Transplant Activity Worldwide 1968-2015: increased use of both autologous and allogeneic HCT
Number of First Allogeneic HCTs in the US By Year
Reasons for Increased Use

- Better outcomes
- Expanding Indications: MDS, follicular lymphoma, myeloma
- Expanding Age Range: up to 75 for both autos and allos
- Expanding Donor Availability
Indications for HCT in the US: Recent Growth in Allotransplants for MDS, NHL and CLL

- Allogeneic (Total N~8,000)
- Autologous (Total N~12,000)

Diseases and Conditions:
- Multiple Myeloma
- NHL
- AML
- HD
- ALL
- MDS/MPD
- CLL
- Other Cancer
- CML
- Aplastic Anemia
- Other Non-Malignant Disease
Unrelated Donor HCTs Facilitated by NMDP: Dramatic Growth in Use in Patients older than 50

Source: National Marrow Donor Program/Be The Match FY 2014
Allogeneic Transplant Recipients in the US, by Donor Type

- HLA-identical Sib
- Alternative Donor
- Total
WHAT IS A SUITABLE DONOR?

• Source of hematopoietic stem cells that will provide durable engraftment, good immunologic recovery and acceptable risk of graft-versus-host disease.

• Requires donor-recipient matching for Human Leukocyte Antigens (HLA)
  – Gold standard: HLA-identical sibling
  – HLA-identical sibling available for about 30% of transplant candidates
Top 100 Caucasian A,B,C & DRB1 High-Resolution Haplotypes all have frequencies <8%; most <1%

Extensive HLA diversity

Why – ensures that the human population has protection from a wide variety of organisms

Frequencies of HLA types vary in different populations
Bone Marrow Donors Worldwide – Adult Donors

- 28,273,571 unrelated donors
  - 74 stem cell donor registries from 53 countries
Treatment-Related Mortality after Unrelated Donor HCT for Leukemia or Lymphoma Has Decreased Substantially over Past 3 Decades From ~40% to ~20%
### 1-Year Survival after Allogeneic HCT in the US in 2016 Center-Specific Outcomes Analysis

<table>
<thead>
<tr>
<th></th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>Prob (95% CI)</strong></td>
<td><strong>N</strong></td>
<td><strong>Prob (95% CI)</strong></td>
</tr>
<tr>
<td>Related donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related donor</td>
<td>3036</td>
<td>73% (72-75%)</td>
<td>3182</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>4248</td>
<td>65% (64-67%)</td>
<td>4675</td>
</tr>
</tbody>
</table>
Influence of HLA match on Survival After Unrelated Donor HCT

8/8 Match  7/8 Match  6/8 Match

Early Disease Stage

Intermediate Disease Stage

Advanced Disease Stage

S. Lee, et al. Blood 2007 Showed impact of single allele mismatch at A, B, C and DRB1; no difference between antigen and allele level matching
Impact of Donor Type on one-year mortality of after HCTs done in 2012-2014

<table>
<thead>
<tr>
<th>Donor Type</th>
<th>Number (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sib</td>
<td>7438</td>
</tr>
<tr>
<td>Oth match rel</td>
<td>369</td>
</tr>
<tr>
<td>8/8 MUD</td>
<td>8642</td>
</tr>
<tr>
<td>7/8 MUD</td>
<td>2000</td>
</tr>
</tbody>
</table>

- Sib N=7438
- Oth match rel N=369
- 8/8 MUD N=8642
- 7/8 MUD N=2000

[Graph showing mortality rates: 1.00, 0.93, 0.92, 0.65]
US Transplants by Race, Year and Donor Type

- Matched relative
- MUD
- MMUD
- Other

Cauc-2010: Matched relative - 2000, MUD - 3000, MMUD - 1000, Other - 0
Cauc-2015: Matched relative - 2000, MUD - 5000, MMUD - 0, Other - 0
Afric-2010: Matched relative - 500, MUD - 0, MMUD - 0, Other - 0
Afric-2015: Matched relative - 500, MUD - 0, MMUD - 0, Other - 0
Other-2010: Matched relative - 0, MUD - 0, MMUD - 0, Other - 0
Other-2015: Matched relative - 0, MUD - 0, MMUD - 0, Other - 0
7/8 and 8/8 Allele, Available-Match Rates in the Adult Donor Registry in 21 Different Populations

Gragert, NEJM 2014
Unrelated Adult Donor Transplants in the US by Graft Type: BM vs PB
BMT CTN 0201: BM vs PB  
(Anasetti, et al. NEJM 2012)

• Randomized trial of unrelated donor bone marrow vs. peripheral blood for transplantation for hematologic malignancies

• Results showed similar survival, DFS, TRM

• BM had a higher rate of graft failure (9% vs. 3%, p=0.002)

