A multicenter trial of BMT for patients with Fanconi Anemia

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ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

PATIENT

DONOR

FA
In order to do a transplant successfully, we need to get rid of all 3 elements. That is the Conditioning Regimen or Cytoreduction.
<table>
<thead>
<tr>
<th>Bone Marrow Cells</th>
<th>T-cells</th>
<th>AML clone/cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFECTS:</strong></td>
<td><strong>Different agents have different properties:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>FA</strong></td>
<td><strong>can attack all 3</strong></td>
<td></td>
</tr>
<tr>
<td>Radiation (TBI)</td>
<td>attacks primarily BM cells and AML cells</td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td>attacks primarily the T-cells</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>attacks primarily the T-cells ( +/- AML cells)</td>
<td></td>
</tr>
<tr>
<td>Fludarabine</td>
<td>attacks only the T-cells</td>
<td></td>
</tr>
<tr>
<td>ATG</td>
<td><strong>OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td>attacks primarily BM cells and AML cells</td>
<td></td>
</tr>
<tr>
<td>Thiotepa</td>
<td>can attack all 3</td>
<td></td>
</tr>
<tr>
<td>Clofarabine</td>
<td>attacks primarily BM and AML cells</td>
<td></td>
</tr>
</tbody>
</table>
These agents also have **SIDE EFFECTS**: Side effects can be acute-early or late

Some of the acute effects:
- Mouth sores
- Stomach problems
- Low counts
- Hemorrhagic cystitis

Some of the late effects
LATE EFFECTS POST HSCT


So what is the deal with transplant for FA

Why is it so hard?
FA and allogeneic HSCT

1990’s

NMDP – N=58
Overall Survival
1995–2003

Survival

- Graft rejection / failure
- Acute and chronic GvHD
- Transplant related organ toxicity
- Infections
- DFS: ~ 30%

OS = 34%
Late 1990’s - 2000’s

Can we improve on these results?

Trial(s) #1 – Single center studies
New York - Cincinnati - Minnesota
G-CSF 10 mcg/Kg/dose Daily SC

PBSC Collection

CD34+ E-rosetting

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SD TBI 450 cGy

Flu

Flu

Flu

Flu

Flu

CD34+E-T-cell depleted PBSCT

ATG

ATG

ATG

ATG

G-CSF

Start Tacro

Steroids
5 year overall success: 60-75%  
*Depending on disease, age, infections, donors, …*

But also

Risk of GvHD: 9.6%  
Risk of Rejection: 3.8%  
*Despite 21 of 26 patients with mismatched donors*
Can we perform allogeneic HSCT in patients with FA without the use of TBI?

Hypothesis 1:
Rejection and GvHD problems significantly better
Can we perform these transplants with comparable outcome results while decreasing the acute TBI-related acute toxicity?

Hypothesis 2:
Can we reduce the late effects of TBI including secondary malignancies
Why is this relevant in the FA host?
NON FA
The risks of secondary neoplasms post HSCT is significantly higher in the patients who have received TBI-based cytoreductive regimens

Lowsky et al. 1994 – Journal of Clinical Oncology
Deeg et al. 1996 – Blood
Kolb et al. 1999 – Annals of internal medicine

FA
Survival in patients with FA after HSCT with the use of T-cell depleted transplants and Fludarabine-containing cytoreductive regimens has significantly improved

HOWEVER, patients with FA continue to succumb to a high rate of secondary malignancies.

The prevention of these secondary malignancies must be a priority for us physicians caring for patients with FA:
(1) HPV – (2) Chronic GvHD – (3) Radiation
TRIAL DESIGN
• Centers involved in multicenter protocol

• 2004
  – USA
    • Memorial Sloan-Kettering
    • Cincinnati Children’s Hospital
    • University of Minnesota
    • Boston Children’s Hospital
    • Children’s Hospital Wisconsin
    • Hackensack Medical Center
  – OTHER
    • Hopital Saint Louis - France
    • Ospedale Pediatrico Gaslini – Genova - Italy
    • Hadassah Hospital - Israel

• 2008
  – USA
    • Memorial Sloan-Kettering
    • Cincinnati Children's Hospital
    • Boston Children’s Hospital
    • Children’s Hospital Wisconsin
    • + 2013 Fred Hutchinson Cancer Research Center
**DONOR**

- G-CSF 6 mcg/Kg/dose BID SC
- PBSC Collection
- CD34+ T-cell depletion

**PATIENT**

- Flu
- Flu
- Flu
- Flu

- CY
- CY
- CY
- CY

- ATG
- ATG
- ATG
- ATG

- G-CSF
- Start CSA
The primary objectives of this trial are to establish:

1. Engraftment and hematopoietic reconstitution.
2. Organ Toxicity
3. Acute GvHD and chronic GVHD.

Secondary objectives of this study are to establish initial estimates of:

4. the incidence of overall survival and disease-free survival over time

5. The incidence of late effects post transplant
6. The incidence of secondary malignancies
Design – Patient Numbers

• This phase II trial is designed to investigate the safety and efficacy of hematopoietic stem cell transplantation for the treatment of patients with Fanconi Anemia lacking a genetically identical donor. A maximum of **25 patients** will be accrued onto the study. It is anticipated that the accrual will last 3 years, and will include patients from 5 different centers.

