Allogeneic Transplant Conditioning regimens: does the choice matter?

Steven Devine MD
The Ohio State University
Comprehensive Cancer Center
TBI Dose and outcomes in AML

Clift et al, Blood, 1990
Does conditioning dose intensity matter prior to an allograft?

What has 15 years of data taught us?
Trends in Transplants by Transplant Type and Recipient Age*
1989-2009

* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
Allogeneic Transplants, Registered with the CIBMTR, 2000-2009
- by Conditioning Regimen Intensity & Age -

Number of Transplants

- Reduced Intensity Conditioning, Age >= 50 yrs
- Reduced Intensity Conditioning, Age < 50 yrs
- Standard Myeloablative Conditioning

* Data incomplete
Trends in France

Blaise and Castagna ASH Education Book 2012
TRM and relapse by regimen intensity
CIBMTRR analysis

Luger BMT 2012
DFS and OS by regimen intensity
CIBMTR analysis

Luger BMT 2012
EBMT analysis by regimen intensity

Relapse in the initial 12 months

Cumulative incidence of relapse

- NMA, 41% (95% C.I. 28-62)
- IntermRIC, 22% (95% C.I. 16-31)
- ConvMC, 15% (95% C.I. 13-18)
- HyperMC, 13% (95% C.I. 8-21)

Months since transplantation

Martino BMT 2012
EBMT analysis by regimen intensity

Martino BMT 2012
Cumulative incidence of relapse of RIC and FI for adult Ph-ALL.


©2010 by American Society of Hematology
Adjusted probability of OS of RIC and FI for adult Ph-ALL.

Does anyone do prospective research in BMT?
German Randomized trial: Dose Intensity of TBI

198 patients registered for inclusion

3 patients ineligible*

195 patients randomly assigned

99 randomly allocated to receive reduced-intensity conditioning
   94 received reduced-intensity conditioning
   2 received other conditioning regimens
   1 had increased concentrations of aminotransferases
   1 refused allogeneic transplantation
   1 relapsed and died before transplantation

99 patients in the intention-to-treat population
   94 in the per-protocol population§

96 randomly allocated to receive standard conditioning
   90 received standard conditioning
   3 received other conditioning regimens
   1 refused total-body irradiation
   1 had had previous radiotherapy†
   1 had pathological creatinine clearance difficulties‡

96 patients in the intention-to-treat population
   90 in the per-protocol population§

Bornhauser Lancet Oncology 2012
German Randomized trial: TBI dose intensity

Bornhauser Lancet Oncology 2012
### Influence of Busulfan dose on outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Patient age, y</th>
<th>N</th>
<th>Donor</th>
<th>Diseases</th>
<th>CTX</th>
<th>CTX</th>
<th>Proph GVHD</th>
<th>a-GVHD</th>
<th>c-GVHD</th>
<th>NRM</th>
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<tbody>
<tr>
<td>Russell^83</td>
<td>Retrospective PK studies</td>
<td>41</td>
<td>70</td>
<td>HLAd sb MUD</td>
<td>AML</td>
<td>FBUATG</td>
<td>F 250 mg/m², ivBU 3.2 mg/kg × 4d, ATG 4.5 mg/kg</td>
<td>CSA + MTX 9%</td>
<td>38%</td>
<td>@100 d: 5%; @2 y: 10%</td>
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<tr>
<td>de Lima^87</td>
<td>Retrospective with once-daily ivBU PK studies</td>
<td>45</td>
<td>96</td>
<td>HLAd sb 55%; MUD 38%;</td>
<td>AML, MDS</td>
<td>FBU</td>
<td>F 160 mg/m², ivBU 130 mg/m² × 4d</td>
<td>FK506 + mMTX 25%</td>
<td>55%</td>
<td>@100 d: 5%; @1 y: 3%</td>
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<tr>
<td>Chae^84</td>
<td>Retrospective comparing 2 CTX</td>
<td>38</td>
<td>40 vs 55</td>
<td>HLAd sb 69%; MUD 11%;</td>
<td>AL 76%, AL 80%</td>
<td>FBU vs BuCy2</td>
<td>F 160 mg/m², ivBU 3.2 mg/kg × 4d</td>
<td>CSA + MTX 15% vs 71%</td>
<td>44% vs 94%</td>
<td>@2 y: 10% vs 34%</td>
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<tr>
<td>Russell^81</td>
<td>Matched-pair analysis</td>
<td>42</td>
<td>54 vs 54</td>
<td>HLAd sb 100%</td>
<td>Not stated</td>
<td>FBUATG vs MAC no ATG</td>
<td>F 250 mg/m², ivBU 3.2 mg/kg × 4d, ATG 4.5 mg/kg</td>
<td>CSA + MTX 19% vs 32%</td>
<td>55% vs 96%</td>
<td>@100 d: 4% vs 17%; @4 y: 3% vs 34%</td>
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<tr>
<td>Chunduri^85</td>
<td>Retrospective</td>
<td>44</td>
<td>36</td>
<td>HLAd sb 47%; MUD 53%</td>
<td>AL 94%</td>
<td>FBU</td>
<td>F 160 mg/m², ivBU 3.2 mg/kg × 4d</td>
<td>FK506 + mMTX 19%</td>
<td>37%</td>
<td>@100 d: 5%</td>
<td></td>
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<tr>
<td>Bredeson^86</td>
<td>Matched-pair analysis</td>
<td>46</td>
<td>120 vs 215</td>
<td>HLAd sb 100%; MUD 56%;</td>
<td>AL 56%, AL 64%</td>
<td>FBUATG vs BUscy2</td>
<td>F 250 mg/m², ivBU 3.2 mg/kg × 4d, ATG 4.5 mg/kg</td>
<td>CSA + MTX 15% vs 34%</td>
<td>39% vs 32%</td>
<td>@1 y: 9% vs 24%; @5 y: 12% vs 34%</td>
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<tr>
<td>Andersson^73</td>
<td>Retrospective comparison</td>
<td>46</td>
<td>145 vs 75</td>
<td>HLAd sb 61%; MUD 36%;</td>
<td>AML/MDS 100% vs FM</td>
<td>FBU vs BUscy</td>
<td>F 180 mg/m², ivBU 130 mg/m² × 4d</td>
<td>FK506 + mMTX 15% vs 32%</td>
<td>34% vs 36%</td>
<td>@12 y: 27%*</td>
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</tr>
<tr>
<td>using Bayesian method</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Alatrash^14</td>
<td>Retrospective</td>
<td>58</td>
<td>74</td>
<td>HLAd sb 52%; MUD 48%</td>
<td>AML/MDS</td>
<td>FBU</td>
<td>F 160 mg/m², ivBU 130 mg/m² × 4d</td>
<td>FK506 + mMTX 41%</td>
<td>42%</td>
<td>@1 y: 21%</td>
<td></td>
</tr>
</tbody>
</table>
Busulfan dose intensity and outcomes: influence of remission status

