Cyclophosphamide-Induced Tolerance Following Blood or Marrow Transplantation

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Fred Hutchinson Cancer Research Center
Clinical Problem: Identification of a Donor for Allogeneic Transplantation

Preferred donor: HLA-matched sibling (~30%)

Initiate Search for Unrelated Donor (~70%)

- Find MURD (~35%)
  - Transplanted (~23%)

- Search for Alternative Donor (~35%)
  - Mismatched related “haploidentical” donor
  - Unrelated Cord blood

Transplanted (~23%)
Barriers in Haploidentical Transplants
Ablative or Nonablative

• High failure rates due to ≥ 30% NRM at 1 yr
  • Severe GvHD
  • Graft rejection
  • Opportunistic infections

• Problem to overcome: Alloreactive Donor/Recipient T-cells
  • Direct recognition of foreign HLA
  • ≤ 10% T-cell repertoire
Alloreactive T-cells in Haploidentical BMT

Recipient: HLA-A₁A₂

Donor: HLA-A₂A₃

Severe GvHD

Recipient Tissues

TLR

Anti-A₁

HLA-A₁

Rejection

Anti-A₃

HLA-A₃

SC
Strategy: Drug-induced Tolerance

Anti-mitotic drug
(Cyclophosphamide)

Antigen → Response
2-5 days

• Soluble antigen
  
  Schwartz & Dameshek, Nature 1959
  Berenbaum & Brown, Immunology 1964

• Skin grafting
  
  Santos & Owen, Fed Proc 1964

• Solid organ transplantation
  
  Maeda, et al. Immunology 1993

• Haploidentical BMT
  
Reduced Intensity Conditioning
Flu 30 mg/m²/day

TBI 200 cGy

Allograft Infusion

BMT Day

-6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180

Haploidentical BMT
Storb Nonablative BMT Platform

Conditioning: Induce host tolerance

GvHD Prophylaxis:
Calcineurin-inhibitor, MMF
Add: Post-transplant Cy to delete alloreactive T-cell clones
Hopkins RIC Protocol
Haploidentical Donors

O’Donnell, et al. BBMT 2002
Luznik, O’Donnell et al. BBMT 2008
BMT CTN Parallel Phase II Trials
RIC: High-Risk Hematologic Malignancies


Minnesota Protocol

Hopkins Protocol
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>dUCB CTN 0604</th>
<th>Haplo-BM CTN 0603</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>50</td>
<td>50</td>
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<tr>
<td>Median age (range), yr</td>
<td>58 (16-69)</td>
<td>48 (7-70)</td>
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<tr>
<td>Ethnic minorities (%)</td>
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<td>20</td>
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<td>High-risk malignancies (%)</td>
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<td>Myeloid (AML)</td>
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<td>Lymphoid</td>
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<td>28</td>
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Hematopoietic Recovery

A. Double UCB – Neutrophil Recovery

- Neutrophils $\geq 500/\mu l$
- Days: 15 d

B. Double UCB – Platelet Recovery

- Platelet recovery
- Lines: $\geq 20,000/\mu l$, $\geq 50,000/\mu l$
- Days: 38 d

C. Haplo-marrow – Neutrophil Recovery

- Days: 16 d

D. Haplo-marrow – Platelet Recovery

- Days: 24 d
Graft-versus-Host Disease

A. Double UCB – Acute GVHD
- grades II-IV: 40%
- grades III-IV: 21%

B. Double UCB – Chronic GVHD
- 25%

C. Haplo-marrow – Acute GVHD
- grades II-IV: 32%
- grades III-IV: 0%

D. Haplo-marrow – Chronic GVHD
- 13%
BMT CTN 1101: Multi-center, Phase III, Randomized Trial of Haplo-BM vs. dUCB

• **Eligibility**
  • Same criteria as Phase II trials
    • *Both donor sources must be suitable and available*

• **Intent-to-treat analysis**
  • Pointwise PFS at 2 yr (nonproportional hazards)
  • N=410; 80% power to detect 15% difference

• **Secondary endpoints**
  • Will also include QOL, immune reconstitution and cost effectiveness analysis

• **Expected activation: July 2012**
Haploidentical PBSC
Guy’s – King’s College - Seattle

TBI 200 cGy
Cy 14.5 mg/kg/day

PBSC Infusion

G-CSF
MMF tid
Tacrolimus

HCT Day
-6 -1 0 3 4 5 10 20 30 40 50 180

Flu 30 mg/m²/day
Cy 50 mg/kg
GvHD after Haplo-PBSC

Acute GVHD

Chronic GVHD

Grades II-IV

Grades III-IV

cGVHD

Days after transplantation

Days after transplantation

Cumulative incidence (%)

