BMT CTN History and Scientific Impact
Council Meeting 2016

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Disclosures
The following faculty and planning committee staff have no financial disclosures:

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Mary Horowitz, MD, MS</td>
<td>CIBMTR, Medical College of Wisconsin</td>
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<td>Daniel Weisdorf, MD</td>
<td>University of Minnesota</td>
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<td>Stephanie J. Lee, MD, MPH</td>
<td>Seattle Cancer Care Alliance, FHCRC</td>
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<tr>
<td>Ashley Spahn</td>
<td>CIBMTR</td>
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<tr>
<td>Stephen Spellman</td>
<td>CIBMTR</td>
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<tr>
<td>Del Steckler</td>
<td>NMDP – Be The Match</td>
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</tbody>
</table>
Learning objectives

At the conclusion of this session, attendees will be able to:

• Describe the development of the BMT CTN.
• State the impact of the BMT CTN on the hematopoietic stem cell transplant community.
• Summarize important finds from BMT CTN clinical trials.
• Describe BMT CTN usage of patient reported outcomes in clinical trials.

BMT CTN: A Model of a Focused (and Successful) Clinical Trials Network
BMT Clinical Trials Research in the United States in the 1990s

- Largely single institution
  - Investigator initiated
  - Mostly Phase I & II exploring new strategies
  - R01 or P01 funded
    - Few Pharma-funded
- Few multi-center trials
- Few definitive trials

Challenges in BMT

- Small, heterogeneous population
- Multiple competing risks thus unattractive setting for pharma to test new drugs
- NCI funded Cooperative Groups focused on cancer; not transplantation

Blood and Marrow Transplant Clinical Trials Network (BMT CTN)

  - 20 Core Centers/Consortia
  - >80 Affiliate Centers
  - 1 Data and Coordinating Center

- Goal of the Program:
  - Provide the infrastructure needed to allow promising HCT therapies to be developed/evaluated in high quality multicenter studies
Advantages of a Network

• Greater opportunity to enroll patients
  – More likely to reach target enrollment
  – Address problems requiring larger trials
• Greater opportunity for patients to have access to trials
• Uses heterogeneity of the community to gain validity – new approaches tested in the broad range of transplant centers where it will be applied
• Shared ideas and resources for research
Challenges of a Network

- **Requires** investigator cooperation—Their ideas may not be adopted
- **Requires** individual center cooperation—Their trials may have to wait
- **Requires**
  - Infrastructure for data collection, auditing and analysis
  - Monitoring outcomes for safety
  - Flexibility and adaptability to new ideas
Elements of BMT CTN’s Success

• Streamlined infrastructure
  – Shared decision making
  – DCC with integrated medical expertise
  – Continuous efforts to improve
• CIBMTR Database
• Inclusivity/collaboration
• Financial support/stewardship

BMT CTN Organizational Structure
Rotating Leadership positions

• Vice-chair elected every two years
  – Serves 2 years as vice-chair, 1 year as chair-elect, 2 years as chair, 1 year as immediate-past chair
  – Provides 3 people to interact with DCC (and NIH) on a regular basis
  – Gives a lot of people experience with the challenges of running the Network

RESPONSIBILITIES AND INTERACTIONS OF DCC MEMBERS

CIBMTR

EMMES

NMDP
Elements of BMT CTN’s Success

• Streamlined infrastructure
  – Shared decision making
  – DCC with integrated medical expertise
  – Continuous efforts to improve
• CIBMTR Database
• Inclusivity/collaboration

CIBMTR: 440,000 Cases Registered, up to ~10,000 variables per person (most with repeated observations, some extending over >30 years), >1000 publications