• PB had a higher rate of chronic GVHD (53% vs. 41%, p=0.01)
Chronic GVHD

<table>
<thead>
<tr>
<th></th>
<th>Marrow</th>
<th>PBSC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Extensive</td>
<td>32%</td>
<td>48%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Off therapy at 2 yrs</td>
<td>57%</td>
<td>37%</td>
<td>0.026</td>
</tr>
</tbody>
</table>

P value = 0.014
Parent Trial Eligibility Criteria

• Age up to 66 years
• First transplant
• Acute and chronic leukemia, MDS, MF
• 5/6 or 6/6 match at HLA-A, B, DRB1
  – 98% 7/8 or 8/8 matched
• No active infection
Parent Trial Study Design

• Four myeloablative/RIC regimens allowed
  – Cyclophosphamide/TBI
  – Cyclophosphamide/Busulfan
  – Fludarabine/Busulfan/ATG
  – Fludarabine/Melphalan

• Two GVHD prophylaxis regimens
  – Cyclosporine/methotrexate +/- others
  – Tacrolimus/methotrexate +/- others
Overall Survival with 5 Years Minimum Follow-up

Median FU 73 months
P=0.84

Bone marrow
Peripheral Blood Stem Cells
## Five year QOL data with BM vs PB (76% Response Rate)

<table>
<thead>
<tr>
<th>QOL scale</th>
<th>Bone marrow (n=102)</th>
<th>Peripheral blood (n=93)</th>
<th>P value</th>
<th>Difference between BM and PB (95% CI)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-BMT TOI (↑ better)</td>
<td>76.7 +/- 1.6</td>
<td>70.5 +/- 1.9</td>
<td>0.014</td>
<td>6.2 (1.3-11.1)</td>
</tr>
<tr>
<td>Mean +/- SE</td>
<td>(n=79)</td>
<td>(n=69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHI – Psychological well-being (↑ better)</td>
<td>78.9 +/- 1.7</td>
<td>72.2 +/- 1.9</td>
<td>0.011</td>
<td>6.7 (1.6-11.8)</td>
</tr>
<tr>
<td>Mean +/- SE</td>
<td>(n=80)</td>
<td>(n=72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHI-Psychological Distress (↓ better)</td>
<td>16.0 +/- 1.3</td>
<td>19.0 +/- 1.5</td>
<td>0.128</td>
<td>-3.0 (-6.8,0.9)</td>
</tr>
<tr>
<td>Mean +/- SE</td>
<td>(n=80)</td>
<td>(n=71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic GVHD symptoms (↓ better)</td>
<td>13.1 +/- 1.5</td>
<td>19.3 +/- 1.6</td>
<td>0.004</td>
<td>-6.3 (-10.5, -2.0)</td>
</tr>
<tr>
<td>Mean +/- SE</td>
<td>(n=80)</td>
<td>(n=72)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FACT-BMT TOI, Functional Assessment of Cancer Therapy, Bone Marrow Transplant Trial Outcome Index; MHI, Mental Health Inventory; GVHD, Graft-versus-Host Disease; SE, standard error

¹0.5 x STD

²Adjusted for enrollment values and missing data using inverse probability weighting using significant clinical characteristics
Return to work

- Likelihood of return to full or part time work outside the home was higher for BM
  - RR 1.5, 95% CI 1.2-2.0, p=0.002
  - Adjusted for work status before transplant
  - Missing data imputed based on graft source, disease risk, and age
Conclusions

• At 5 years after HCT, recipients of unrelated donor BM, compared with PB, have:
  – Better psychological well-being
  – Less burdensome chronic GVHD symptoms
  – Are 50% more likely to go back to work
  – Similar survival, relapse, TRM

• No outcome for which PB was better

• PB is still used for >70% of unrelated donor transplants – cause for concern?
Unrelated Adult Donor Transplants in the US by Graft Type: Percent BM vs PB

- Bone Marrow
- Peripheral Blood

Other HLA/Donor Characteristics Associated with Outcome

• Low-expression HLA alleles (DQ, DP, DRB3,4,5)
  – Permissive versus non-permissive DP mismatches
  – Multiple mismatches

• Donor age – age >46 about equivalent to a single locus mismatch

• Non-HLA genomics – KIR Phenotype

• Others – CMV, sex-match, ABO-match
Donor Availability

- HLA-matched relative  25-30%
- Unrelated donor  40-90%
  - Optimally selected*  10-60%

*HLA-matched, permissive DP mismatch, age <30, (ABO, CMV, sex)
Patients Without an Adult Donor May be Helped by Banked Umbilical Cord Blood

Advantages:

- Immediately available (important for patients with rapidly progressive diseases)
- No risk to donor
- Allows more HLA-mismatch with lower risk of GVHD
Bone Marrow Donors Worldwide – Cord Blood Units

