Haploidentical Transplantation
An Overview
ACBSCT Meeting September 2020

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Medical College of Wisconsin
Conflict of Interest

- I have no financial conflict of interest
## Distribution of Donor Types in 2019 in the U.S

<table>
<thead>
<tr>
<th>Type</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-matched sibling</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>HLA-haploidentical relative</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>HLA-matched/mismatched unrelated adult</td>
<td>55%</td>
<td>35%</td>
</tr>
<tr>
<td>Umbilical cord blood</td>
<td>5%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Courtesy CIBMTR June 2020
Haploidentical Relative Donor Transplants

- Increasing common approach to HCT in the US
  - Malignant and non-malignant hematologic diseases
  - Bone marrow or peripheral blood
  - GVHD prophylaxis
    - Post-transplant cyclophosphamide (PT-Cy)
    - Reduced intensity or myeloablative conditioning
      - Low dose TBI/cyclophosphamide/ATG
      - Alkylating agent/fludarabine ± ATG
Is a Haploidentical Relative Comparable to Matched Unrelated Donor?

• Donor selection varies between centers

• Some centers prioritize a haploidentical relative if a matched relative is not available

• So is a haploidentical relative comparable to a matched unrelated donor?
  – Post-transplant cyclophosphamide overcomes the HLA barrier – but to what extent?
Overall Survival Haplo vs MUD in AML

**Mycloablative**

- HAPLO 45% (36-54); N=104
- MUD 50% (47-53); N=1245
- HR 0.93, p=0.58

**Reduced Intensity**

- HAPLO 46% (35-56); N=88
- MUD 44% (40-47); N=737
- HR 1.06, p=0.70

Ciurea S, Blood 2015
Overall Survival 2019: Acute Myeloid Leukemia

Myeloablative

- MUD 51% (48 – 54)
- HAPLO 49% (44 – 54)

Reduced intensity

- MUD 44% (39 – 50)
- HAPLO 43% (39 – 47)

P=0.61  P=0.66

Years

Probability, %

0  1  2  3

0  20  40  60  80  100

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 Courtesy CIBMTR February 2019
Overall Survival Haplo vs. MUD with Post-transplant Cyclophosphamide: Acute Myeloid Leukemia

**Myeloablative**
- MUD 77% (68-85); N=97
- HAPLO 75% (72-78); N=825

**Reduced intensity**
- MUD 67% (60-74); N=187
- HAPLO 54% (51-57); N=1200

HR 0.74, p=0.20

HR 0.65, p=0.001

Courtesy CIBMTR July 2020
Haplo-HCT: Bone Marrow vs.Peripheral Blood Chronic Graft vs. Host Disease

HR 2.85, p<0.0001

Severity: mild vs. moderate vs. severe (p=0.64)
BM: 62% vs. 28% vs. 10%
PB: 58% vs. 30% vs. 12%

PB: 41% (33 – 48)
BM: 20% (16 – 24)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Bashey A J Clin Oncol 2016
Haplo-HCT: Bone Marrow vs. Peripheral Blood Overall Survival

PB: 57% (49 – 65)
BM: 54% (49 – 59)

HR 1.03, p=0.86

Bashey A J Clin Oncol 2016
Donor age: Adult Unrelated Donors

• Younger donors are associated with best survival
  – For every 10-year increment in donor age there is a 5.5% increase in the hazard ratio for overall mortality

• So, are younger haploidentical donors better than older haploidentical donors?

• Are there other donor characteristics to consider?