Transplants

Variable 1

Variable 2

Variable 3
BMT CTN Specimen Inventory

<table>
<thead>
<tr>
<th>BMT CTN Protocol</th>
<th># Aliquots Stored</th>
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<tr>
<td>0701</td>
<td>95</td>
</tr>
<tr>
<td>0702</td>
<td>41,454</td>
</tr>
<tr>
<td>0801</td>
<td>4,654</td>
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<tr>
<td>0802</td>
<td>3,645</td>
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<td>1101</td>
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<td>1102</td>
<td>2,908</td>
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<tr>
<td>1202</td>
<td>259,382</td>
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<tr>
<td>1203</td>
<td>6,844</td>
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<td>1204</td>
<td>3,252</td>
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<tr>
<td>1301</td>
<td>58</td>
</tr>
<tr>
<td>1302</td>
<td>150</td>
</tr>
<tr>
<td>TOTAL</td>
<td>333,635</td>
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Elements of BMT CTN’s Success

- Streamlined infrastructure
  - Shared decision making
  - DCC with integrated medical expertise
  - Continuous efforts to improve
- CIBMTR Database
- Inclusivity/collaboration
## Core Centers

<table>
<thead>
<tr>
<th>Core Center</th>
<th>PBMTC Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylor, Houston</td>
<td>Case Western, Cleveland</td>
</tr>
<tr>
<td>Children’s National, Washington, DC</td>
<td>Oregon Health Sciences (Adults), Portland</td>
</tr>
<tr>
<td></td>
<td>Cleveland Clinic</td>
</tr>
<tr>
<td></td>
<td>West Virginia University, Morgantown</td>
</tr>
<tr>
<td>Case Western, Cleveland</td>
<td>Dana Farber, Boston</td>
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<tr>
<td>Oregon Health Sciences (Adults), Portland</td>
<td>Brigham &amp; Women’s, Boston</td>
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<tr>
<td>Cleveland Clinic</td>
<td>Mass General, Boston</td>
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<tr>
<td>West Virginia University, Morgantown</td>
<td>Boston Children’s</td>
</tr>
<tr>
<td>Duke, Durham, North Carolina</td>
<td>Fred Hutchinson CC, Seattle</td>
</tr>
<tr>
<td>Moffitt CC, Tampa</td>
<td>Johns Hopkins, Baltimore</td>
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<tr>
<td>Memorial Sloan-Kettering CC, New York</td>
<td>Northside Hospital, Atlanta</td>
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<tr>
<td>Ohio State, Columbus</td>
<td>University of Michigan, Ann Arbor</td>
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<tr>
<td>Roswell Park CC, Buffalo</td>
<td>Mayo Clinic, Rochester, Minnesota</td>
</tr>
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<td>Univ North Carolina, Chapel Hill</td>
<td>Mt. Sinai Hospital, New York</td>
</tr>
<tr>
<td>Univ California-San Francisco</td>
<td></td>
</tr>
<tr>
<td>Virginia Commonwealth, Richmond</td>
<td></td>
</tr>
<tr>
<td>Pediatric Blood &amp; Marrow Transplant Consortium, 70 centers in the US and</td>
<td>University of Florida, Gainesville, Atlanta, Georgia</td>
</tr>
<tr>
<td>Canada</td>
<td></td>
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<tr>
<td>Stanford Hospital, Palo Alto</td>
<td>MD Anderson, Houston</td>
</tr>
<tr>
<td>Univ Minnesota, Minneapolis</td>
<td>Univ Pennsylvania, Philadelphia</td>
</tr>
<tr>
<td>Univ Nebraska, Omaha</td>
<td>Washington Univ, St. Louis</td>
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<td>Univ Kansas, Kansas City</td>
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### BMT CTN Centers

>125 centers have enrolled >9,100 patients since 2003
Protocols with Major Public-Private Partnerships

- 0303 – Miltenyi: pivotal phase 2 trial that led to preliminary approval of CD34 selection device (assisted by comparison to a non-T-cell depleted cohort from CIBMTR)
- 0702 – Celgene, Millenium: posttransplant consolidation for myeloma
- 1301 – Miltenyi: phase 3 registration trial of CD34 selection device
- 1506 – Astellas: registration trial of gilteritinib for maintenance after allotransplant for flt3+ AML
- 1602 – Gilead: filgotinib for treatment of high risk acute GVHD
BMT CTN TRIALS - SUMMARY