All patients

In remission

Not in remission

Shimoni Leukemia 2010
Comparing Flu/Bu ablative to Bu/Cy

Lee J et al. JCO 2013;31:701-709
Survival differences between the busulfan-cyclophosphamide (BuCy) and busulfan-fludarabine (BuFlu) arms.

Lee J et al. JCO 2013;31:701-709
IV busulfan dose influence

Parmar BBMT 2013
Comparison of Conditioning Regimens Using Intravenous Busulfan versus Total Body Irradiation for Allogeneic Hematopoietic Stem Cell Transplantation in Hematologic Malignancies

CIBMTR Study SC09-01
Background

- Historical data are conflicting regarding the superiority of cyclophosphamide + TBI ablative conditioning regimens vs. oral busulfan-based ablative conditioning regimens.
- IV-BU with or without pharmacokinetic monitoring is better tolerated than oral busulfan.
- IV-BU based conditioning regimen use is increasing and TBI-based conditioning regimen use decreasing without comparative data.
Rationale

❖ To evaluate the efficacy of ablative IV BU-based conditioning regimens compared to ablative TBI-based regimens.
Study Characteristics

- Design: **Prospective** cohort study
- Primary Objective: to test the non-inferiority of overall survival between IV-BU and TBI-based ablative conditioning regimens.
  - Power of 80% for HR<1.26 (overall mortality) with IV-BU compared to TBI.
    - Equivalent to a difference of less than 7.5% in 1-year overall survival.
  - Targeted accrual of 1460, accrual rate of 730pts/y
- Primary Endpoint: overall survival
Eligibility

- Age ≤ 60 yrs
- First allogeneic transplant
- Myeloablative conditioning regimen
  - IV BU (>9mg/kg) + cyclophosphamide or fludarabine
  - TBI (≥ 500cGY single fraction or ≥ 800cGY fractionated) + cyclophosphamide or etoposide
- Related or unrelated BM or PB donor
- Diagnosis of AML, MDS, CML
- Calcineurin inhibitor-based GVHD prophylaxis
- No ex vivo T-cell depletion
Study Accrual

- Enrollment from March 2009 to February 2011
- 1,483 patients (1025 BU, 458 TBI)
- Accrual rate of 740 pts/y
- 120 Centers from North and South America
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IV Bu (N=1025)</th>
<th>TBI (N=458)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;20 yrs</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>20-49 yrs</td>
<td>44</td>
<td>60</td>
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<tr>
<td>&gt;=50 yrs</td>
<td>40</td>
<td>29</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td><strong>Performance Score ≥ 90</strong></td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td><strong>AML</strong></td>
<td>68</td>
<td>78</td>
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<tr>
<td><strong>MDS</strong></td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td><strong>CML</strong></td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td><strong>HCI-CI ≤3</strong></td>
<td>81</td>
<td>83</td>
</tr>
<tr>
<td><strong>Advanced disease</strong></td>
<td>31</td>
<td>29</td>
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## Donor Characteristics

<table>
<thead>
<tr>
<th>Description</th>
<th>IV Bu %</th>
<th>TBI %</th>
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<tbody>
<tr>
<td>HLA-identical sib</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>8/8 matched unrel</td>
<td>47</td>
<td>51</td>
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<tr>
<td>Male Donor</td>
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<td>61</td>
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<tr>
<td>Age &gt;/= 40y</td>
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<td>39</td>
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<tr>
<td>CMV Positiv</td>
<td>39</td>
<td>39</td>
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<tr>
<td>PB graft</td>
<td>77</td>
<td>76</td>
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## Treatment Characteristics

<table>
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<tr>
<th>Description</th>
<th>IV Bu</th>
<th>TBI</th>
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<tbody>
<tr>
<td><strong>Conditioning</strong></td>
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<td></td>
</tr>
<tr>
<td>FluBU +/- ATG/Campath</td>
<td>41%</td>
<td>0%</td>
</tr>
<tr>
<td>BUCY-based +/- ATG/Campat</td>
<td>59%</td>
<td>0%</td>
</tr>
<tr>
<td>CyTBI-based +/- ATG/Campath</td>
<td>0%</td>
<td>96%</td>
</tr>
<tr>
<td>VP16TBI-based +/- ATG/Campath</td>
<td>0%</td>
<td>4%</td>
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<td><strong>GVHD Prophylaxis</strong></td>
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<tr>
<td>CNI+MTX+/.-other</td>
<td>77%</td>
<td>86%</td>
</tr>
<tr>
<td>CNI+MMF+/.-other</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>CNI+/.-other (no MTX/MMF)</td>
<td>7%</td>
<td>7%</td>
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<tr>
<td>ATG/Campath</td>
<td>28%</td>
<td>14%</td>
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## Busulfan Dosing

