Retrospective Analyses in Hematopoietic Stem Cell Transplant (HCT) Outcomes: The critical role of HCT registries and biorepositories

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CRP/DM Conference
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What is a Registry?

- Organized system that uses observational study methods to collect uniform data to evaluate *specified outcomes* for a population defined by a *particular disease, condition or exposure* that serves one or more *predetermined* scientific, clinical, or policy purposes – *US Agency for Healthcare Research and Quality*
  - Provides “real world” assessments of diseases and their treatments
Outcomes Registries

• Provide the data to do observational studies with greater statistical power
  – Descriptive studies
  – Prognostic scores
  – Comparative effectiveness
  – Immunobiologic correlations

• Require:
  – Many centers (large numbers)
  – High data quality
  – Appropriate scientific and statistical analysis to be informative and reliable
CIBMTR Observational Database

• More than 465,000 registered patients from 1968 - 2016 at > 300 centers worldwide

• Patient data collected at
  – Time of transplant
  – 100 days, six months post-transplant
  – Annually as long as patient is surviving
  – At time of death

• Database is foundational to all CIBMTR scientific programs
What is a Biorepository?

• A biological materials repository that collects, processes, stores, and distributes biospecimens to support future scientific investigation.
Donor-Recipient Research Repository

• Unrelated Donor Repository (est. 1988)
  – >39,000 Adult Recipient / Donor pairs
  – >5,300 Recipient / Cord pairs

• Related Donor Repository (est. 2007)
  – >6,900 Adult Recipient / Donor pairs

• >2.5 million aliquots stored
• >8,200 samples distributed to investigators in 2017
Why Are Registries and Biorepositories Important in HCT?

1. **Small numbers**
2. Many important clinical issues cannot be addressed in randomized trials
3. Few trials can be done – we need to select and design them carefully
4. HCT has the potential for late effects – requires long-term monitoring
5. National funding and regulatory bodies want increasing amounts of data on efficacy and quality
6. Issues of cost and access need to be addressed
Annual Numbers of HCTs vs Numbers of Other Selected Malignancies

- Breast
- Pancreas
- HCT
- Ovary
- Stomach
- Brain
- Liver
- Sarcomas
Indications for Hematopoietic Cell Transplant in the US, 2014

Number of Transplants

- **Allogeneic (Total N=8,211)**
- **Autologous (Total N=12,831)**

Myeloma / PCD

- NHL
- AML
- HD
- ALL
- MDS / MPN
- CLL
- Other Cancer
- CML
- Aplastic Anemia
- Other Non-Malignant Disease
Indications for Hematopoietic Cell Transplant in the US, 2014

Allogeneic (Total N=8,211)
Individual transplant centers treat relatively few patients and these patients are heterogeneous in many factors that affect outcomes.
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Case Study

Evaluation of HLA matching in Unrelated Donor HCT
Donor-Recipient Pair Project

- Started in 1994 with funding from U.S. Office of Naval Research

- Goals:
  - Generate data to determine the impact of allele level matching of HLA-A, B and DRB1 on HCT outcomes
  - Determine the contribution of matching at other loci (HLA-C, DPA1, DPB1, DQA1, and DQB1)

- Unanswered questions:
  - What is the importance of matching alleles?
  - If an allele level match is not possible, what is the next best alternative?
  - Are some loci more important than others to match?
Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome

Study population

- $N = 1,874$
- US transplants between 1988 - 1996
- AML, ALL, CML, other
- 100% Bone marrow
- 100% Myeloablative transplants
- Median follow-up 9 years

Flomenberg et al., Blood 2004
Mismatching at HLA-A, B, C and DRB1 impacts overall survival

Flomenberg et al., Blood 2004
High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

Study population

- N = 3860
- US transplants between 1988 - 2003
- AML, ALL, CML, MDS
- Myeloablative conditioning
- Bone marrow 94%
- Median follow-up 6 years

Lee et al., Blood 2007
### HLA-DQ Lacked Impact

#### As a Single Mismatch

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th></th>
<th>TRM</th>
<th></th>
<th>Acute GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>p</td>
<td>RR</td>
<td>p</td>
<td>RR</td>
</tr>
<tr>
<td>10/10</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>DQ MM</td>
<td>0.97</td>
<td>0.77</td>
<td>1.08</td>
<td>0.50</td>
<td>1.03</td>
</tr>
</tbody>
</table>

#### As a Second Mismatch

<table>
<thead>
<tr>
<th></th>
<th>8/10</th>
<th>9/10</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DQ MM</td>
<td>191</td>
<td>797</td>
<td>1.14 (0.94-1.38)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Lee et al., Blood 2007
Single Antigen vs. Allele

- No statistical difference if mismatched at antigen or allele level, except for C – Antigen worse than Allele

<table>
<thead>
<tr>
<th></th>
<th>Antigen</th>
<th>Allele</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>1.16</td>
<td>1.19</td>
<td>0.69</td>
</tr>
<tr>
<td>DFS</td>
<td>1.16</td>
<td>1.17</td>
<td>0.92</td>
</tr>
<tr>
<td>TRM</td>
<td>1.34</td>
<td>1.32</td>
<td>0.86</td>
</tr>
<tr>
<td>Relapse</td>
<td>0.80</td>
<td>0.93</td>
<td>0.31</td>
</tr>
<tr>
<td>Engraftment</td>
<td>0.74</td>
<td>1.08</td>
<td>0.07</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>1.52</td>
<td>1.24</td>
<td>0.06</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>0.95</td>
<td>0.97</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Lee et al., Blood 2007
Impact of HLA Matching varies by disease stage