<table>
<thead>
<tr>
<th>Category</th>
<th>All Trials</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>Donor/Graft Source</td>
<td>13</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>GVHD</td>
<td>7</td>
<td>5</td>
<td>4</td>
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<tr>
<td>Infection</td>
<td>3</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Disease Control</td>
<td>15</td>
<td>12</td>
<td>8</td>
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<td>Regimen Toxicity</td>
<td>5</td>
<td>8</td>
<td>4</td>
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<tr>
<td>QOL</td>
<td>8</td>
<td>3</td>
<td>4</td>
</tr>
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<td><strong>TOTAL</strong></td>
<td><strong>39</strong></td>
<td><strong>18</strong></td>
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Network Productivity

<table>
<thead>
<tr>
<th>Category</th>
<th>Funding Periods</th>
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<tr>
<td></td>
<td>2001-5(^a)</td>
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<tr>
<td>Trials Opened</td>
<td>7</td>
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<tr>
<td>Primary results papers</td>
<td>0</td>
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<tr>
<td>Ancillary papers</td>
<td>0</td>
</tr>
<tr>
<td>Methodologic papers</td>
<td>2</td>
</tr>
<tr>
<td>Other publications</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total Publications</strong></td>
<td><strong>3</strong></td>
</tr>
</tbody>
</table>
BMT CTN

- Major findings
- Highlights of important trials
- Impact and future influences on the field

Daniel Weisdorf MD
University of Minnesota

Transplant Questions Addressed

- Best prevention and treatment for GVHD
- Best treatment strategy
- What type of transplant or graft or conditioning regimen for specific diseases

- Best supportive care/quality of life
BMT CTN Major trials

- GVHD Treatment: more drugs vs. fewer
  - GVHD prophylaxis: drugs or graft manipulations
- Conditioning intensity
  - Radioimmunotherapy added for NHL autografts
  - Myeloablative vs. Reduced Intensity Conditioning
- Infection prevention: Fluconazole vs. Vori
- Myeloma: several approaches
- Graft choices
  - Haplo vs. UCB Reduced intensity transplants
  - Single vs. Double UCB for Children
  - BM vs. PBSC for URD transplants

GVHD Treatment: BMT CTN 0302 & 0802

Initial systemic treatment of acute GVHD: a Phase II randomized trial evaluating
etanercept, mycophenolate mofetil, denileukin diftitox (Ontak), and pentostatin

- Previously—nothing was better than steroids alone for treating new acute GVHD

  [wished we could change practice].
## aGVHD Response at Day 28

<table>
<thead>
<tr>
<th></th>
<th>Etanercept N=46</th>
<th>MMF N=45</th>
<th>Denil N=47</th>
<th>Pentostatin N=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (Overall)</td>
<td>26%</td>
<td>60%</td>
<td>53%</td>
<td>38%</td>
</tr>
<tr>
<td>Skin</td>
<td>33% (12/36)</td>
<td>60% (21/35)</td>
<td>49% (17/35)</td>
<td>41% (14/34)</td>
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<tr>
<td>Lower GI</td>
<td>33% (4/12)</td>
<td>67% (5/12)</td>
<td>36% (5/14)</td>
<td>41% (7/17)</td>
</tr>
<tr>
<td>Upper GI</td>
<td>50% (5/10)</td>
<td>92% (11/12)</td>
<td>71% (10/14)</td>
<td>62% (8/13)</td>
</tr>
<tr>
<td>Liver</td>
<td>33% (2/6)</td>
<td>71% (5/7)</td>
<td>43% (3/7)</td>
<td>40% (2/5)</td>
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<tr>
<td>CR (excl. prior MMF)</td>
<td>28%</td>
<td>60%</td>
<td>48%</td>
<td>39%</td>
</tr>
<tr>
<td>CR or PR</td>
<td>48%</td>
<td>78%</td>
<td>60%</td>
<td>62%</td>
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<tr>
<td>Progression</td>
<td>15%</td>
<td>2%</td>
<td>6%</td>
<td>10%</td>
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</table>