**IV Bu (N=1025)**

<table>
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<tr>
<th>Description</th>
<th>%</th>
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<tr>
<td>BU Schedule</td>
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<tr>
<td>Daily</td>
<td>42</td>
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<tr>
<td>Q6H</td>
<td>57</td>
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<tr>
<td>BU Pharmacokinetics (PK)</td>
<td>56</td>
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<tr>
<td>If PK, BU adjusted</td>
<td>78</td>
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</tbody>
</table>
Overall Survival of Recipients of IV-BU Compared to TBI-based Myeloablative Conditioning

**IV-Bu:** 56% (95% CI 53-60%) @ 2y

**TBI:** 48% (95% CI 43-54%) @ 2y

P=0.019*

*pointwise p-value at 2 years*
Overall Survival of Recipients of IV-BU Compared to TBI-based Myeloablative Conditioning by Disease Status at Transplant

Early Disease
- IV-Bu (64%)
- TBI (51%)

Intermediate Disease
- IV-Bu (57%)
- TBI (56%)

Advanced Disease
- IV-Bu (43%)
- TBI (38%)

P=0.006*
P=NS*
P=NS*

*pointwise p-value at 2 years
Overall Survival of Recipients of IV-BU Compared to TBI-based Myeloablative Conditioning by Transplant Indication

**AML**
- IV-Bu (57%)
- TBI (46%)

**MDS**
- TBI (59%)
- IV-Bu (46%)

**CML**
- IV-Bu (71%)
- TBI (59%)

*pointwise p-value at 2 years*

P=0.003*

P=NS*

P=NS*
Multivariate Analysis: Bu vs. TBI

Relapse
- TBI (RR=1.0)
- IV-BU

TRM
- TBI (RR=1.0)
- IV-BU

Overall Survival
- TBI (RR=1.0)
- IV-BU

Relapse: p=0.49
TRM: p=0.14
Overall Survival: p=0.030

Xz19_13.ppt
Conclusions

- IV BU-based ablative conditioning regimens prior to allogeneic HCT are associated with improved survival compared to TBI-based regimens

- Non-relapse mortality, relapse, PFS, grade II-IV aGVHD, cGVHD were similar between the two approaches

- IV BU was associated with a small but greater risk of VOD/SOS than TBI
Conclusions

- The results suggest ablative IV BU-based regimens should be preferentially used instead of ablative TBI-based regimens for patients with myeloid malignancies undergoing HCT from an HLA-Id sib or volunteer unrelated donor.

- Further study is required to explain the improved survival and the role, if any, of PK monitoring / dose adjustment on the outcomes.

- This study illustrates the value of prospective cohort studies for studies using large number of transplant patients.
Busulfan Dose Intensity and Outcomes in Reduced Intensity Allogeneic Stem Cell Transplantation for MDS / AML

RIC at DFCI / MGH

- **Bu1**
  - Busulfan 0.8 mg/kg/day IV x 4 = **3.2 mg/kg**
  - Fludarabine 30 mg/kg/day x 4

- **Bu2**
  - Busulfan 0.8 mg/kg/BID IV x 4 = **6.4 mg/kg**
  - Fludarabine 30 mg/kg/day x 4
• Retrospective analysis comparing outcomes between Bu1 vs Bu2 RIC SCT for patients with MDS or AML between 2004-2009
  – Total of 217 patients
    • 135 received Bu1 RIC SCT (median f/u 4.4 yrs)
    • 82 received Bu2 RIC SCT (median f/u 3.2 yrs)
  – Choice based on institutional standard, enrollment on specific protocols, physician preference
NRM and Relapse

**NRM**
Bu1 8.9% vs. Bu2 9.8%
Bu2 HR 0.80 (0.29, 2.21) $p = 0.67$

**Relapse**
Bu1 54.0% vs. Bu2 50.0%
Bu2 HR 0.95 (0.62, 1.46) $p = 0.82$
Progression-Free Survival

Bu1 39.3% vs. Bu2 42.7%
Bu2 HR 0.82 (0.57, 1.30)
p = 0.33
Overall Survival

Bu1 47.4% vs. Bu2 48.8%
Bu2 HR 0.96 (0.64, 1.44)
p = 0.85
What do we not know about conditioning intensity?

• Focus is on patients who are candidates for both MA and RIC
  – Are RIC regimens the same, better, or worse, particularly in AML, MDS, ALL?
  – Are there particular settings where one type of conditioning is better than the other?
    • When considering both patient and disease characteristics
  – Is there a “sweet spot” that can be achieved, balancing efficacy and toxicity
    • Best example here is Bu targeting
BMT CTN 0901: A Multi-center Phase III Study Comparing Myeloablative to Reduced Intensity Conditioning in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia
MAVRIC
BMT CTN 0901

Advanced MDS/AML < 5% blasts

Patients randomized

GVHD Prophylaxis per Institutional guidelines

RIC regimens
- Flu/Bu
- Flu/Mel

MA Regimens
- Bu/Flu
- Bu/Cy
- Cy/TBI

18 Month Overall Survival

Centers will choose one myeloablative and one reduced intensity regimen for each patient at time of randomization.

