Outcomes of pediatric bone marrow transplantation for leukemia and myelodysplasia using matched sibling, mismatched related or matched unrelated donors

Immunobiology Working Committee
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No conflicts of interest to disclose

Outline

• Why is this an important question to answer?

• Discuss the analysis process and hiccups along the way

• Results and final conclusions

Background

• Benchmark for best survival is an HLA matched sibling donor (MSD)
  • 1/3 patients do not have an MSD

• What is the best alternative donor choice?
  • 20-30 years ago unrelated donors not readily available
  • Used less well matched family donors

Risks and benefits of mismatched donors

Historical prioritization of family donors

• Considered ‘equivalent’ to MSD and superior to matched unrelated donors
  • CCG-213 allowed 0-1 Ag (mis)matched donors
  • COG AAML0531 – MFD = 7/8 or 8/8 allele matched family donor

HLA Match definitions have changed

• 20 years ago:
  • Antigen level matching at HLA-A, B and DRB1 (6/6)
  • Transition to DRB1 allele matching

• Current:
  • Matching at HLA-C and/or DQB1
  • Allele-level matching (8/8 or 10/10)
**NMDP HLA matching guidelines**

<table>
<thead>
<tr>
<th>HLA Locus</th>
<th>Search Strategy</th>
<th>Matching</th>
<th>Resolution of Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Yes</td>
<td>Recommended</td>
<td>High</td>
</tr>
<tr>
<td>B</td>
<td>Yes</td>
<td>Recommended</td>
<td>High</td>
</tr>
<tr>
<td>C</td>
<td>Yes</td>
<td>Recommended</td>
<td>High</td>
</tr>
<tr>
<td>DRB1, DRB4, DQA1, DQB1</td>
<td>Yes (DRB1)</td>
<td>Recommended</td>
<td>High</td>
</tr>
<tr>
<td>DQB1</td>
<td></td>
<td>Yes</td>
<td>Uncertain</td>
</tr>
<tr>
<td>DPB1</td>
<td></td>
<td>No</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

*Hurley et al. BBMT 2003 and Bray et al. BBMT, 2008*

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**Improvements in URD matching from 2003-2009**

![Graph showing HLA Match Grade by Year](chart)

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**One-year survival after myeloablative conditioning for acute leukemias in any remission phase, CML or MDS, age <50 years, by year of transplant and graft source, 1988-2008**

![Graph showing survival rates](chart)

- **5/6 sibling**
  - Patient: A 24,24 B 60,60 DRB1 1202,1501
  - Sibling: A 24,24 B 35,60 DRB1 1202,1501

- **7/10**
  - Patient: A 24,24 B 60,60 C 10,10 DRB1 1202,1501 DQB1 0301,0602
  - Sibling: A 24,24 B 35,60 C 10,12 DRB1 1202,1501 DQB1 0301,0601

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**Original study aim**

- Evaluate mismatched related donor HCT outcomes in the "Era of Molecular Typing"
- Unfortunately.....
  - Only 2% of data was at allele-level
  - ~1/2 of related donors had data reported for HLA-C

*Pasquini and Wang CIBMTR 2010*

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**Study aims**

When a child has a donor who is:
- Matched sibling donor (MSD) vs.
- 1-Ag mismatched/phenotypically matched related cohort (mmRD) vs.
- 8/8 allele matched unrelated donor (URD)

Compare:
- Acute GVHD and Chronic GvHD
- Treatment Related Mortality/Overall Survival
- Relapse and Disease Free Survival

*Pasquini and Wang CIBMTR 2010*
Study population

- AML, ALL, CML and MDS pediatric patients
- First myeloablative BM transplant with T-replete grafts from 1993-2006
- GVHD prophylaxis calcineurin inhibitor based and known disease status

Donor Type:
- MSD (from mmRD centres) n=1208
- mmRD: 1-Ag Mismatched or 6/6 Phenotypically matched related donor n=151
- URD 8/8 HLA-A,B,C,DRB1 allelic match n=266

HLA Data Cleaning and Match Assignment

- Reviewed all forms submitted on mmRD cohort
  - Combined HLA data from multiple sources
    - Serology and DNA
    - Match grades assigned

Current process

- Data entered into the system
- HLA verified by standardized algorithm*
- Comparison of DNA & Serology
- Patient & Donor/CBU match grade & match rate assigned