## Response at Day 56

<table>
<thead>
<tr>
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<th>Etanercept (N=46)</th>
<th>MMF (N=45)</th>
<th>Denil (N=47)</th>
<th>Pentostatin (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>44%</td>
<td>73%</td>
<td>55%</td>
<td>62%</td>
</tr>
<tr>
<td>Complete Response (Excl. prior MMF)</td>
<td>53%</td>
<td>73%</td>
<td>61%</td>
<td>64%</td>
</tr>
<tr>
<td>Treatment Failure *</td>
<td>24%</td>
<td>9%</td>
<td>26%</td>
<td>29%</td>
</tr>
</tbody>
</table>

* Treatment Failure = no response, progression, or addition of another immunosuppressive agents by day 56.
Overall Survival

(A) All Patients

(B) Excludes Prior MMF Use

Relapse-Free Survival
F/U Randomized Trial: 0802

MMF vs. Placebo + steroids for initial aGVHD therapy

No advantage to adding MMF

©2014 by American Society of Hematology

Survival and DFS by study arm

(P = .34)  

©2014 by American Society of Hematology
GVHD Treatment: BMT CTN 0302/0802

- MMF + steroids seemed to provide a benefit in 0302; Not confirmed follow-up Phase III randomized trial (BMT CTN 0802)

- GVHD biomarker panels can be used for identification at high or low risk: biomarker panels may provide opportunities for early intervention and improved survival following HCT.

Next trials

- Distinguish high vs. low risk by clinical and biomarkers
- Testing Pred vs Sirolimus for low risk

Multiple Myeloma

Auto/Auto vs. Auto/Allo transplantation

Post Auto maintenance

Post Auto strategies
BMT CTN 0102  Auto/Auto vs. Auto/Allo for myeloma

Multiple Myeloma

High-dose melphalan (200 mg/m²) + autologous PBSC transplant

HLA typing of all patients with siblings

Biologic assignment*

Eligible HLA-matched sibling donor

60 to 120 days

Non-myeloablative conditioning TBI 200 cGY allogeneic PBSC transplant

No eligible HLA-matched sibling donor

High-dose melphalan (200 mg/m²) + autologous PBSC transplant

Observation

Thalidomide Dexamethasone x12 months.

** Biologic assignment occurred when HLA-typing results were available after enrollment.

** Randomization occurred once patients were assigned to auto-auto

PRIMARY ENDPOINT : 3yr Progression Free Survival

Progression-free Survival by Treatment Arm

Standard Risk

<table>
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<tr>
<th>Treatment Arm</th>
<th>@ 6 years</th>
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<tbody>
<tr>
<td>Auto/Auto (n=435)</td>
<td>27 (22-31)</td>
</tr>
<tr>
<td>Auto/Allo (n=189)</td>
<td>21 (15-27)</td>
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</tbody>
</table>

P-value=0.1089
Overall Survival by Treatment Arm
Standard Risk

Probability, %
0 20 40 60 80 100
Years Post 1st Transplant
0 2 4 6 8

P-value = 0.5763

Auto/Auto (n=435)
Auto/Allo (n=189)

High Risk

Probability, %
0 20 40 60 80 100
Years Post 1st Transplant
0 2 4 6 8

P-value = 0.4896

Auto/Auto (n=48)
Auto/Allo (n=37)

@ 6 years
Auto/Auto: 59 (54-64)
Auto/Allo: 58 (51-66)

@ 6 years
Auto/Auto: 14 (5-26)
Auto/Allo: 27 (14-42)
Overall Survival by Treatment Arm
High Risk

P-value=0.8553

Auto/Auto (n=48)
Auto/Allo (n=37)

@ 6 years
Auto/Auto 47 (33-61)
Auto/Allo 51 (35-67)

Multiple Myeloma: BMT CTN 0704

A Phase III, randomized, double-blind study
maintenance therapy with
Lenalidomide or placebo
following autologous transplantation for Myeloma