1 Bu ≤ 8mg/kg PO or IV equivalent, Mel < 150mg/m²
2 IV or PO Bu
3 T-replete bone marrow or peripheral blood. Post-transplant cytoxan excluded.

4 Bu 16mg/kg oral or IV equivalent
TBI 12-14.2 Gy
Endpoints

- **Primary Endpoint**
  - Overall Survival at 18 months

- **Secondary Endpoints**
  - Disease-free survival
  - Relapse
  - TRM
  - Engraftment and donor/recipient chimerism
  - Primary and secondary graft failure
  - Toxicity
  - GVHD
  - Infections
  - QOL
Eligibility: Inclusion Criteria

- Age 18-65 years
- AML or MDS <5% bone marrow blasts
- HLA-matched related or unrelated donor (8/8 or 7/8)
- HCT-CI ≤ 4
- Peripheral blood or bone marrow stem cells
Additional agents studied

- Clofarabine by multiple groups
- Treosulfan by multiple groups
- IMRT by some
- Post transplant maintenance
  - Lenalidomide
  - HMA (5AC, decitabine)
Cumulative incidence of Relapse in Non-remission AML

- CloBu4
- All other myeloablative conditioning

P=0.04

Kindly provided by Shin Mineishi
Post-Transplant Maintenance with 5-Azacytidine

Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>Median (Range)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>45</td>
<td>60.6 (24.3-73.8)</td>
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<tr>
<td>Bone marrow blast at transplantation (%) (all patients)</td>
<td>45</td>
<td>6 (0-80)</td>
</tr>
<tr>
<td>Median bone marrow blasts at transplantation</td>
<td>30</td>
<td>10 (6%-80%)</td>
</tr>
<tr>
<td>(in patients with active disease)</td>
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<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Women</td>
<td>21 (46.7)</td>
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<tr>
<td>Men</td>
<td>24 (53.3)</td>
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<td>Diagnosis</td>
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<tr>
<td>AML</td>
<td>37 (82.2)</td>
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<tr>
<td>MDS</td>
<td>8 (17.8 )</td>
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<tr>
<td>Cytogenetics^{11,35}</td>
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<tr>
<td>Bad^a</td>
<td>18 (40.0)</td>
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<tr>
<td>Intermediate</td>
<td>26 (57.8)</td>
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<td>Good</td>
<td>1 (2.2 )</td>
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<td>Complete remission at transplantation</td>
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<tr>
<td>No</td>
<td>30 (66.7)</td>
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<td>Primary induction failure</td>
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<td>First and second recurrence</td>
<td>11 and 1</td>
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<td>Untreated high-risk MDS</td>
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<tr>
<td>Yes</td>
<td>15 (33.3)^b</td>
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</tr>
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</table>

Recommended 32 mg/m2 x5 days, 4 or more cycles

de Lima et al, Cancer 2010
Post-Transplant Maintenance with 5-Azacytidine

OS

DFS

de Lima et al, Cancer 2010
A Phase II Study of the Addition of 5-Azacytidine to Reduced-Intensity Allogeneic Transplantation for Myelodysplasia (MDS) and Older patients With AML

Study Chair: Ravi Vij, MD
Transplant Committee Chair: Steven Devine, MD
Leukemia Committee Chair: Richard Larson, MD
Leukemia Correlative Science Chair: Guido Marcucci, MD

Statistician: Kouros Owzar, PhD
Rationale

• For MDS patients with high-risk features, the relapse rate after RIC regimens has been high.

• We also hypothesize that we can improve outcomes by improving disease control without an increase in TRM by using a higher busulfan dose, aiming for an AUC that is 75% of “standard” rather than 50%.

• By adjusting the busulfan dose based on PK measurements, we anticipate keeping the busulfan AUC within a relatively narrow range in order to avoid excess toxicity.

• We will study whether the addition of post-transplant 5 azacytidine decreases the risk of relapse.
Objectives

- Primary Objective: To determine if this treatment can improve 2-year progression-free survival (PFS) in patients with high risk MDS and AML > 60 yrs age.

- Secondary objectives:
  - Safety and feasibility of using post-transplant azacytidine
  - The ability to use PK-directed busulfan to achieve AUC within 20% of target AUC in > 80% of patients
  - Rate of grade II-IV and III-IV acute GVHD
  - Incidence of extensive chronic GVHD
  - Treatment-related mortality at 100 days and one year
  - 5-year Overall survival
Eligibility

• Age ≥ 60 yrs and <75 years

• 6/6 (low resolution) HLA-matched related donor or 8/8 high-resolution matched unrelated donor.

• MDS with high-risk features defined as any of the following:
  – IPSS risk > Int -2
  – RAEB
  – High-risk cytogenetics, either complex or -7

• AML in first remission ("leukemia free state"), with all of the following:
  – Bone marrow blasts < 5%
  – Remission achieved < 2 cycles of intensive induction therapy or ≤ 4 cycles of azacytidine or decitabine.
  – Within 6 months of achieving remission
  – May have received 1-2 cycles of consolidation

• Patients are encouraged to have received treatment with azacytidine or decitabine prior to study enrollment
Conditioning Regimen

- **Test dose**
  - Busulfan 25 mg/m2 IV over 45 minutes  day -9 to -14
  - Measure Busulfan levels at: end of infusion (0h), 1h, 2h, 4h, 6h