Raj, Paliucca, O’Donnell, unpublished
Relapse and Survival After Haplo-PBSC

Raj, Paliucca, O’Donnell, unpublished
Myeloablative Conditioning
Pilot: Radiolabeled anti-CD45 (\(^{131}\text{I}-\text{BC8}\))
Myeloablative Haploidentical BMT

- **Dosimetry Dose**: Therapeutic Dose Med 15 Gy to Liver Med 9 Gy to BM*
- **Fludarabine 30 mg/m\(^2\)/day**
- **Cy 14.5 mg/kg/day**
- **TBI 200 cGy**
- **Haplo-BM Infusion**
- **G-CSF**
- **MMF tid**
- **Tacrolimus**
- **Cy 50 mg/kg**

*Currently treated*
# Patients and Outcomes

<table>
<thead>
<tr>
<th>Dx</th>
<th>Age</th>
<th>aGvHD</th>
<th>Relapse</th>
<th>NRM</th>
<th>EFS (d)</th>
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<td>+</td>
<td>78</td>
<td>140</td>
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*Pagel & O’Donnell, unpublished*
2-Step Myeloablative Haplo-PBSC

Recipient

- STEP 1: DLI
  - 2e8 CD3/kg
- 12 Gy TBI

- STEP 2: PBSCT
  - 3.6e6 CD34/kg
- Cy 60 mg/kg/d
- GM-CSF

Donor

- Apheresis:
  - DLI
  - PBSC
- Cell Processing: CD34 Selection (Isolex 300i)/OKT3:


Tacrolimus to D60

MMF to D28
Outcomes: 2-Step Haplo-PBSC

- Acute GVHD
  - Grades II-IV
  - Grades III-IV

- Mortality
  - Non-Relapse Mortality
  - Relapse Related Mortality

- Overall Survival
  - No Disease at HSCT
  - All Patients
  - Disease at HSCT

Grosso, et al Blood 2011
Myeloablative (BuCy) Conditioning

HLA-Matched Related and Unrelated Donors

High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus-host disease

Leo Luznik,1 Javier Bolaños-Meade,1 Marianna Zahurak,2 Allen R. Chen,3 B. Douglas Smith,1 Robert Brodsky,1 Carol Ann Huff,1 Ivan Borrello,1 William Matsui,1 Jonathan D. Powell,1 Yvette Kasamon,1 Steven N. Goodman,2 Allan Hess,1 Hyam I. Levitsky,1 Richard F. Ambinder,1 Richard J. Jones,1 and Ephraim J. Fuchs1

Bone Marrow Infusion

BMT Day
-6 -5 -4 -3 -2 -1 0 1 2 3 4 5 10 20 30 40 50 60 80 180

Busulfan IV/PO (pharmacokinetic adjustment)

Cy 50 mg/kg/day

Blood 2010
### Patient Characteristics

<table>
<thead>
<tr>
<th>N</th>
<th>78 MSD + 39 MURD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>50 (21-66) yr</td>
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<tr>
<td><strong>% Myeloid</strong></td>
<td>68% (50% AML)</td>
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<td><strong>% CR</strong></td>
<td>48%</td>
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<tr>
<td><strong>% Relapse</strong></td>
<td>52%</td>
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*Luznik et al. Blood 2010*
Transplant Outcomes

Luznik et al. Blood 2010
Use of Secondary Immunosuppressants

Luznik et al., unpublished
Summary

• “Low tech” approach of post-transplant Cy is a safe and effective means of inducing donor-host tolerance after blood or marrow transplantation
  • Matched or mismatched donors
  • Ablative or non-ablative conditioning
  • Inexpensive ($300)
  • Low incidences of:
    • Graft failure
    • Severe acute and chronic GvHD (BM and PBSC)
    • Non-relapse mortality
    • Serious opportunistic infections
  • Non-myeloablative: autologous hematopoietic recovery after graft failure
Ted Gooley
Elizabeth Harrington
Lisa Getzendaner
Sandy Warnock
Laurie Burroughs
Brenda Sandmaier
David Maloney
Fred Appelbaum
Rainer Storb
Mary Flowers
John Pagel
Wendy Wilson
Terry Furlong
Barry Storer
Katherine Guthrie

Ephraim Fuchs
Leo Luznik
Heather Symons
Yvette Kasamon
Richard Jones
Javier Bolanos-Meade
Marianna Zahurak
Michele Kaup
Judy Baker

Claudio Brunstein
Mary Eapen
Jennierose D’Elia
Jason Thompson
Mary Horowitz
Shelly Carter
Juan Wu
Kate Barowski

Guy’s/St. Thomas’ Hospital, London
Kavita Raj
King’s College Hospital, London
Anthony Paliucca

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And, especially the nurses, the patients and their families