BMT CTN was an important contributor to this study, which was led by Cancer and Leukemia Group B (CALGB).
Network power: Accelerated enrollment after CTN joins in BMT CTN #0704 / CALGB 100104

Progression Free & Overall Survival

Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival. HSCT denotes hematopoietic stem-cell transplantation.
Multiple Myeloma: BMT CTN 0704

Maintenance therapy with Lenalidomide or placebo following autologous transplantation for Myeloma

➢ Lenalidomide maintenance therapy prolongs remission and survival after autologous HCT for multiple myeloma

➢ Major change in clinical practice, with most myeloma patients now receiving lenalidomide maintenance after HCT.

[change of practice] McCarthy, NEJM

0702 Post Autograft strategies for Myeloma

Autologous HCT

then either:

Nothing; 2nd (Tandem) autograft; 4 cycles consolidation Chemotherapy [RVD]

All get Lenalidomide maintenance

Results coming soon
Multiple Myeloma

Auto/Auto vs. Auto/Allo transplantation

Post Auto maintenance

Post Auto strategies

---------------------------
Early vs. Late Autograft

Allotransplant + maintenance

Cellular vaccine post autotransplantation

Supportive Care: BMT CTN 0101

**Fluconazole versus voriconazole** for the prevention of invasive fungal infections in allogeneic HCT recipients

> Fluconazole, a low-cost antifungal agent, has similar efficacy as and is more cost-effective than the more expensive drug, voriconazole, in preventing serious fungal infections in the first six months after HCT.  
  
  *change of practice*

> Demonstrated that voriconazole may be a cost-effective primary antifungal prophylaxis for a subset of patients undergoing an allogeneic HCT for AML.
Exploring New Graft Sources that Can Better Serve Minorities

- BMT CTN 0603 and 0604: Parallel Phase II study of reduced intensity HCT in adults:
  - haploidentical bone marrow or
  - unrelated donor umbilical cord blood
Neutrophil Recovery

A. Double UCB – Neutrophil Recovery

B. Double UCB – Platelet Recovery

C. Haplo-marrow – Neutrophil Recovery

D. Haplo-marrow – Platelet Recovery

Platelet recovery

Brunstein 2011

GVHD.

aGVHD

B. Double UCB – Acute GVHD

A. Double UCB – Acute GVHD

C. Haplo-marrow – Acute GVHD

D. Haplo-marrow – Chronic GVHD

cGVHD

Brunstein 2011
Haplo-Identical Transplantation for Hematologic Malignancy

Other centers vs. CTN 0603 centers

Number of Transplants

0603/0604 paper published
Graft Sources: BMT CTN 0603/0604

- Reduced-intensity conditioning and haploidentical bone marrow transplantation or double UCB transplantation in adults with hematologic malignancies
- Acceptable outcomes with either double cord or haploidentical bone marrow
- Many more adults should be offered HCT, even if an HLA-matched adult donor is not available. [change of practice]
- Haplo vs. UCB being compared in a randomized Phase III trial (BMT CTN 1101).

Is More Better

- Reduced Intensity Conditioning
  
  Less toxic
  Suitable for Older or more frail patients
Conditioning Intensity in AML/MDS: High vs. Reduced Intensity Conditioning

- CALGB 100701/CTN 0502: Reduced intensity AlloBMT for elderly patients with AML
  - Would not have completed without BMT CTN

CALGB 100103/BMT CTN 0502
Disease Free Survival

Median follow up: 4.9 yrs

Devine et al, JCO
BMT CTN 0901  Best Conditioning Regimen in AML/MDS: Randomized Trial of High vs. Reduced Intensity Conditioning

– Study stopped after 272 of planned 356 patients enrolled (ahead of schedule) -- apparent outcome benefit in the high-dose arm

– BMT CTN is the *only* way that this question could have been addressed

Increasing Use of Reduced Intensity Conditioning in Allogeneic Transplants in Adults with AML & MDS