- **Treatment doses**
  - Fludarabine 30 mg/m2/d IV x 5  days -7 to -3
  - Busulfan * mg IV over 3 h q day x 4*  days -6 to -3
    *Target to 4000 uMol*min. (time 0 – infinity)
    Measure Busulfan levels after first dose at end of infusion (0h), 1h, 2h, 4h, 6h
  - Rabbit ATG (Thymoglobulin®)
    - Unrelated donors (total dose 6 mg/kg)
      1.5 mg/kg  day -6
      2.0 mg/kg  day -5
      2.5 mg/kg  day -4
    - Sibling donors (total dose 3 mg/kg)
      1.5 mg/kg  day -6
      1.5 mg/kg  day -5
Post transplant 5 azacytidine:

- Post-transplant 5 azacytidine will start at day +42 to +90 provided the following conditions are met:
  - Serum creatinine <2.0 mg/dl
  - Serum bilirubin < 2.0 mg/dl
  - AST ≤ 3 X ULN
  - Platelets ≥ 50,000
  - ANC ≥ 1000
  - No acute GVHD Grade III or IV
  - No life threatening infections or bleeding

- Treatment will be:
  - 5-azacytidine 32 mg/m² SQ daily x 5 days
  - Cycles will be repeated x 4 every 4-6 weeks as tolerated
Sample Size

- 64 eligible patients.

- If at least 21 out of these 64 patients are progression-free for at least two years, this design will have the power to reject 0.25 against the local alternative 0.4 with error rates of $\alpha = \beta = 0.1$.

- The annual projected accrual rate of eligible patients is 18. As such, the projected accrual period is 3.6 years. As the last patient may have to be followed for a period of at least two years, the projected study period is 5.6 years.
Thank You!
Eligibility: Exclusion Criteria

- Circulating myeloblasts
- Prior autograft or allograft
- Active CNS disease at time of enrollment.
- HCT CI >4, KPS <70
- Organ function:
  - EF <35%
  - Tbil ≥ 2X ULN and ALT/AST ≥ 3X ULN
  - DLCO <50%
  - Creatinine clearance <50mL/min
- T-cell depleted grafts
- Post-transplant Cyclophosphamide as GvHD prophylaxis
- HIV positive
Statistical Considerations

- Superiority trial to test a difference of 15% in 18 mo OS.
- Plan accrual of 356 patients
  - 178 per arm
- Randomization will be stratified by center
- No stopping rules
Impact of anti–T-cell antibody infusion on outcome of RTC transplantation.

(A) Cumulative incidence of nonrelapse mortality in patients younger than 50 years of age receiving reduced intensity conditioning (RIC; dashed line) or myeloablative conditioning (MAC; gold line).

Ringdén O et al. JCO 2009;27:4570-4577
(A) Cumulative incidence of nonrelapse mortality in patients ≥ 50 years of age receiving reduced intensity conditioning (RIC; dashed line) or myeloablative conditioning (MAC; gold line).

Ringdén O et al. JCO 2009;27:4570-4577
Relapse incidence and NRM in AML. The cumulative incidence of relapse (A) and NRM (B) for AML patients (n = 31).

Survival in AML. Kaplan-Meier survival plots for OS (A) and EFS (B) for AML patients (n = 31).

Register for Intergroup Leukemia Study S1203

HLA typing upfront

Randomize

7+3  Ida-HD AraC  Ida-HD AraC-Vorinostat

CR

Follow-up

Induction Failure (x 2)

Transplant with CloBu4 if a donor is available

Randomize

Yes  Maintenance

Follow-up

No
Correlative Science Objectives

- to determine if the dose of post-transplant azacitidine results in changes in DNA methylation, measured globally and in selected target genes known to be hyper-methylated in MDS

- to determine if the expression of these genes is enhanced following azacitidine administration

- to measure the effect of post-transplant azacitidine on microRNA levels that may be associated with changes in immune function
GVH prophylaxis

• **Sibling donors**
  - Tacrolimus day -2 start
    Target level 5-10 ng/ml
  - Methotrexate 5 mg/m2 IV x 3 days +1, +3, +6

• **Unrelated donors**
  - Tacrolimus day -2 start
    Target level 5-10 ng/ml
  - Methotrexate 5 mg/m2 IV x 4 days +1,+3, +6, +11

• Taper off tacrolimus (as clinically possible) days +90 to +150
Probability of Survival after Autologous and HLA-matched Sibling Donor Hematopoietic Cell Transplantation for CLL, 2000-2009 by Donor Type and Conditioning Regimen Intensity

- Autologous transplant (N=253)
- Myeloablative conditioning (N=425)
- Reduced-intensity conditioning (N=752)

P < 0.0001
A, Cumulative incidence of nonrelapse mortality of 27% at 5 years among 372 patients 60 years or older treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference (P = .81, likelihood ratio statistics from Cox regression model) detected in cumulative incidences of nonrelapse mortality among patients 60 through 64, 65 through 69, and 70 years or older.
From: Long-term Outcomes Among Older Patients Following Nonmyeloablative Conditioning and Allogeneic Hematopoietic Cell Transplantation for Advanced Hematologic Malignancies


Figure Legend:

A, Rate of disease progression or relapse of 41% at 5 years among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference (P = .38, likelihood ratio statistics from Cox regression model) detected in rates of disease progression or relapse among patients 60 through 64, 65 through 69, and 70 years or older.
From: Long-term Outcomes Among Older Patients Following Nonmyeloablative Conditioning and Allogeneic Hematopoietic Cell Transplantation for Advanced Hematologic Malignancies


Figure Legend:
Vertical lines indicate censored events. A, Kaplan-Meier estimate of overall survival of 35% at 5 years among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference (P = .18, likelihood ratio statistics from Cox regression model) detected in rates of overall survival among patients 60 through 64, 65 through 69, and 70 years or older.
BMT 0901 Protocol Team