Haplo-HCT: Donor Characteristics

- Strong correlation between:
  - Recipient age and donor relationship \( (r = 0.66, p<0.0001) \)
  - Donor age and donor relationship \( (r = -0.61, p<0.0001) \)

- No correlation between patient and donor age \( (r = 0.06, p=0.06) \)

- Higher mortality for patients aged \( \geq 55 \) years

McCurdy S, Blood Adv 2018
Overall survival by donor-recipient age and relationship

Donor-Recipient relationship

Donor-Recipient age

McCurdy S, Blood Adv 2018
Graft failure by donor-recipient age and relationship

Donor-Recipient relationship

Donor-Recipient age

Cumulative Incidence, %

Patient age 18 - 54
- Parent donor
- Sibling donor
- Offspring donor

Patient age 55 - 78
- Sister donor
- Offspring donor

Years

Years

0 1 2

0 1 2

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McCurd S, Blood Adv 2018
Summary: Haplo-HCT and Donor Characteristics

- Patient age is a more important predictor for survival than donor age or donor-recipient relationship
  - Higher mortality in patients aged ≥55 years

- Avoid parents as donors: higher risk for graft failure

- Donor sex, parity, CMV serostatus, donor-recipient ABO match: not associated with outcomes
Summary: Haplo-HCT for Leukemia

- Haploidentical relatives are suitable alternative donors:
  - When matched sibling is not available
  - In unselected populations: similar 2-year survival to that after matched unrelated donor transplant
  - Selected populations: HLA-matched unrelated is preferred (higher survival)
    - Similarly, HLA-matched sibling preferred
    - AML is the predominant disease
- Bone marrow or peripheral blood?:
  - Higher chronic GVHD with peripheral blood
  - No difference in survival
Outcomes: Allogeneic HCT for Sickle Cell Disease

Event-free Survival

- Matched sibling, 89%
- MUD, 69%
- MMUD, 63%
- Haploidentical, 49%

P<0.0001

Overall Survival

- Matched sibling, 96%
- MUD, 82%
- MMUD, 85%
- Haploidentical, 84%

P<0.0001

Eapen M, Lancet Haematol 2019
Graft failure: Allogeneic HCT for Sickle Cell Disease

Eapen M, Lancet Haematol 2019
Summary: Allogeneic HCT for Sickle Cell Disease

- Event-free survival is highest in children aged <13 years and after matched sibling transplant HCT
- Mortality and graft failure higher after alternative donor HCT
- The data does not favor one alternative donor over another
  - However, higher graft failure with haploidentical and mismatched unrelated donor compared to matched unrelated donor HCT
  - Graft failure continued beyond 2 years after haploidentical donor HCT underscoring the need for continued follow-up

Eapen M, Lancet Haematol 2019
Considerations for HCT in Sickle Cell Disease

• Deciding whether to recommend HCT for sickle cell anemia is not straightforward
• Severity of disease vary and there are several disease modifying drugs
• To assist in counselling for HCT we propose a simple risk score
  – Developed and validated in a cohort of 1425 patients
  – Risk score was developed on age at HCT and donor type
## Sickle Cell Risk Group Composition

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Risk group</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 12 years</td>
<td>Good Score = 0</td>
<td>1.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Matched sibling donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤ 12 years</td>
<td>Intermediate Score = 1</td>
<td>2.52</td>
<td>0.043</td>
</tr>
<tr>
<td>Matched unrelated donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥13 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched sibling donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤ 12 years</td>
<td>High Score = 2, 3</td>
<td>7.71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mismatched donors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥13 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative donors</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Brazauskas R, Blood 2020
# Outcomes by Sickle Cell Risk Group

<table>
<thead>
<tr>
<th>Age yrs</th>
<th>Age score</th>
<th>Donor</th>
<th>Donor score</th>
<th>Total score</th>
<th>EFS</th>
<th>Death</th>
<th>Graft failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤12</td>
<td>0</td>
<td>Matched sib</td>
<td>0</td>
<td>0</td>
<td>92%</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>≤12</td>
<td>0</td>
<td>Haplo</td>
<td>2</td>
<td>2</td>
<td>62%</td>
<td>8%</td>
<td>30%</td>
</tr>
<tr>
<td>≤12</td>
<td>0</td>
<td>Matched URD</td>
<td>1</td>
<td>1</td>
<td>83%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>≤12</td>
<td>0</td>
<td>Mismatched URD</td>
<td>2</td>
<td>2</td>
<td>68%</td>
<td>5%</td>
<td>27%</td>
</tr>
<tr>
<td>≥13</td>
<td>1</td>
<td>Matched sib</td>
<td>0</td>
<td>1</td>
<td>87%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>≥13</td>
<td>1</td>
<td>Haplo</td>
<td>2</td>
<td>3</td>
<td>52%</td>
<td>10%</td>
<td>38%</td>
</tr>
<tr>
<td>≥13</td>
<td>1</td>
<td>Matched URD</td>
<td>1</td>
<td>2</td>
<td>50%</td>
<td>29%</td>
<td>21%</td>
</tr>
<tr>
<td>≥13</td>
<td>1</td>
<td>Mismatched URD</td>
<td>2</td>
<td>3</td>
<td>49%</td>
<td>23%</td>
<td>28%</td>
</tr>
</tbody>
</table>
EFS by Risk Score in Sickle Cell Disease