• As of April 2012, patient accrual is nearly complete in the HSCT Fanconi Anemia study. As a result, after the completion of the planned 25 patient study, we have amended the protocol to accrue at most an **additional 20 patients** in order to gain clinical experience using alternative levels of Busulfan.

• Initial cohort: **Busulfan doses 0.8 – 1.0 mg/Kg**  
  Subsequent cohort: **Busulfan doses 0.6 – 0.8 mg/Kg**

• **Stopping rules for (1) rejection, (2) GvHD, (3) TRM**

• **Trial patient number reached - Stopping rules NOT achieved -**
**BU CY FLU - CD34+ T-cell depleted HSCT**

**N= 45**

<table>
<thead>
<tr>
<th>Age</th>
<th>Median 8.2 (range 0.4 – 44)</th>
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<tbody>
<tr>
<td>&lt; 10 years</td>
<td>27</td>
</tr>
<tr>
<td>10-18 years</td>
<td>13</td>
</tr>
<tr>
<td>&gt; 18 years</td>
<td>5</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>SAA</td>
<td>29</td>
</tr>
<tr>
<td>MDS</td>
<td>11</td>
</tr>
<tr>
<td>Severe Single Lineage Cytopenia</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched Unrelated</td>
<td>25</td>
</tr>
<tr>
<td>Mismatched Unrelated</td>
<td>14</td>
</tr>
<tr>
<td>Mismatched Related</td>
<td>5</td>
</tr>
<tr>
<td>Phenotypically matched related</td>
<td>1</td>
</tr>
</tbody>
</table>

**Centers:** CCH 29 – MSKCC 10 – BCH 3 – FHCRC 2 – WCH 1
BU CY FLU - CD34+ T-cell depleted HSCT
N= 45

• F/U 10.4 months (range: 8.7 - 61)

• GvHD
  Acute: Grade 1-2 FOUR – Grade 3-4: ZERO 0%
  Chronic: Limited 3 6.7%

• Outcome Alive N=37 - Overall Survival: 81%
  8 people left us (incl. 4 of the 5 pts older than 18 years)
  Infection: 5 (inc. botulism)
  BMT related toxicity: 3
BU CY FLU - CD34+ T-cell depleted HSCT

N= 45

DFS 78%

Aplastic anemia (N=34)  DFS  84%
Age < 10 years (N=27)  DFS  87%

Follow-up in months post transplant
CONCLUSIONS (1)

• The use of **T-cell depletion** has allowed to perform transplants successfully in patients with FA with no graft rejection and minimal risk of GvHD.

• The use of **FLU + low dose TBI and CY** followed by T-cell depleted transplants, has been associated with promising outcome in patients with FA and AA or MDS/AML.

• The use of **FLU + low dose BU and CY** followed by T-cell depleted transplants in patients with FA has been associated with no graft rejection and minimal GvHD as well. It is associated with comparable toxicity and comparable outcome.

• Longer follow-up is needed to assess (1) late effects and (2) secondary neoplasms.
HSCT CHECK – WISH LIST

- Cytoreduction
- HSCT
- Rejection
- Infections
- Toxicity
- GvHD
- Relapse
- Late Effects
FUTURE DIRECTIONS

Infections:
- We presently have the **Cell therapy** approach for CMV, EBV, Adeno
- Role for **Interleukin 7**?

Toxicity - Leukemia

- We need a better laboratory (animal?) model to answer certain questions that are important for future HSTC trials.
  - The use of **Palifermin (KGF)** decrease **toxicity**
  - The use of other Cytoreductive agents for myeloablation and dosing determination with less **toxicity** than Busulfan including:
    - **Thiotepa** - Melphalan - Clofarabine
  - The use of **anti-leukemic** agents in patients with myeloid malignancies including
    - **5-Azacytidine or Decytabine** - Clofarabine

With the difference in results based on age and disease, we are proceeding with our Multi-Center Protocol #2 which is led, and will be presented by:
Thanks

- Eva Guinan
- Stella Davies and Parinda Mehta
- David Williams and Leslie Lehmann
- David Margolis
- Scott Baker and Akiko Shimamura
- The Fanconi anemia Research Fund
- MSKCC
- All the Attending Physicians, Nurse Practitioners, Nurses at MSKCC
- Elizabeth Klein – Data management at MSKCC

The FAMILIES
The PATIENTS - the ones who are with us
Especially the ones who are no longer with us