Co-Chairs
Bart Scott
Mitchell Horwitz

Shelly Carter
Joachim Deeg
Steven Devine
Sergio Giralt
Callie Heaton
Mary Horowitz

Jennifer LeRademacher
Richard Maziarz
Willis Navarro
David Porter
Marcelo Pasquini
Erica Warlick
FHCRC #1992

Advanced MDS/AML < 5% blasts

Patients randomized

NMA regimens
Flu/TBI 200
GVHD Prophylaxis
MMF/CSA

MA Regimens
Bu/Flu
Bu/Cy
GVHD Prophylaxis
Tac/MTX

2y Survival
CIBMTR Retrospective Analysis of Impact of Regimen Intensity on Outcome

- Allogeneic bone marrow or PBSC transplantation
- Matched sibling or Matched Unrelated Donors
- AML or MDS, reported to the CIBMTR, 1997-2004
- Age 18-70 years
- M3 AML, T-cell depletion excluded

Adjusted Probability of Overall Survival

NST (TBI 2 Gy/Flu) vs Myeloablative, p<0.01
NST vs RIC PB, p=0.02

RIC PB (N = 768)
Myeloablative (N = 3,731)
RIC BM (N = 273)
NST (N = 407)

Additional Analysis

- Select only the BMT CTN 0901 Regimens
  - RIC
    - Bu≤8/Flu, Flu/Mel
  - MAC
    - (Bu>9/Flu, Bu/Cy and Cy/TBI)
- Include Flu/TBI 2 Gy for comparison
- Year 2000-2004
- Ages 40-60 years
- Adjusted probability of OS
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Flu/TBI 2 GY (NMA)</th>
<th>Flu/Mel (RIC)</th>
<th>Flu/Bu (RIC)</th>
<th>Myeloablative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>72</td>
<td>65</td>
<td>108</td>
<td>637</td>
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<tr>
<td><strong>40-49y</strong></td>
<td>14 (19)</td>
<td>21 (32)</td>
<td>29 (27)</td>
<td>361 (57)</td>
</tr>
<tr>
<td><strong>50-59y</strong></td>
<td>58 (81)</td>
<td>44 (68)</td>
<td>79 (73)</td>
<td>276 (43)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>41 (57)</td>
<td>35 (54)</td>
<td>62 (57)</td>
<td>334 (52)</td>
</tr>
<tr>
<td><strong>AML</strong></td>
<td>47 (65)</td>
<td>43 (66)</td>
<td>66 (61)</td>
<td>436 (68)</td>
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<tr>
<td><strong>MDS</strong></td>
<td>25 (35)</td>
<td>22 (34)</td>
<td>42 (39)</td>
<td>201 (32)</td>
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<tr>
<td><strong>Disease Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CR1</strong></td>
<td>31 (44)</td>
<td>32 (49)</td>
<td>40 (38)</td>
<td>309 (44)</td>
</tr>
<tr>
<td><strong>≥ CR2</strong></td>
<td>16 (23)</td>
<td>11 (17)</td>
<td>24 (23)</td>
<td>121 (19)</td>
</tr>
<tr>
<td><strong>MDS treated</strong></td>
<td>15 (21)</td>
<td>9 (14)</td>
<td>26 (25)</td>
<td>107 (17)</td>
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<tr>
<td><strong>MDS untreated</strong></td>
<td>9 (13)</td>
<td>13 (20)</td>
<td>15 (14)</td>
<td>88 (14)</td>
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<tr>
<td><strong>BM</strong></td>
<td>7 (10)</td>
<td>11 (17)</td>
<td>9 (8)</td>
<td>217 (34)</td>
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<tr>
<td><strong>PBSC</strong></td>
<td>65 (90)</td>
<td>54 (83)</td>
<td>99 (92)</td>
<td>420 (66)</td>
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<tr>
<td><strong>HLA-match Sib</strong></td>
<td>24 (33)</td>
<td>30 (46)</td>
<td>76 (70)</td>
<td>331 (52)</td>
</tr>
<tr>
<td><strong>URD</strong></td>
<td>48 (67)</td>
<td>35 (54)</td>
<td>32 (30)</td>
<td>306 (48)</td>
</tr>
</tbody>
</table>
Relative Risk of Treatment-Related Mortality

Myeloablative
RIC BM
RIC PB
NST

Relative Risk (95% CI)

≤3 months
p=0.03
p<0.01
p=0.02

>3 months
p=0.04
p=0.02
p<0.01
Adjusted Probability of OS in patients with AML/MDS by conditioning regimen
Data suggest equipoise between RIC and MAC, however selection bias may significantly impact overall survival and treatment-related mortality.

CTN 0901 hypothesis based on the assumption that TRM will be lower and relapse rate will be similar with RIC transplants when selection bias is eliminated from the equation.
Bu Dose Intensity in AML/MDS: Importance of Disease Status

Shimoni et al. *Leukemia* 2006;20:322-328

**Active Disease**

- BuCy, n=28
- FB4, n=16
- FB2, n=14, P=0.01

**Remission**

- FB2, n=27
- BuCy, n=17
- n=10, p=NS
Progression in Patients Responding to Chemotherapy

Scott et al. *Leukemia* 2006;20:128-135

![Graph showing progression in patients responding to chemotherapy. The graph compares nonmyeloablative (n=20) and myeloablative (n=16) treatments, with a P-value of 0.64.](image-url)
Hypothesis

- RIC regimens are superior to MAC regimens for treatment of AML and MDS.
BMT CTN 0901 Revision Considerations

- Reduced intensity regimens needed to be added in order to improve accrual potential

