CONSIDERATIONS IN DESIGNING ACUTE GVHD PREVENTION TRIALS:
Patient Selection, Concomitant Treatments, Selecting and Assessing Endpoints
Potential conflicts/disclosures

Research support for BMT CTN trials:
  Roche, Easai, Ligand, Merck, Amgen, Supergen, Therakos, Pfizer

Research support for CIBMTR studies:
  Otsuka, Amgen, Fujisawa

Analysis of Fujisawa clinical trial data done in collaboration with industry investigators; all other analyses conducted with no knowledge or input form industry supporters
ISSUES IN DESIGNING GVHD PREVENTION TRIALS

- Heterogeneity of patients
- Heterogeneity of preparative regimens
- Heterogeneity in GVHD assessment and treatment philosophies
- Multiple competing risks
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SURVIVAL AFTER HEMATOPOIETIC STEM CELL TRANSPLANTS, 1998-2003

- HLA-identical sib (N = 14,473)
- Unrelated (N = 5,358)
- Autotransplant (N = 23,857)
<table>
<thead>
<tr>
<th>GOOD</th>
<th>INTERMEDIATE</th>
<th>POOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-identical sibling BMT: Early leukemia Aplastic anemia Hemoglobinopathies Immune deficiencies</td>
<td>HLA-identical sibling BMT: Acute leukemia CR2+ CML BP Children with ALL-rel MDS</td>
<td>HLA-identical sibling, URD, auto-transplants for advanced or chemotherapy-refractory disease</td>
</tr>
<tr>
<td>URD BMT: Same, in children / young adults</td>
<td>URD BMT: Adults with MDS / early leuk Aplastic anemia</td>
<td></td>
</tr>
</tbody>
</table>
## FACTORS CONSISTENTLY ASSOCIATED WITH HCT OUTCOME

<table>
<thead>
<tr>
<th>GENERAL</th>
<th>DISEASE-SPECIFIC</th>
<th>???</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor type: auto vs allo; related vs unrelated; HLA-matched vs mismatched</td>
<td>Leukemia: Duration of disease/remission; time to achieve first remission; prior consolidation (auto); cytogenetics; WBC at diagnosis</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Disease: malignant vs non-malignant; solid tumor vs hematologic cancer</td>
<td>Lymphoma: Histology; chemosensitivity; prior therapy</td>
<td>CLL</td>
</tr>
<tr>
<td>Disease stage: early vs intermediate vs late</td>
<td>Aplastic anemia: Duration of disease; prior transfusions</td>
<td>Some lymphomas</td>
</tr>
<tr>
<td>Age: children vs adolescents vs young adults vs older adults</td>
<td></td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Performance status: KPS &lt; 90 vs KPS ≥ 90</td>
<td></td>
<td>Rare diseases</td>
</tr>
<tr>
<td>CMV status: + vs -</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cumulative Incidence of Grades B-D Acute GVHD
HLA-identical Sib Transplants for Leukemia and MDS
Cumulative Incidence of Grades C-D Acute GVHD
HLA-identical Sib Transplants for Leukemia and MDS

Days after Transplant

CI, %

0 50 100 150 200 250 300

0 10 20 30 40 50 60 70 80 90 100

0-9 y
10-19 y
20-29 y
30-39 y
40-49 y
50-59 y
>60 y
Cumulative Incidence of Grades C-D Acute GVHD
Unrelated Donor Transplants for Leukemia and MDS
Cumulative Incidence of Grades B-D Acute GVHD
HLA-identical Sib Transplants for Leukemia, MDS, SAA

AML, ALL, CML, MDS (n=2279)
SAA (n=51)
Cumulative Incidence of Grades B-D Acute GVHD
Unrelated Donor Transplants for Leukemia, MDS, SAA

AML, ALL, CML, MDS (n=4764)
SAA (n=64)

Days after Transplant

CI, %
PROGNOSTIC FACTORS FOR AGVHD in 1,960 adults receiving HLA-identical sib transplants

<table>
<thead>
<tr>
<th>Factor</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 40y vs Younger (only for BM grafts)</td>
<td>1.43</td>
</tr>
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</tr>
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<td>1.54</td>
</tr>
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<td>1.35</td>
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<td>KPS &lt;90 vs 90-100</td>
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</tr>
<tr>
<td>CyTBI vs BuCy</td>
<td>1.40</td>
</tr>
<tr>
<td>D/R CMV -/- vs not</td>
<td>1.20</td>
</tr>
</tbody>
</table>
Does This Really Matter?

