Graft Sources for Hematopoietic Cell Transplantation

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The National Marrow Donor Program

1968  First successful related donor transplants
1973  First successful unrelated donor transplant
1979  Laura Graves URD transplant for ALL
1986  NBMDR established
1987  Two transplants completed
Today:  World’s largest registry
>14 million donors
>230,000 CBUs
>73,000 Transplants completed

The Success of NMDP is coupled to 29 years of uninterrupted Federal support

National Marrow Donor Program Adult Donors & Cord Blood Units – April 10, 2016

- Non-profit 501(c)3 corporation headquartered in Minneapolis, Minnesota
  - 900 employees
  - $400 million annual budget
- Contracted to operate the legislatively authorized CW “Bill” Young Cell Transplantation Program
  - Four separate contracts – BMCC, CBCC, SPA/OPA and SCTOD
  - bloodcell.transplant.hrsa.gov
- BE THE MATCH® branding
  - www.bethematch.org
  - www.bethematchclinical.org

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Simon Bostic, URD Transplant Recipient

The National Marrow Donor Program

4/18/2016

The National Marrow Donor Program

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NMDP Transplants Facilitated by Fiscal Year 1987–2015
>73,000 Total

Survival After Unrelated Donor Transplantation
Age <50 years, myeloablative conditioning, acute leukemia in remission or MDS

Odds of 1-year survival increased by 8% per year (95% CI, 7-9%) on average between 1990 and 2011

Influence of HLA
- 8/8 Match
- 7/8 Match
- 6/8 Match


Other HLA/Donor Characteristics Associated with Outcome
- Low-expression HLA alleles (DQ, DP, DRB3,4,5)
  - Permissive versus non-permissive DP mismatches
  - Multiple mismatches
- Donor age - age >50 about equivalent to a single locus mismatch
- Non-HLA genomics – KIR Phenotype
NMDP Transplants Facilitated by Fiscal Year 1987–2014
>73,000 Total

Study Characteristics
- **Design**: Randomized, multicenter trial.
- **Primary endpoint**: Two-year survival by intent-to-treat.
- **Randomization**: PBSC vs. marrow, 1:1.
- **Stratification**: Transplant center and disease risk.
- **Accrual**: 550 donor-recipient pairs.
- **Power**: 80% to detect a 12.5% difference, alpha 0.05.
- **Enrollment**: March 31, 2004 to September 9, 2009.
- **Analysis**: as of November 15, 2011.
- **Median follow-up**: 36 months

Analysis after Transplantation

Non-relapse Mortality

<table>
<thead>
<tr>
<th>Incidence, %</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBSC</td>
<td>0</td>
</tr>
<tr>
<td>Marrow</td>
<td>5 days</td>
</tr>
</tbody>
</table>

Relapse

<table>
<thead>
<tr>
<th>Incidence, %</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBSC</td>
<td>0</td>
</tr>
<tr>
<td>Marrow</td>
<td>7 days</td>
</tr>
</tbody>
</table>

Platelets > 20k

<table>
<thead>
<tr>
<th>Incidence, %</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBSC</td>
<td>0</td>
</tr>
<tr>
<td>Marrow</td>
<td>7 days</td>
</tr>
</tbody>
</table>

**BMT CTN 0201**

Results of a Phase III Randomized Multicenter Trial of HLA compatible Unrelated Donor Transplantation:

G-CSF Mobilized Peripheral Blood Stem Cells (PBSC) Versus Bone Marrow

**BMT CTN 0201**

Overall Survival Disease-free Survival

<table>
<thead>
<tr>
<th>Probability, %</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBSC</td>
<td>0</td>
</tr>
<tr>
<td>Marrow</td>
<td>2-year point P value = 0.335</td>
</tr>
<tr>
<td>PBSC</td>
<td>0</td>
</tr>
<tr>
<td>Marrow</td>
<td>2-year point P value = 0.382</td>
</tr>
</tbody>
</table>

Preplanned subset analyses did not find study arm interaction with:
- Disease Risk
- Donor HLA matching
- Patient Age

**BMT CTN 0201**

Analysis after Transplantation

Platelets > 20k

<table>
<thead>
<tr>
<th>Incidence, %</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBSC</td>
<td>0</td>
</tr>
<tr>
<td>Marrow</td>
<td>180</td>
</tr>
</tbody>
</table>

**BMT CTN 0201**

Engraftment after Transplantation

Neutrophils

<table>
<thead>
<tr>
<th>Incidence, %</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBSC</td>
<td>0</td>
</tr>
<tr>
<td>Marrow</td>
<td>7 days</td>
</tr>
</tbody>
</table>

| P value = 0.986 |
| P value = 0.735 |

**BMT CTN 0201**
Summary

- Survival is not different after marrow or PBSC transplants from unrelated donors.
- Other outcomes are similar, with the exception of better engraftment and more chronic extensive GVHD with PBSC.
- Is the shift to greater PBSC use justified?