Comparison of 6/6 phenotypically matched related and 1-Ag mm related

<table>
<thead>
<tr>
<th>Variables</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD grade 0.5-1</td>
<td>0.77 (0.53-1.13)</td>
<td>0.404</td>
</tr>
<tr>
<td>Acute GVHD grade 3-4</td>
<td>0.62 (0.32-1.22)</td>
<td>0.249</td>
</tr>
<tr>
<td>Chronic GVHD*</td>
<td>0.79 (0.56-1.12)</td>
<td>0.220</td>
</tr>
<tr>
<td>Relapse</td>
<td>0.52 (0.26-1.09)</td>
<td>0.107</td>
</tr>
<tr>
<td>TRM</td>
<td>0.88 (0.46-1.70)</td>
<td>0.798</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>0.72 (0.45-1.17)</td>
<td>0.186</td>
</tr>
<tr>
<td>Overall survival</td>
<td>0.85 (0.52-1.38)</td>
<td>0.609</td>
</tr>
</tbody>
</table>

*Indicates parameter test against 1-Ag matched related

Study design

- Logistic regression for 100-day mortality and Cox proportional hazards regression models for all other outcomes
- 1-Ag mismatch and phenotypically matched related groups combined (into mmRD) as no significant differences were found
- Subset analysis to evaluate the impact of extended matching, i.e. HLA-C, on mmRD cohort
### Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>MSD N(%)</th>
<th>mmRD N(%)</th>
<th>URD N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1208</td>
<td>151</td>
<td>266</td>
</tr>
<tr>
<td>Median age, years</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>447 (37)</td>
<td>42 (28)</td>
<td>67 (25)</td>
</tr>
<tr>
<td>ALL</td>
<td>559 (46)</td>
<td>67 (44)</td>
<td>136 (51)</td>
</tr>
<tr>
<td>CML</td>
<td>97 (8)</td>
<td>23 (15)</td>
<td>26 (10)</td>
</tr>
<tr>
<td>MDS</td>
<td>105 (9)</td>
<td>19 (13)</td>
<td>37 (14)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>608 (50)</td>
<td>69 (46)</td>
<td>76 (29)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>445 (37)</td>
<td>54 (36)</td>
<td>134 (50)</td>
</tr>
<tr>
<td>Advanced</td>
<td>155 (13)</td>
<td>28 (19)</td>
<td>56 (21)</td>
</tr>
<tr>
<td>Median (range) from Dx to Tx, mo</td>
<td>7 (-1-153)</td>
<td>8 (194)</td>
<td>14 (-1-115)</td>
</tr>
<tr>
<td>Median (range) follow-up of survivors, mo</td>
<td>79 (2-171)</td>
<td>62 (3-177)</td>
<td>61 (12-168)</td>
</tr>
</tbody>
</table>

### Comparison of Matched sibling vs. mmRD and URD

### Comparison of mmRD vs. URD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>URD vs. mmRD RR (95%CI), p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD 1-4</td>
<td>0.63 (0.49-0.86), 0.003</td>
</tr>
<tr>
<td>Acute GVHD 1-4</td>
<td>0.75 (0.40-1.14), 0.177</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>1.27 (0.92-1.72), 0.198</td>
</tr>
<tr>
<td>TRM&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.16 (0.77-1.64), 0.739</td>
</tr>
<tr>
<td>Relapse&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.09 (0.74-1.60), 0.661</td>
</tr>
<tr>
<td>Disease-free survival&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.02 (0.77-1.35), 0.904</td>
</tr>
<tr>
<td>Overall survival&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.94 (0.71-1.26), 0.686</td>
</tr>
</tbody>
</table>

No substantive differences between the groups.

### Cumulative Incidence of Grades III-IV Acute GVHD by Donor Type

### Cumulative Incidence of Chronic GVHD by Donor Type

### Cumulative Incidence of Treatment-Related Mortality by Donor Type
Cumulative Incidence of Relapse by Donor Type

Probability of Disease-free Survival by Donor Type

Probability of Overall Survival by Donor Type

What about mmRD with extended HLA typing?

- 75 mmRD cases with HLA-C typing
  - 8/8 N=26
  - 7/8 N=29
  - ≤6/8 N=21

- Compared 7/8 and 8/8
  - Found no difference
  - Combined in final analysis

Summary

- For Pediatric ALL, AML, CML, and MDS recipients of traditionally defined 0-1Ag mismatched related donors have outcomes comparable to 8/8 allelic matched URD.

- Both are have toxicities and complications that are higher than MSD

- Encourage centers to include high resolution evaluation of mmRD to confirm degree of mismatch
**Remaining questions**

- Does extended HLA typing/matching identify better mmRD donors?

- Where does cord blood factor into the equation?