• 28,273,571 unrelated donors
• 697,698 CBU
• 74 stem cell donor registries from 53 countries
• 49 cord blood banks from 33 countries
Cord Blood Transplantation

• Multiple studies from individual centers, Eurocord, the NYBC, EBMT and CIBMTR document that Umbilical Cord Blood cells
  – Can establish durable hematopoiesis
  – Have potent graft-versus-tumor effects
  – Can lead to successful transplant outcomes in a variety of malignant and non-malignant diseases in adults and children

• Outcomes of UCB transplants have improved over time
Leukemia-free Survival in Children – depends on HLA Match and Cell Dose: Better, the Same or Slightly Worse than Matched Bone Marrow (Eapen, Lancet, 2007)

- CB 1-Ag MM high (n=157), 41%
- BM matched (n=369), 40%
- CB 1-Ag MM low (n=44), 36%
- CB 2-Ag MM (n=267), 33%
- BM MM (n=123), 30%
Leukemia-free Survival In Adults
Transplantation in Remission: Slightly worse than Matched Marrow of Peripheral Blood

- 8/8 BM, 52%
- 7/8 BM, 41%
- 8/8 PBPC, 50%
- 7/8 PBPC 39%
- 4-6/6 UCB, 44%

Eapen et al; Lancet Oncol 2010
Leukemia-free Survival in Adults: Transplantation Not in Remission: Similar to Matched or Mismatched BM or PB

Eapen et al; Lancet Oncol 2010

Note very low TRM with 8/8 match

Likely to change the paradigm for cord selection

P < 0.001

Years

Incidence, %
### Lesser (intermediate resolution A, B; high resolution DRB1) vs. Allele-level HLA-match

<table>
<thead>
<tr>
<th>Loci mismatched using usual typing</th>
<th>Loci mismatched using high resolution typing for A, B, C, DRB1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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**Note:** The table represents the percentage of loci mismatched using high resolution typing compared to usual typing. The values indicate the mismatch percentages for different numbers of loci mismatches.
## Cord Blood Availability in the US

<table>
<thead>
<tr>
<th></th>
<th>Likelihood of suitable unit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8/8</td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td>5%</td>
</tr>
<tr>
<td><strong>South East Asian</strong></td>
<td>7%</td>
</tr>
<tr>
<td><strong>Alaskan Native</strong></td>
<td>11%</td>
</tr>
<tr>
<td><strong>Native American Indian</strong></td>
<td>10%</td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td>36%</td>
</tr>
</tbody>
</table>
Cell Dose

• Major limitation to Cord Blood Transplantation is the small number of cells in each unit
  – Slow hematopoietic recovery
  – Slow immune recovery
  – Graft failure

• Strategies:
  – Selection of large units
  – Double cord transplantation (expensive)
  – Expansion and homing techniques (in development, often requires two units)
The “New” Alternative – Haploidentical

- Europe: haplo-transplants using T-depleted peripheral blood grafts long used for a small but important proportion of transplants
- China: intensive immune suppression allows successful haplo-transplantation
- US: very few haplo-transplants until last 6 years
  - No approved CD34 selection or T-depletion device
  - Hopkins approach using post-transplant cyclophosphamide increased interest
  - Technically simple, costs similar to HLA-identical sib transplantation
BMT CTN 0603 and 0604: Parallel Single Arm Studies of Haplo and CB Transplants

- Age ≤ 70
- Diseases
  - Leukemia: high risk, in remission
  - Lymphoma
    - Hodgkin, mantle cell, or large cell: chemosensitive relapse, not eligible for autologous SCT
    - Follicular or marginal zone: multiply relapsed
- Adequate organ function, performance score >60%
- N=50 in each trial
- Primary endpoint: 6-month survival
Comparisons of clinical outcomes: CB vs Haplo (BMT CTN 0603/0604)

### Overall survival

- Months Post Transplant: 0, 12, 24, 36
- Probability, %:
  - Months 0: Haplo: 84%, Cord: 74%
  - Months 12: Haplo: 68%, Cord: 52%
  - Months 24: Haplo: 54%, Cord: 46%
  - Months 36: Haplo: 54%, Cord: 39%

### Progression-free survival

- Months Post Transplant: 0, 12, 24, 36
- Probability, %:
  - Months 0: Haplo: 35%, Cord: 36%
  - Months 12: Haplo: 40%, Cord: 38%
  - Months 24: Haplo: 54%, Cord: 46%
  - Months 36: Haplo: 54%, Cord: 39%
BMT CTN 1101: Randomized Comparison of Haplo and Double Cord HCT

• Primary: 2 year Progression-free survival
• Secondary: Engraftment, hematopoietic recovery, GVHD, TRM, relapse/progression, infections, hospitalizations, health-related quality of life