Patients Without an Adult Donor May be Helped by Banked Umbilical Cord Blood

- Advantages:
  - Immediately available (important for patients with rapidly progressive diseases)
  - No risk to donor
  - Allows more HLA-mismatch with lower risk of GVHD
- Disadvantages:
  - Low cell numbers - inadequate cell dose for many adults, requiring two units (expensive)
  - Slow hematopoietic recovery and higher risk of graft failure

Cord Blood Transplantation

- Multiple studies from individual centers, Eurocord, the NYBC, EBMT and CIBMTR document that Umbilical Cord Blood cells
  - Can establish durable hematopoiesis
  - Have potent graft-versus-tumor effects
  - Can lead to successful transplant outcomes in a variety of malignant and non-malignant diseases in adults and children
- Outcomes of UCB transplants have clearly improved over time
Leukemia-free Survival in Children – depends on HLA Match and Cell Dose: Better, the Same or Slightly Worse than Matched Bone Marrow (Eapen, Lancet, 2007)

![Graph showing Leukemia-free Survival in Children](image)

Lesser (intermediate resolution A, B; high resolution DRB1) vs. Allele-level HLA-match

<table>
<thead>
<tr>
<th>Loci mismatched using usual typing</th>
<th>Loci mismatched using high resolution typing for A, B, C, DRB1</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>11%</td>
</tr>
<tr>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Effect of Allele-level Matching at A, B, C, DRB1 on Transplant-related Mortality after Cord Blood Transplantation

![Graph showing Effect of Allele-level Matching](image)

Cell Dose

- Major limitation to Cord Blood Transplantation is the small number of cells in each unit
  - Slow hematopoietic recovery
  - Slow immune recovery
  - Graft failure
- Strategies:
  - Selection of large units
  - Double cord transplantation (expensive)
  - Expansion and homing techniques (in development, often requires two units)

A Comprehensive Model for Registry Match Rates

![Graph showing A Comprehensive Model for Registry Match Rates](image)
8/8 match likelihoods by year-end using current donor availability, extending recruitment trends to 2017

≥ 5/6 CBU match rates for children by year

The “New” Alternative – Haploidentical

- In Europe, haploidentical transplants using T-cell depleted peripheral blood grafts have been used for a small but important proportion of transplants
- In the US, very few haploidentical transplants were performed until the last five years
  - No approved CD34 selection or T-cell depletion device available
- Introduction of the Johns Hopkins approach using post-transplant cyclophosphamide increased interest
  - Technically simple
  - Costs similar to HLA-identical sibling transplant

≥ 5/6 CBU match rates for adults by year

Cyclophosphamide-induced tolerance

Proliferating ALLOREACTIVE cells are killed

Non-proliferating non-allloreactive cells are spared

Cell Dose ≥ 2.5 x 10^7 per Kg

Cell Dose ≥ 2.5 x 10^7 per Kg
BMT CTN PROTOCOL #0603
A Phase II Trial of Reduced Intensity Conditioning and Transplantation of Partially HLA-Mismatched Bone Marrow for Patients with Hematologic Malignancies

BMT CTN PROTOCOL #0604
A Phase II Trial of Reduced Intensity Conditioning and Transplantation of Umbilical Cord Blood from Unrelated Donors in Patients with Hematologic Malignancies

Brunstein, Fuchs, et al Blood 2011

Parallel Designs
- Age ≤ 70
- Diseases
  - Leukemia: high risk, in remission
  - Lymphoma
    - Hodgkin, mantle cell, or large cell: chemosensitive relapse, not eligible for autologous SCT
    - Follicular or marginal zone: multiply relapsed
- Adequate organ function, performance score >60%
- N=50 in each trial
- Primary endpoint: 6-month survival

Comparisons of clinical outcomes: UCB vs Haplo (BMT CTN 0603/0604)

Overall survival

Progression-free survival

Haplo-Identical Transplantations
Hematologic Malignancy

Distribution of Alternative (not an HLA-matched adult donor) Graft Sources

Eapen, et al BBMT 2014
Some Unknowns About Haplos with Post-Transplant Cyclophosphamide

- Long-term control of malignancy
- Engraftment/outcomes in non-malignant diseases
- Outcomes in Children
- Suitability of Older Donors
  - More graft failure
  - Clonal hematopoiesis more common with older donors – uncertain significance
  - Able to donate bone marrow?
- Question: might results be better using post-transplant Cy with younger mismatched unrelated bone marrow donors with appropriate CMV/KIR status?