- Lumping NST (TBI 2 Gy/Flu) with RIC (Bu 8/Flu or Flu/Mel 140) not appropriate
  - Concerns with ongoing relapse with the NMA regimen (Flu/TBI 2 Gy)

- Three-armed study comparing NST vs RIC vs MAC not feasible
  - Sample size too large

- True non inferiority design not feasible
  - Sample size too large
Reduced Intensity Conditioning
Flu/Bu

- Flu 30 mg/m²/d, D-6 to -2
- HCT 3.2 mg/kg/d IV or 4 mg/kg/day, D-5 and -4
- MTX 10 mg/m², D1,3,6,11
- TAC 0.015 mg/kg IV every 12 hrs
Myeloablative Conditioning
Flu/Bu

Flu
30 mg/m²/d
D-6 to -2

HCT

MTX 10 mg/m²
D1,3,6,11

TAC 0.015 mg/kg IV every 12 hrs

Flu 30 mg/m²/d D-6 to -2
BU 3.2 mg/kg/d IV
Or 4 mg/kg/day D-5 to -2
Ancillary Studies

- Bu pharmacokinetics for RIC
  - Collect samples for future testing
- Immune reconstitution
- Samples for the biorepository
Activated 6/2/11
- 15 core
- 14 affiliated

356 target
- 42 total
  - 130% of predicted
Background

- RIC regimens have allowed many patients to undergo allogeneic SCT
- Intensity of RIC varies
When RIC has been compared to MAC:
- Overall outcomes similar
- Higher TRM with MAC
- Higher relapse rates with RIC

Prospective studies will answer this question

Variations in RIC have not been well studied
- Importance of busulfan dose intensity in RIC?
Clinical and Cytogenetic Risk Groups

Clinical Disease Risk

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>MDS</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>&lt; 5% blasts, treatment responsive</td>
<td>CR1</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>CR2</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>≥ 5% blasts</td>
<td>CR3 or subsequent CR</td>
</tr>
</tbody>
</table>

Active disease

Cytogenetic Risk

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>MDS and MDS to AML</th>
<th>De novo AML</th>
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</thead>
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<tr>
<td>Favorable</td>
<td>N/A</td>
<td>Inv16 without other abnormality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(8;21)</td>
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<tr>
<td></td>
<td></td>
<td>11q23 abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal karyotype</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Del 5q, Del 20q</td>
<td>Trisomy 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal chromosome 5 or 7</td>
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<tr>
<td></td>
<td></td>
<td>Inv16 with complex karyotype</td>
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<tr>
<td></td>
<td></td>
<td>Three abnormalities</td>
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<tr>
<td></td>
<td></td>
<td>Any other abnormality</td>
</tr>
<tr>
<td>Adverse</td>
<td>Chromosome 7 abnormalities, ≥ 3 abnormalities</td>
<td>≥ 4 abnormalities</td>
</tr>
</tbody>
</table>
Acute GVHD

Bu1 17.0% vs. Bu2 8.5%
Bu2 HR 0.56 (0.22, 1.41)  
\( p = 0.22 \)
Chronic GVHD

Bu1 41.5% vs. Bu2 28.0%
Bu2 HR 0.70 (0.42, 1.17)
p = 0.09
Causes of NRM

Bu1

- Aplasia: 27%
- GVHD: 27%
- Secondary malignancy: 27%
- ID: 7%
- Other: 13%

Bu2

- VOD: 11%
- Pulmonary: 22%
- Secondary malignancy: 33%
- Other: 34%
Next Steps

- Will look at AML CR1 subset in this study
- Ongoing and future prospective randomized trials will further define the optimal intensity of conditioning
  - Mostly investigating MAC vs. RIC
- At MGH / DFCI, we currently have a phase II trial investigating Bu2 + clofarabine for RIC PBSCT
- It is unclear if different intensities of RIC will matter relative to the other interventions ongoing to prevent disease relapse
Study Methodology: Center and Patient Selection

1. Invitation to Centers
2. Center Participation
3. Pre TED Reporting
4. Eligibility Screening
5. Standard CIBMTR Data collection
6. Study Cohort
   - FormsNet CRF Track
7. Study Specific Data Collection
8. Forms Compliance Monitoring

December 2012: All Study Forms due at 2 years with >92% compliance
Writing Committee

- C. Bredeson
- J. Le-Rademacher
- X. Zhu
- J. Burkart
- K. Kato
- E. Armstrong
- Y. Sun
- A. Smith
- V.T. Ho
- P. McCarthy
- K. Cooke
- J.D. Rizzo
- M. Pasquini

On behalf of:
the Regimen-related Toxicity/Supportive Care Working Committee and the Center for International Blood and Marrow Transplantation Research

Sponsored by Otsuka Pharmaceutical Development and Commercialization, Inc.
<table>
<thead>
<tr>
<th>Complication</th>
<th>IV Bu 1025</th>
<th>TBI 458</th>
<th>P-value</th>
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<tbody>
<tr>
<td>VOD/SOS</td>
<td>5</td>
<td>1</td>
<td>&lt;0.01</td>
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<tr>
<td>IPN</td>
<td>4</td>
<td>6</td>
<td>0.05</td>
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<tr>
<td>Dialysis @ 1yr</td>
<td>6</td>
<td>7</td>
<td>0.24</td>
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<tr>
<td>Acute GVHD</td>
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<tr>
<td>Grade II-IV</td>
<td>46</td>
<td>51</td>
<td>0.17</td>
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<tr>
<td>Grade III-IV</td>
<td>18</td>
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<tr>
<td>Chronic GVHD @1y</td>
<td>50</td>
<td>48</td>
<td>0.45</td>
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<tr>
<td>Description</td>
<td>IV Bu (N=400)</td>
<td>TBI (N=207)</td>
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<tr>
<td>-------------------------------------</td>
<td>---------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
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<td>Primary disease</td>
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<td>Organ Failure</td>
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<tr>
<td>Infection</td>
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<td>Other</td>
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<tr>
<td>Thromboembolic/Hemorrhage</td>
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<td>Graft Failure</td>
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<tr>
<td>Second Malignancy</td>
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<td>1</td>
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</table>
Participating Centers

