Related Haploidentical BMT
(Repurposing Cyclophosphamide: Back to the Future)

Richard J. Jones, M.D.

Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Mismatched allogeneic BMT
Historically prohibitively toxic

Early Leukemia

<table>
<thead>
<tr>
<th>Disease State/Type of Donor†</th>
<th>No.</th>
<th>TRM (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA- identical sibling</td>
<td>805</td>
<td>21 ± 2</td>
<td>—</td>
</tr>
<tr>
<td>1-Antigen mismatched related</td>
<td>104</td>
<td>53 ± 5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>2-Antigen mismatched related</td>
<td>24</td>
<td>55 ± 11</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Matched unrelated</td>
<td>181</td>
<td>53 ± 4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>1-Antigen mismatched unrelated</td>
<td>40</td>
<td>69 ± 8</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

IBMTR
Szydlo et al *JCO* 1997
Development of High-Dose Cy
Santos & Owens (1960s-70s)

• Explored alternative to TBI for BMT
  - Evaluated immunosuppressive properties of all known anti-cancer agents
  - High-dose Cy most immunosuppressive → allo-engraftment of mice

• First 36 BMTs at Hopkins (1968-75), high Cy alone
  - Still conditioning regimen for aplastic anemia
  - High relapse rate in leukemia, busulfan added
Cy for GVHD Prophylaxis

Back to the future

- Cy post alloBMT prevented GVHD in mice (Santos/Owens - 1960s)
  - Only high doses (150-300 mg/kg) effective
  - Lower doses - limited activity

- Standard Hopkins prophylaxis (1975-1984)
  - Low dose - 7.5 mg/kg/d x 4 (MTX schedule) because of hematologic toxicity fears

- Randomized trial - less effective than CsA (Santos et al Clin Transplant 1986)
Cyclophosphamide

History

• Synthesized by Brock, Arnold, & Bourseaux - 1958
  8th anticancer agent FDA-approved - 1959

• Rationally designed to target cancer cells
  Cancers over-express phosphamidase which can cleave P-N bond, releasing nitrogen mustard
  Prodrug - but activation not via phosphamidase
  Metabolic pathway of Cy unclear until 1984 (Hilton and Colvin)
Cyclophosphamide and cancer: golden anniversary


Ashkan Emadi, Richard J. Jones and Robert A. Brodsky
**Aldehyde Dehydrogenase**

*Of stem cells, vitamin A, & cyclophosphamide*

- Group of 18 isoenzymes
- ALDH1 family is rate limiting step in generating retinoic acid (RA) from vitamin A
  - ALDH1 also know as retinaldehyde dehydrogenase
  - HSCs and other stem cells require RA and highly express ALDH1 to generate RA
- Cells expressing high ALDH1 resistant to Cy
  - By serendipity, the Cy metabolic intermediate aldophosphamide is a substrate for ALDH1
ALDH distinguishes normal and leukemic CD34+CD38- cells

CD34+CD38- ALDH^{int} = 96% AML by FISH

CD34+CD38- ALDH^{high} = 1.2% AML by FISH

Gerber et al Blood 2012
Cy Spares Memory T cells
Via their expression of ALDH1

Kanakry et al Sci Transl Med 2013
Santos/Owens experiments from 1960s reconsidered
- High dose Cy (200 mg/kg) prevented GVHD after haploBMT in mice (Luznik/Fuchs 2001)
- 3 decades later, we now knew from both lab and clinical data that HSCs and memory lymphs are resistant to high-dose Cy

Launched clinical trial that frightened George Santos
• High-dose Cy is immunoablative but allows rapid hematopoietic and immunologic recovery in autoimmunity
  - ANC >500 – median 13 (8-22) days
  - Last platelet transfusion – 12 (0-24) days
  - No opportunistic infections

• 5 year actuarial survival 91% and EFS 21% in 140 pts with refractory autoimmunity
Most lymphocytes express low levels of ALDH 1 and are sensitive to Cy
- Memory lymphs and HSCs express high levels and are resistant to high dose Cy

Unmanipulated Haploidentical Bone Marrow Transplantation and Posttransplantation Cyclophosphamide for Hematologic Malignancies after Myeloablative Conditioning  **BBMT 19: 117-22, 2013**