Summary

- Few patients will lack an acceptable donor/graft source
- All donor/graft types (8/8 or 7/8 adult, haplo, cord) produce survival outcomes that, if not identical, are in the same range
  - Maximum differences in survival, compared to 8/8 adult donor, are in the range of 10%-15%
  - Outcomes now more driven by patient and disease factors

How Universal Donor Availability Might Change Things

- HCT more likely to impact treatment of a disease since it is available to more people
- Choice of donor/graft will depend on factors other than HLA
  - Availability
  - Other donor characteristics: age, CMV status, etc.
  - Disease recurrence risk
  - Infection risk
  - Planned conditioning regimen
  - Cost

Relative risks and benefits of different cell sources: acquisition issues

<table>
<thead>
<tr>
<th></th>
<th>UD</th>
<th>Cord</th>
<th>Haplo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suitable HLA match</td>
<td>90% Caucasian</td>
<td>Increased chance</td>
<td>Usually, but other donor characteristics might not be optimal</td>
</tr>
<tr>
<td>available</td>
<td>Much lower for</td>
<td>(especially rarer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>other ancestries</td>
<td>tissue types)</td>
<td></td>
</tr>
<tr>
<td>Availability</td>
<td>Variable</td>
<td>Predictable</td>
<td>Generally predictable</td>
</tr>
<tr>
<td>Speed of acquisition</td>
<td>Medium</td>
<td>Fast</td>
<td></td>
</tr>
<tr>
<td>Cell dose</td>
<td>Predictable</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Second donations/DLI</td>
<td>Possible</td>
<td>Not possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Cost</td>
<td>Higher than sibling</td>
<td>Much higher</td>
<td>Equal to sibling</td>
</tr>
</tbody>
</table>

限 nelation of this Analysis - POWER

<table>
<thead>
<tr>
<th>COMPARISONS OF 3-Year SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloablative: 1245 MUD/104 Haplo</td>
</tr>
<tr>
<td>Point Estimate</td>
</tr>
<tr>
<td>Matched Unrelated</td>
</tr>
<tr>
<td>Haploidentical</td>
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相对风险和益处的不同细胞来源：获取问题

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<td>适合 HLA 匹配可用</td>
<td>90% 白种人</td>
<td>增加机会</td>
<td>通常，但其他供者特点可能不是最佳</td>
</tr>
<tr>
<td>可用性</td>
<td>可变</td>
<td>预测</td>
<td>通常可预测</td>
</tr>
<tr>
<td>速度的获取</td>
<td>中</td>
<td>快</td>
<td>快</td>
</tr>
<tr>
<td>细胞剂量</td>
<td>可预测</td>
<td>慢</td>
<td>高</td>
</tr>
<tr>
<td>第二次捐赠/DLI</td>
<td>可能</td>
<td>不可能</td>
<td>可能</td>
</tr>
</tbody>
</table>
| 成本 | 高于同胞 | 比同胞高得多 | 相等于同胞
Relative risks and benefits of different cell sources: clinical outcomes

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<th>UD</th>
<th>Cord</th>
<th>Haplo*</th>
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<tbody>
<tr>
<td>Engraftment</td>
<td>Fast</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Graft failure</td>
<td>Rare</td>
<td>More common</td>
<td>Slightly more common</td>
</tr>
<tr>
<td>GvHD</td>
<td>High (esp with mismatch)</td>
<td>Lower than expected with mismatch</td>
<td>Low due to techniques used</td>
</tr>
<tr>
<td>Relapse</td>
<td>Possibly lower than sibling</td>
<td>Possibly lower than sibling</td>
<td>Higher</td>
</tr>
</tbody>
</table>

* In adults with malignancy

A Side Note: Implications of Better Chronic GVHD Prevention

- Possible with both CD34 selection and post-transplant cyclophosphamide in both myeloablative and reduced intensity settings
- Makes allogeneic transplantation more attractive for non-malignant diseases such as
  - Sickle cell disease
  - Inborn errors of metabolism
  - Lower risk MDS

Conclusions

- HCT as a therapy should be considered early based on relative efficacy/toxicity compared to non-HCT therapy – not donor availability
  - Timing should be optimized
- Randomized comparisons (rather than biologic assignment, ie., donor vs no donor) of HCT vs non-HCT therapy are now possible in many situations, particularly in adults with hematologic malignancies, and should be pursued

Thank You!