Results of 0901 May Reverse This Trend
Challenging “conventional wisdom”: is More better

- BMT CTN 0501: Randomized comparison of one vs. two cord blood units in children (collaboration with COG)
  - Only randomized trial in cord blood transplantation ever
  - Accrued 224 patients on time (1 yr survival endpoint)

Wagner, NEJM, 2014
Survival: similar in both groups

No. at Risk
Double-unit group 111 95 80 76 71 64 59 57 54
Single-unit group 113 103 93 87 82 75 71 66 63

Major Complications

III-IV aGVHD

Relapse

Treatment related mortality

Major Complications

Treatment related mortality

cGVHD
Challenging “conventional wisdom”: More is not better

• BMT CTN 0501: Randomized comparison of one vs. two cord blood units in children (collaboration with COG)
  
  – Similar survival with two versus one unit:
  – Two unit transplants were associated with more GVHD and slower platelet recovery
  
  – Important implications for practice/ public policy

Wagner, NEJM, 2014

Challenging “conventional wisdom”: Bone Marrow vs Peripheral Blood

• BMT CTN 0201: Compared bone marrow vs. peripheral blood for unrelated donor transplantation
  
  – Largest study of unrelated donor transplantation ever done
  – Close collaboration with National Marrow Donor Program

Anasetti NEJM 2012
Challenging “conventional wisdom”: Bone Marrow vs Peripheral Blood

- **BMT CTN 0201**: Compared bone marrow vs. peripheral blood for unrelated donor transplantation

  - Results challenged the conventional wisdom that peripheral blood stem cells are better (used for ~70% of transplants)

- **No survival benefit with peripheral blood**
- **More chronic GVHD with PBSC requiring prolonged immune suppression**

Anasetti  NEJM 2012
Network Challenges

- Pick the best questions
- Address those requiring multicenter participation and more accrual
- Test approaches that can change the field
- Add correlative studies to inform the next trials

Five Year Results of BMT CTN 0201

Clinical Implications

No relevant conflicts of interest
Background

- BMT CTN 0201 was a RCT of unrelated donor bone marrow (BM) vs. peripheral blood (PB) 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)

Anasetti C et al, NEJM 2012; 367:1487

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
- More than 80% of similar transplants use PB

QOL was a secondary endpoint

- Stephanie J. Lee
- Brent Logan
- Peter Westervelt
- Corey Cutler
- Ann Woolfrey
- Shakila P. Khan
- Edmund Waller
- Richard Maziarz
- Juan Wu
- Bronwen Shaw
- Dennis Confer
- Mary Horowitz
- Claudio Anasetti
QOL Eligibility Criteria/Study Design

- Age >16
- English or Spanish speaking
- Patient-reported outcomes (PROs) collected prior to randomization and at 0.5, 1, 2 and 5 years after transplantation
  - FACT-BMT
  - MHI (mental health inventory)
  - Lee chronic GVHD symptom scale (post-HCT only)
  - Occupational functioning

Study Design cont.

- Data collection centralized
  - One organization collected baseline, 0.5, 1, 2 years
  - NMDP/Be The Match collected 5 year assessments
- Response rates, for surviving patients
  - Baseline (n=368) – 72%
  - 0.5 year (n=146) – 40%
  - 1 year (n=123) – 41%
  - 2 year (n=71) – 29%
  - 5 year (n=148) – 76%
Responder characteristics

<table>
<thead>
<tr>
<th></th>
<th>Enrollment, pre-HCT</th>
<th>5 year assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responder</td>
<td>Non-responders</td>
</tr>
<tr>
<td>High risk disease, n (%)</td>
<td>102 (25.8)</td>
<td>47 (38.5)</td>
</tr>
<tr>
<td>Karnofsky score ≥90%, n (%)</td>
<td>245 (62.0)</td>
<td>55 (45.1)</td>
</tr>
<tr>
<td>Karnofsky score &lt;90%, n (%)</td>
<td>108 (27.3)</td>
<td>32 (26.2)</td>
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<tr>
<td>Karnofsky score Missing</td>
<td>42 (10.6)</td>
<td>35 (28.7)</td>
</tr>
<tr>
<td>Age ≥ 40, n (%)</td>
<td>245 (62.0)</td>
<td>72 (59.0)</td>
</tr>
</tbody>
</table>

No difference in graft source, diagnosis, sex, race, conditioning regimen, GVHD prophylaxis, HLA mismatching.