Benefits of HLA matching diminish as disease progresses

Lee et al., Blood 2007
Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation

Study population

• N = 8003
• US transplants between 1999 - 2011
• AML, ALL, CML (16%), MDS
• Myeloablative conditioning (57% TBI-based)
• Bone marrow 44%
• Median follow-up ~4 years

Pidala et al., Blood 2014
Validation: Impact of HLA Matching varies by disease stage

As before….. benefits of HLA matching diminish as disease progresses

Pidala et al., Blood 2014
Incorporated recommendations on:

- Role of anti-HLA antibodies (Spellman et al. Blood 2010)
- PBSC transplantation (Woolfrey et al. BBMT 2011)
- HLA-C matching in UCB HCT (Eapen et al. Lancet Oncology 2011)
- Transplantation for non-malignant disease (Horan et al. Blood 2012)
- Matching at low expression loci (Fernandez-Vina et al. Blood 2013)

*Revision incorporating data through 2017 in process
Immunobiology Studies

• Linking clinical data with analysis of biospecimens

• Validation (or not) of findings identified in small/single center studies, eg.:
  – SNPs (IL-1, CTLA-4, IL-7, NOD2/CARD15)
  – HLA alloreactivity/similarity algorithms
Practice changing discoveries....

RAS pathway mutation

Myeloablative conditioning improves survival and reduces relapse

The NEW ENGLAND JOURNAL OF MEDICINE
Not all findings validate...
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Consideration of GVHD Prophylaxis Strategies to Pursue

- Six strategies with “promising” results in single center trials
- Major differences in study populations

<table>
<thead>
<tr>
<th>N=74</th>
<th>N=66</th>
<th>N=117</th>
<th>N=291</th>
<th>N=44</th>
<th>N=33</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>15%</td>
<td>17%</td>
<td>4%</td>
<td>12%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- All disease status
- 80% PBSC
- MA
- URD

- All
- 80% BM
- MA
- URD

- All
- BM
- MA
- MRD/URD

- Early
- PBSC
- MA
- RIC
- MRD/URD
- URD
- URD
Benchmark Analysis Done Using CIBMTR Tacrolimus+MTX Data as Control

<table>
<thead>
<tr>
<th>Candidate GVHD Prophylaxis</th>
<th>Control</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGVHD 3-4</td>
<td>1.00</td>
<td>0.86</td>
<td><strong>0.50</strong>*</td>
<td>0.90</td>
<td><strong>0.31</strong>*</td>
<td>0.48</td>
<td>0.91</td>
</tr>
<tr>
<td>CGVHD</td>
<td>1.00</td>
<td>1.50</td>
<td><strong>0.60</strong>*</td>
<td><strong>0.24</strong>*</td>
<td><strong>0.10</strong>*</td>
<td>0.73</td>
<td><strong>0.29</strong>*</td>
</tr>
<tr>
<td>Survival</td>
<td>1.00</td>
<td>0.85</td>
<td><strong>0.69</strong>*</td>
<td>1.07</td>
<td><strong>0.68</strong>*</td>
<td><strong>0.53</strong>*</td>
<td>0.80</td>
</tr>
<tr>
<td>GVHD- FS</td>
<td>1.00</td>
<td>1.01</td>
<td><strong>0.73</strong>*</td>
<td>1.07</td>
<td><strong>0.29</strong>*</td>
<td><strong>0.68</strong>*</td>
<td><strong>0.65</strong>*</td>
</tr>
<tr>
<td>DFS</td>
<td>1.00</td>
<td>0.92</td>
<td><strong>0.65</strong>*</td>
<td>1.21</td>
<td><strong>0.66</strong>*</td>
<td>0.67</td>
<td>1.20</td>
</tr>
</tbody>
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*P<0.05
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Cumulative Incidence of Second Malignancies after Allogeneic HCT

Rizzo JD, Curtis RE et al CIBMTR 2008
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Arizona Medicaid drops coverage of unrelated HCT for AML

- Arizona Medicaid (AHCCCS) announced potential new cuts, to include transplantation in April 2009

- Lewin report
  - “Hematopoietic Cell Transplant (HCT) allogeneic unrelated: Eliminate coverage of all types (i.e. stem cell, cord blood, bone marrow). Scientific literature suggests no increase in life expectancy over other available treatment.”
Arizona Medicaid Decision

- **Open forum held in June 2009**
  - Attended by all BMT programs in AZ as well as NMDP
- **June 2010**
  - Arizona Spending Bill eliminated funding for MUD transplants for patients over age 21
  - First state to deny such coverage
- **October 2010**
  - MUD transplants no longer a covered service
- **New legislation to restore service introduced, but no action taken**
Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia

Wael Saber, Shaun Opie, J. Douglas Rizzo, Mei-Jie Zhang, Mary M. Horowitz and Jeff Schriber

<5 months after legislation enacted in Arizona
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Rate of HCT for Hematologic Malignancies

Caucasians vs. African-Americans

Results valid with up to 20% under reporting of HCT among African American [OR=1.15, (1.10-1.2)]
Summary

- Observational Registry and Biospecimen studies play an important role in moving the HCT field forward:
  - Small numbers
  - Important clinical issues that cannot be addressed in randomized trials
  - Efficient design of clinical trials
  - Late effects – long-term monitoring
  - Funding and regulatory agencies data needs on efficacy and quality
  - Issues of cost and access
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