• Planned ancillary studies:
  • Immune reconstitution
  • Cost effectiveness
  • 267 of 410 patients accrued to date
Haploidentical Transplantations for Hematologic Malignancy

Years of 0603/0604 trial

Year 0603/0604 paper was published
Distribution of Graft Sources: 2015 vs 2010

- HLA-ident sib
- Matched unrelated
- Mism unrelated
- Haploident
- Cord

2010 vs 2015 comparison graph showing the distribution of graft sources.
Distribution of Alternative (not an HLA-matched adult donor) Graft Sources - 1

2010  2015

- Mism unrelated
- Haploidentical
- Cord

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Distribution of Alternative (not an HLA-matched adult donor) Graft Sources - 2

- Mism unrelated
- Haploidentical
- Single Cord
- Double Cord

2010 vs 2015
Distribution of Alternative (not an HLA-matched adult donor) Graft Sources - 3

- Mism unrelated
- Haploidentical
- Cord
- Total

2010: Blue bars, 2015: Green bars.
Change From 2010 to 2015

- Mism unrelated: 45
- Haploident: 332
- Cord: -115
- Total: 303
US Transplants by Race, Year and Donor Type (2)
US Transplants in non-Caucasians by Year and Donor Type (2)
Overall Survival, Adjusted for Age, Disease Risk, Secondary AML (Ciurea, Blood, 2015)

**Myeloablative**
- 1245 MUD/104 Haplo
  - MUD 50% (47-53)
  - HAPLO 45% (36-54)
  - HR 0.93 (95% CI 0.70 – 1.22), p=0.58

**Reduced Intensity**
- 737 MUD/88 Haplo
  - HAPLO 46% (35-56)
  - MUD 44% (40-47)
  - HR 1.06 (95% CI 0.79 – 1.43), p=0.70
**Limitation of this Analysis - POWER**

### COMPARISONS OF 3-Year SURVIVAL

<table>
<thead>
<tr>
<th></th>
<th>Myeloablative: 1245 MUD/104 Haplo</th>
<th>Reduced Intensity: 737 MUD/88 Haplo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point Estimate</td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Matched Unrelated</td>
<td>50%</td>
<td>47%</td>
</tr>
<tr>
<td>Haploidentical</td>
<td>45%</td>
<td>36%</td>
</tr>
</tbody>
</table>
Impact of Donor Type on one-year mortality after HCTs done in 2012-2014

Matched related or unrelated

6/6 CB; 7/8 unrelated; haploidentical

Mismatched CB

- Sib N=7438
- Single 6/6 CB N=182
- Multiple 5/6 CB N=477
- Single 4-5/6 CB N=728
- Multiple 4/6 CB N=774
- Oth match rel N=369
- Haplo N=1350
- 8/8 MUD N=8642
- 7/8 MUD N=2000
What Do We Know About Haplos with Post-tx Cyclophosphamide?

- Haploidentical HCT can be performed with low GVHD and low early TRM and acceptable 2-3 year overall mortality, when used with postCy
- Haploidentical HCT is increasingly used, predominantly for adult patients who do not have an HLA-matched adult donor – and some who do
Some Unknowns About Haplos with Post-tx Cyclophosphamide

• Long-term control of malignancy
• Engraftment in non-malignant diseases
• Optimal graft type (PB or BM) or conditioning regimen
• Suitability of Older Donors
  – More graft failure
  – Clonal hematopoiesis more common with older donors – uncertain significance
Some Other Important Unknowns About Post-tx Cyclophosphamide

- Roles in HLA-mismatched unrelated donor transplantation
- Role in HLA-matched related and unrelated donor transplantation
- Viral immunity
- Are the same donor and recipient risk factors important for TRM, relapse and survival
US National Trials Addressing Some of These Issues

- BMT CTN 1101: Haplo vs Cord with **reduced intensity conditioning**
- BMT CTN 1203: PostCy as GVHD prophylaxis with **matched donors and reduced intensity conditioning**
- BMT CTN 1301: PostCy as GVHD prophylaxis with **matched donors and myeloablative conditioning**
- BMT CTN 1502: Haplo with PostCy and UCB for **aplastic anemia**
- BMT CTN 1507: Haplo with PostCy in **Sickle Cell Disease**
- RCI BMT MMUD: PostCy as GVHD prophylaxis with **multiply mismatched unrelated donors**
Allogeneic HCTs for all Standard Indications
Conclusions

• Few patients lack an acceptable donor
• All donors (8/8, 7/8 adult, haplo, cord) produce outcomes that, if not identical, are in same range
  – Maximum differences in survival, compared to 8/8 adult donor, are in the range of 10%-15%
• Donor availability cannot fully account for differences in access to HCT in diverse ethnic and racial groups