Anna Maria Raiola, Alida Dominiello, Anna Ghiso, Carmen Di Grazia, Teresa Lamparelli, Francesca Gualandi, Stefania Bregante, Maria Teresa Van Lint, Simona Geroldi, Silvia Luchetti, Filippo Ballerini, Maurizio Miglino, Riccardo Varaldo, Andrea Bacigalupo"
T-Cell–Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation

HaploBMT with PTCy

↑'ing mismatch does not worsen outcome

Grade II-IV acute GVHD

Kasamon et al BBMT 2010
Post-transplant Cy (PTCy)

Immune recovery is excellent

- PTCy selectively targets alloreactive T cells, which are maximally proliferative early after BMT
  - T cells specific for infectious agents are quiescent and thus less sensitive to Cy
  - Memory T cells, like other stem-like cells, highly express ALDH1 and are thus resistant to Cy

- All haplotransplants are not created equal
Improved Early Outcomes Using a T Cell Replete Graft Compared with T Cell Depleted Haploidentical Hematopoietic Stem Cell Transplantation

Stefan O. Ciurea,1 Victor Mulanovich,2 Rima M. Saliba,1 Ulas D. Bayraktar,1 Ying Jiang,2 Roland Bassett,3 Sa A. Wang,4 Marina Konopleva,5 Marcelo Fernandez-Vina,6 Nivia Montes,7 Doyle Bosque,7 Julienne Chen,7 Gabriela Rondon,7 Geetha Alatras,7 Amin Aflous,7 Qaiser Bashir,7 Martin Korbling,7 Muzaffar Qazilbash,7 Simrit Parmar,7 Elizabeth Shpall,8 Yago Nieto,8 Chitra Hosing,9 Partow Kebriaei,9 Issa Khouri,9 Uday Popat,1,10 Marcos de Lima,9 Richard E. Champlin
Thymic T-cell development in allogeneic stem cell transplantation

Werner Krenger,¹ *Bruce R. Blazar,² and *Georg A. Holländer¹,³ Blood 117(25):6768-6776, 2011

T cell regeneration after allogeneic BMT:

• Thymic-dependent
  - Impaired by thymic damage from conditioning
  - Impaired by GVHD
  - Impaired by age-related involution

• Thymic-independent expansion of peripheral memory T cells
  - Major mechanism in older adults with thymic involution
TCD Haplos and Cord Blood

Immune recovery is impaired

- TCD shows no selectivity toward alloreactive T cells
  - Also eliminates T cells reactive against infectious agents and memory T cells
  - Older adults (with thymic involution) rely on the peripheral expansion of memory T cells

- Immune reconstitution and infections have also been concerns in older adults transplanted with umbilical cord blood
  - Cord blood also deficient in memory T cells
Excellent Immune Recovery with PTCy

Few opportunistic infections are seen

### Table 3. CMV Reactivation and Invasive Mold Infection
(First 68 related haploidentical transplants)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients at high-risk for CMV reactivation</td>
<td>45</td>
</tr>
<tr>
<td>No. of high-risk patients with CMV reactivation (%)</td>
<td>17 (38%)</td>
</tr>
<tr>
<td>No. of high-risk patients with CMV disease</td>
<td>0</td>
</tr>
<tr>
<td>Median days to onset (range)</td>
<td>34 (17-80)</td>
</tr>
<tr>
<td>No. of patients with invasive mold infection (%)</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>


Absence of Post-Transplantation Lymphoproliferative Disorder after Allogeneic Blood or Marrow Transplantation Using Post-Transplantation Cyclophosphamide as Graft-versus-Host Disease Prophylaxis


Jennifer A. Kanakry¹, Yvette L. Kasamon², Javier Bolaños-Meade², Iván M. Borrello², Robert A. Brodsky¹, Ephraim J. Fuchs², Nilanjan Ghosh², Douglas E. Gladstone², Christopher D. Gocke³, Carol Ann Huff², Christopher G. Kanakry², Leo Luznik², William Matsui², Huzefa J. Mogri⁴, Lode J. Swinnen², Heather J. Symons⁵, Richard J. Jones², Richard F. Ambinder²,*
273 consecutive patients aged 50-75

