developed this complication much earlier after transplant (5 and 6 years) than pts without GVHD (10 and 11,7years).
  - ONLY 2 pts are alive
Summary

- SCT can cure the hematological complications in FA pts. Results are much better for pts in Aplastic phase even though results in pts with MDS are improving.

- Long term complications related to the disease and exacerbated by the procedure should be anticipated and intensive screening is mandatory.
Summary

- HLA matched related donors:
  - EXCELLENT PROGNOSIS, LOW TRM: Aplastic phase
    - Decrease the incidence of C-GVHD in order to decrease long term complications
  - CY60 (no RXT or ATG)
  - CY+TAI+ATG or CY+TAI
Summary

- **Unrelated SCT**:
  - Add Fludarabine, transplant earlier (age and transfusions)
  - MUD BM 8/8: 80% with CY+FLU+ATG or other Rxt containing regimens
  - CB: Cell dose matters (and compatibility)
    - TNC> 5x10^7/kg – CB 5/6 or 6/6
- Future perspectives: Thymic Shielding + TBI/ Haplo SCT with post BMT CY/Gene Therapy
Acknowledgments

- BMT Unit
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  - Daniela Pilloneto

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  - Stella Davies - Cincinatti
  - Mouhab Ayas – King Faisal – Saudi Arabia
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  - Gerard Pals – Amsterdam
  - StJude Children Research Hospital - International Outreach program
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