Five year results of BM vs. PB

<table>
<thead>
<tr>
<th>QOL scale</th>
<th>Bone marrow (n=102)</th>
<th>Peripheral blood (n=93)</th>
<th>P value</th>
<th>Clinically significant difference(^1)</th>
<th>Difference between BM and PB (95% CI)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-BMT TOI (↑ better) Mean +/- SE</td>
<td>76.7 +/- 1.6 (n=79)</td>
<td>70.5 +/- 1.9 (n=69)</td>
<td>0.014</td>
<td>8.5</td>
<td>6.2 (1.3-11.1)</td>
</tr>
<tr>
<td>MHI – Psychological wellbeing (↑ better) Mean +/- SE</td>
<td>78.9 +/- 1.7 (n=80)</td>
<td>72.2 +/- 1.9 (n=72)</td>
<td>0.011</td>
<td>8.4</td>
<td>6.7 (1.6-11.8)</td>
</tr>
<tr>
<td>MHI-Psychological Distress (↓ better) Mean +/- SE</td>
<td>16.0 +/- 1.3 (n=80)</td>
<td>19.0 +/- 1.5 (n=71)</td>
<td>0.128</td>
<td>6.5</td>
<td>-3.0 (-6.8,0.9)</td>
</tr>
<tr>
<td>Chronic GVHD symptoms (↓ better) Mean +/- SE</td>
<td>13.1 +/- 1.5 (n=80)</td>
<td>19.3 +/- 1.6 (n=72)</td>
<td>0.004</td>
<td>7.1</td>
<td>-6.3 (-10.5, -2.0)</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
\(^1\)Adjusted for enrollment values and missing data using inverse probability weighting using significant clinical characteristics

Lee et al, JAMA Onc 2016, in press
## Baseline predictors of 5 year PROs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Mean/Slope</th>
<th>Standard error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHI – Psych well-being (↑better)</td>
<td>Graft type</td>
<td>Bone marrow</td>
<td>78.0</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral blood</td>
<td>71.7</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>≤ 30 years</td>
<td>77.2</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31-50 years</td>
<td>69.6</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50 years</td>
<td>77.8</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Baseline MHI Psych well-being</td>
<td>Slope</td>
<td>0.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Chronic GVHD symptoms (Ψ better)</td>
<td>Graft type</td>
<td>Bone marrow</td>
<td>14.4</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral blood</td>
<td>20.5</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>≤ 30 years</td>
<td>13.7</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31-50 years</td>
<td>23.1</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50 years</td>
<td>15.5</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>Female</td>
<td>21.5</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>13.4</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Primary disease</td>
<td>AML</td>
<td>15.5</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALL</td>
<td>16.8</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CML</td>
<td>23.4</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MDS</td>
<td>14.1</td>
<td>2.3</td>
</tr>
</tbody>
</table>