- University of Pennsylvania Medical Center
- Alberta Children's Hospital
- Alfred I. duPont Hospital for Children
- All Children's Hospital
- Ann & Robert H. Lurie Children's Hospital of Chicago
- Barnes Jewish Hospital
- Baylor College of Medicine Center for Cell and Gene Therapy
- Baylor University Medical Center
- British Columbia's Children's Hospital, UBC
- Cancer Centers of the Carolinas
- CancerCare Manitoba/University of Manitoba
- Centre Hospitalier Universitaire Sainte-Justine
- Children's Healthcare of Atlanta at Egleston
- Children's Hospital & Research Center Oakland
- Children's Hospital / LSUHSC
- Children's Hospital of Orange County
- Children's Hospital of Philadelphia
- Children's Hospital of Pittsburgh of UPMC
- Children's Hospital of Wisconsin
- Children's Medical Center Dallas
- Christiana Care
- Cincinnati Children's Hospital Medical Center
- City of Hope Samaritan
- Cleveland Clinic Foundation
- Colorado Blood Cancer Institute
- Dana Farber Cancer Institute - Adults
- Dartmouth Hitchcock Medical Center
- Duke University Medical Center
- Duke University Medical Center; Pediatric Blood and Marrow Transplant
- Emory University Hospital
- Florida Center for Cellular Therapy
- Fred Hutchinson Cancer Research Center
- Froedtert Memorial Lutheran Hospital
- Georgia Health Sciences University
- Greenebaum Cancer Center U of MD
- H. Lee Moffitt Cancer Center and Research Institute
- Hackensack University Medical Center
- Hawaii Medical Center
- HCA Health Services of Oklahoma, Inc., Univ of OK
- Henry Ford Hospital Bone Marrow Transplant Program
- Hospital Amoral Carvalho
- Hospital de Clinicas - UFPR
- Hospital Privado de Cordoba
- Hospital Rebagliati
- Indiana Blood & Marrow Transplantation (IBMT)
- Indiana University Hospital/Riley Hospital for Children
- INOVA Fairfax Hospital
- Instituto Nacional de Cancer
- Jewish Hospital & St. Louis Children's Hospital / Washington University
- LDS Hospital
- Lee's Children's Hospital
- Lila Linda University Cancer Center
- Lima University Medical Center
- Massachusetts General Hospital
- Mayo Clinic Arizona and Phoenix Children's Hospital
- Mayo Clinic Jacksonville/St. Luke's Hospital
- Mayo Clinic Rochester
- Medical City Dallas Hospital
- Medical University of South Carolina
- Memorial Sloan-Kettering Cancer Center - NY, NY
- Mount Sinai Medical Center
- Morgan Stanley Children's Hospital of NewYork-Presbyterian - Columbia University Medical Center
- Mount Sinai Medical Center
- Nemours/Wolfson Children's Hospital & Health System
- North Shore University Hospital
- Northwestern Memorial Hospital
- Ohio State Medical Center, James Cancer Center
- Oregon Health and Science University
- Pediatric Blood & Marrow Transplant Program, Doernbecher Children's Hospital, OHSU
- Penn State Hershey Medical Center
- Primary Children's Medical Center
- Princess Margaret Hospital
- Roger Williams Medical Center
- Roper Hospital
- Roswell Park Cancer Institute
- Rush-Presbyterian/St. Luke's Medical Center
- Scripps Blood & Marrow Transplant Program
- Shands HealthCare & University of Florida
- St. Jude Children's Research Hospital
- Stanford Hospital & Clinics
- Strong Memorial Hospital - Univ. of Rochester Med Ctr
- Texas Tech University Medical Center
- Texas Transplant Institute
- The BMT Program at Northside Hospital
- The Children's Mercy Hospitals and Clinics
- The Nebraska Medical Center
- The University of Michigan
- Tufts Medical Center
- Tulane University Medical Center
- UCLA Center for Health Sciences
- UMass Memorial Medical Center
- University Hospitals Case Medical Center
- University Medical Center (Tucson, AZ)
- University of Alabama at Birmingham
- University of California San Francisco Medical Center
- University of California San Francisco Medical Center (Peds)
- University of California, San Diego Medical Center
- University of California-Davis Medical Center
- University of Chicago Hospitals
- University of Colorado - Children's Hospital
- University of Colorado Hospital
- University of Illinois Medical Center at Chicago
- University of Iowa Hospitals & Clinics
- University of Kentucky Chandler Medical Center
- University of Louisville Hospital/James Brown Cancer Center
- University of Miami/Jackson Memorial Hospital
- University of Minnesota Medical Center, Fairview
- University of North Carolina Hospitals
- University of Pittsburgh Medical Center - Cancer Center
- University of Utah
- University of Wisconsin Hospital and Clinics
- UT Southwestern Medical Center - BMT Program
- Via Christi Hospitals Wichita, Inc.
- Virginia Commonwealth University Massey Cancer Center
- Bone Marrow Transplant Program
- Wake Forest Baptist Health
- Washington University/St. Louis Children's Hospital
- West Virginia University Hospitals, Inc.
- Yale New Haven Hospital