EFS: Training Cohort

- Good Risk score = 0
- Intermediate Risk score = 1
- High Risk score = 2, 3

EFS: Validation Cohort

- Good Risk score = 0
- Intermediate Risk score = 1
- High Risk score = 2, 3

**Risk Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2,3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>490</td>
<td>293</td>
<td>287</td>
</tr>
<tr>
<td></td>
<td>394</td>
<td>230</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>308</td>
<td>175</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>241</td>
<td>122</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>159</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>121</td>
<td>72</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>37</td>
<td>31</td>
</tr>
</tbody>
</table>

Brazauskas R, Blood 2020
Considerations for Haploidentical HCT for Sickle Cell Disease

• Event-free survival
  – 3-year EFS ~60%; 10% mortality, 30% graft failure
  – Are patients willing to accept 10% mortality relatively early after HCT?
  – Or accept ~30% will experience recurrent disease?
  – What is mortality in a patient who did not receive HCT but may be eligible for HCT?
    • General population with sickle cell disease
    • UK: median age of survival, 67 years (single center)
    • US: median age of survival, 48 years (2 centers)
Aplastic Anemia: Haploidentical HCT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>23 years</td>
</tr>
<tr>
<td>Performance score 90-100</td>
<td>54%</td>
</tr>
<tr>
<td>HCT comorbidity index, ≥ 3</td>
<td>36%</td>
</tr>
<tr>
<td>Bone marrow/peripheral blood</td>
<td>81%/19%</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td></td>
</tr>
<tr>
<td>TBI (2 Gy)/Cy/Fludarabine</td>
<td>75%</td>
</tr>
<tr>
<td>TBI (3 or 4 Gy)/Cy/Fludarabine</td>
<td>25%</td>
</tr>
<tr>
<td>GVHD prophylaxis: PT-Cy/CNI/MMF or MTX</td>
<td>100%</td>
</tr>
<tr>
<td>Transplant period</td>
<td>2014-18</td>
</tr>
</tbody>
</table>

Courtesy CIBMTR September 2019
Aplastic Anemia: Haploidentical Relative HCT Outcomes

Graft Failure

Overall Survival

28% (95% CI 19 – 37)

78% (95% CI 68 – 86)

Courtesy CIBMTR September 2019
Aplastic Anemia: Matched Unrelated Donor Outcomes

Graft Failure

Overall Survival

9% (95% CI 6 – 12)

86% (95% CI 82 – 89)

Courtesy CIBMTR September 2019
Considerations for Haploidentical HCT in Aplastic Anemia

• Aplastic Anemia
  – Data reported to transplant registry suggest HLA-matched unrelated donor is preferred to mismatched relative
  – Graft failure is an obstacle
  – Data from single institution(s) suggest survival comparable to matched unrelated donor HCT
  – BMT CTN 1502: completed accrual
    • Results expected 2022
Summary: Haplo HCT for malignant and non-malignant hematologic diseases

• Hematologic malignancy
  – Haploidentical related donors extend the donor pool making transplantation accessible to patients likely to benefit from this treatment
  – Particularly relevant for minorities who face challenges identifying HLA-matched unrelated donors

• Non-malignant hematologic diseases
  – Sickle cell disease and aplastic anemia
    • We must improve current transplant strategies to overcome graft failure after haploidentical donor HCT and overcome GVHD after unrelated donor HCT