NRM
- 50’s
- 60’s
- 70’s

PFS by decade
- 50’s (n = 119)
- 60’s (n = 154)
- 70’s (n = 27)

p = 0.9

50’s - 119 patients
60’s - 127 patients
70’s - 27 patients
<table>
<thead>
<tr>
<th>DRI</th>
<th>Matched 3-year PFS (%)</th>
<th>Haplo 3-year PFS (%)</th>
<th>Matched 3-year OS (%)</th>
<th>Haplo 3-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>66</td>
<td>62</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Intermediate</td>
<td>31</td>
<td>39</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>High / v high</td>
<td>15</td>
<td>25</td>
<td>25</td>
<td>37</td>
</tr>
</tbody>
</table>

DRI – disease-risk index (Armand et al Blood 120: 905-913)
Risk-stratified outcomes of nonmyeloablative, HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide


Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia


Table 5. Multivariate analysis (subset): risks of acute and chronic GVHD, nonrelapse mortality, relapse, and OS by donor type

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Transplant conditioning regimen intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myeloablative* Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>Grade 2-4 acute GVHD</td>
<td></td>
</tr>
<tr>
<td>Matched unrelated donor</td>
<td>1.00</td>
</tr>
<tr>
<td>Haploidentical donor</td>
<td>0.37 (0.23-0.61)</td>
</tr>
<tr>
<td></td>
<td>( P = .0001 )</td>
</tr>
<tr>
<td>Grade 3-4 acute GVHD</td>
<td></td>
</tr>
<tr>
<td>Matched unrelated donor</td>
<td>1.00</td>
</tr>
<tr>
<td>Haploidentical donor</td>
<td>0.33 (0.14-0.81)</td>
</tr>
<tr>
<td></td>
<td>( P = .02 )</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td></td>
</tr>
<tr>
<td>Matched unrelated donor</td>
<td>1.00</td>
</tr>
<tr>
<td>Haploidentical donor</td>
<td>0.44 (0.29-0.66)</td>
</tr>
<tr>
<td></td>
<td>( P = .0001 )</td>
</tr>
</tbody>
</table>
Allogeneic BMT 2015

Should an 8/8 match still be the gold standard?

• No patient in need should be denied BMT
  - Alternative donor results similar to matched, and may even be preferable (probably don’t want sib donor over age 55 – 60)
  - Alternative donors allow minorities equal access - haplo vs cord (CTN 1101) has 30% minority accrual (16% AA, 14% Hispanic)

• Unnecessary delays should not occur - many pts can’t wait 3-4 months for MUD
There is no rheostat for GVHD/GVT - pick your poison
- \(\uparrow\) GVHD - less relapses/higher TRM
- \(\downarrow\) GVHD - lower TRM/more relapses

Combining non-tolerant allo immune system with novel anticancer agents may provide GVT w/o toxicity of GVHD
- AlloBMT followed by FLT3 TKIs for FLT3 AML
- Should everyone get some form of postBMT maintenance?
# Alternative Donor Transplantation

## Pros and cons

<table>
<thead>
<tr>
<th></th>
<th>Availability to patient</th>
<th>Timing</th>
<th>Acquisition cost</th>
<th>Concerns</th>
<th>Potential Advantages</th>
</tr>
</thead>
</table>
| MUD    | 60%                     | 3-4 mos| $35K             | 1. Relapse during search  
2. Availability to all ethnic groups (e.g., AAs)                       | Long track record    |
| Cord   | >90%                    |        |                  | 1. Low stem cell #s  
2. No donor concerns  
2. Young HSCs                                                             | 1. No donor concerns  
2. Young HSCs                                                             |
| Haplo (PTCy) | >95%           | <4 wks | $10K (Total cost=$170K) | 1. Historical GVHD/mortality rates  
2. Relapse – low GVHD rates                                               | 1. Excellent immune reconstitution  
2. Low TRM: allows post-BMT anti-cancer strategies                         |

**Haplo with PTCy is really easy for both patients and medical staff**
Acknowledgments

50 years of Laboratory and team science

George Santos, Albert Owens
Lyle Sensenbrenner
John Hilton, Mike Colvin
Rob Brodsky
Ephraim Fuchs, Leo Luznik
Jon Gerber
Gabriel Ghiaur
Paul O'Donnell
Bill Matsui, Carol Ann Huff
Doug Smith, Yvette Kasamon
Javier B. Meade, Margaret Showel
Milada Vala, Jamie Barber,
Brandy Perkins

Clinic