## Additional results – chronic GVHD

<table>
<thead>
<tr>
<th>Chronic GVHD – skin (0-100, ↓ better)</th>
<th>BM</th>
<th>PB</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean +/- SE</td>
<td>10.8 +/- 1.8 (n=80)</td>
<td>16.2 +/- 2.3 (n=72)</td>
<td>0.06</td>
</tr>
<tr>
<td>Chronic GVHD – eyes (0-100, ↓ better)</td>
<td>Mean +/- SE</td>
<td>21.0 +/- 3.0 (n=80)</td>
<td>44.3 +/- 4.1 (n=72)</td>
</tr>
<tr>
<td>Chronic GVHD – mouth (0-100, ↓ better)</td>
<td>Mean +/- SE</td>
<td>6.7 +/- 2.1 (n=80)</td>
<td>9.2 +/- 1.7 (n=72)</td>
</tr>
<tr>
<td>Chronic GVHD – lung (0-100, ↓ better)</td>
<td>Mean +/- SE</td>
<td>3.8 +/- 0.9 (n=80)</td>
<td>9.2 +/- 1.7 (n=72)</td>
</tr>
<tr>
<td>Chronic GVHD – nutrition (0-100, ↓ better)</td>
<td>Mean +/- SE</td>
<td>3.3 +/- 0.8 (n=80)</td>
<td>5.3 +/- 1.2 (n=72)</td>
</tr>
<tr>
<td>Chronic GVHD – energy (0-100, ↓ better)</td>
<td>Mean +/- SE</td>
<td>25.5 +/- 2.7 (n=80)</td>
<td>37.6 +/- 3.1 (n=72)</td>
</tr>
<tr>
<td>Chronic GVHD – psych (0-100, ↓ better)</td>
<td>Mean +/- SE</td>
<td>20.1 +/- 3.0 (n=80)</td>
<td>23.3 +/- 2.8 (n=72)</td>
</tr>
</tbody>
</table>
Additional 5 yr results – reported by centers

<table>
<thead>
<tr>
<th>Chronic GVHD, n (%)</th>
<th>BM (n=102)</th>
<th>PB (n=93)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cGVHD</td>
<td>72 (71)</td>
<td>46 (49)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mild</td>
<td>17 (17)</td>
<td>21 (23)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>9 (9)</td>
<td>16 (17)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (4)</td>
<td>8 (9)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Skin sclerosis, n (%)</td>
<td>8 (8)</td>
<td>17 (18)</td>
<td>0.03</td>
</tr>
<tr>
<td>Eye involvement, n (%)</td>
<td>15 (15)</td>
<td>31 (33)</td>
<td>0.002</td>
</tr>
<tr>
<td>Musculoskeletal involvement, n (%)</td>
<td>3 (3)</td>
<td>14 (15)</td>
<td>0.003</td>
</tr>
<tr>
<td>Avascular necrosis, n (%)</td>
<td>5 (5)</td>
<td>14 (15)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

No differences in:
- mouth, lung or GI chronic GVHD involvement
- diabetes, dialysis, hypothyroidism, cardiac

Return to work

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

- Median FU 73 months
- P=0.84

Bone marrow
Peripheral Blood Stem Cells

Generalizability

- Compared characteristics and outcomes of 0201 trial participants with non-participants
- Held constant: centers, time period, conditioning regimens and GVHD prophylaxis

Khera N et al, BBMT 2015; 21: 1815
Study population

<table>
<thead>
<tr>
<th>0201 vs. Non-participants</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM 50% vs. 34%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATG 26% vs. 32%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Not different: Pt age, sex, disease, race/ethnicity, HCT-CI, HLA match, time from dx to HCT

Results
Conclusions

- At 5 years after HCT, recipients of unrelated donor BM, compared with PB, have:
  - Similar survival, relapse, TRM (generalizable)
  - Better psychological well-being
  - Less burdensome chronic GVHD symptoms
  - Are 50% more likely to go back to work
- No outcome for which PB was better
- PB is still used for >80% of unrelated donor transplants for similar patients
- Will more bone marrow be used?

Limitations/Implementation Concerns

- Newer GVHD prophylaxis regimens not represented
  - Clinical trials may require PB
- BM is harder to arrange and more difficult to reschedule than PB
- Lingering concerns about engraftment and relapse with BM: large pt/small donor, transit time, disease type and status
- Donor recovery longer with BM, although with time they achieve similar recovery to PB
Case

• 40 y/o with high risk AML in CR1
• Myeloablative conditioning
• Standard tacrolimus/MTX GVHD prophylaxis
• 8/8 young unrelated donor

What graft source would you prescribe?
What graft source would you prescribe?

donate

What graft source would you prescribe?

want