- Ratanatharathorn et al. (Blood, 1998): FK506+MTX vs. CSA+MTX in HLA-identical sibling BM transplants (n=329)
- Stratified on patient age (<40 vs. >=40) and donor/recipient sex match
Incidence of aGVHD grade II-IV


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Worse survival for FK-506 group despite lower aGVHD incidence


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Advanced Disease

CSA+MTX (n=48)

FK-506+MTX (n=68)

Early Disease

Ratanatharathorn, V. et al.
Blood 1998;92:2303-2314

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## FUJISAWA TRIAL OF GVHD PROPHYLAXIS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tacrolimus N=165</th>
<th>Cyclosporine N=164</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of malignancy</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Advanced</td>
<td>41%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>(not in CR, CLL, Myeloma)</td>
<td>59%</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>MDS</td>
<td>4%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>11%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>27%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td>31%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>8%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Hodgkin Disease</td>
<td>1%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Myeloma</td>
<td>9%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>CLL</td>
<td>4%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>5%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>

Ratanatharathorn V, Blood 1998
There is considerable heterogeneity in the Group labeled as “Advanced”

<table>
<thead>
<tr>
<th>100 day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute leukemia, CR1</td>
</tr>
<tr>
<td>Acute leukemia, Rel 1</td>
</tr>
<tr>
<td>Acute Leukemia, CR2</td>
</tr>
<tr>
<td>CML, CP1</td>
</tr>
<tr>
<td>CML, AP</td>
</tr>
<tr>
<td>MDS</td>
</tr>
<tr>
<td>MPS</td>
</tr>
<tr>
<td>NHL / HD, PIF</td>
</tr>
<tr>
<td>NHL / HD, CR1</td>
</tr>
<tr>
<td>NHL / HD, Rel 1</td>
</tr>
<tr>
<td>NHL / HD, CR2</td>
</tr>
<tr>
<td>NHL / HD, Rel 2</td>
</tr>
<tr>
<td>NHL / HD, Other</td>
</tr>
<tr>
<td>CLL</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
</tr>
</tbody>
</table>

Range:
- Early: 13-30
- Advanced: 22-40
Further investigation into whether imbalance in prognostic factors led to survival difference

- Comparison of matched IBMTR controls for advanced disease patients in above trial (n=116)
- Matched on diagnosis, pre-tx disease status, age (within 5 years)
- Controls received CSA+MTX

Horowitz et al, BBMT, 1999)
<table>
<thead>
<tr>
<th>Group</th>
<th>Probability</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FK-treated trial pts</td>
<td>28%</td>
<td>0.01</td>
</tr>
<tr>
<td>FK-matched controls (received CsA)</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>CsA-treated trial pts</td>
<td>58%</td>
<td>0.19</td>
</tr>
<tr>
<td>CsA-matched controls (received CsA)</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>FK-matched controls (received CsA)</td>
<td>50%</td>
<td>&lt;0.67</td>
</tr>
<tr>
<td>CsA-matched controls (received CsA)</td>
<td>45%</td>
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# Two-Year Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Probability</th>
<th>P-value</th>
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<tbody>
<tr>
<td>FK-treated trial pts</td>
<td>27%</td>
<td>0.51</td>
</tr>
<tr>
<td>FK-matched controls (received CsA)</td>
<td>24%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CsA-treated trial pts</td>
<td>42%</td>
<td>0.66</td>
</tr>
<tr>
<td>CsA-matched controls (received CsA)</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>FK-matched controls (received CsA)</td>
<td>24%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CsA-matched controls (received CsA)</td>
<td>45%</td>
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ISSUES IN DESIGNING GVHD PREVENTION TRIALS

- Heterogeneity of patients
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- Heterogeneity in GVHD assessment and treatment philosophies
- Multiple competing risks
Why Does Conditioning Regimen Matter?

- Affects GVHD risk and timing (myeloablative vs reduced intensity vs minimal intensity)
- Affects risk of other competing events (early morbidity and mortality)
- Variable interaction with treatments to be tested
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BMT CTN 0402: FK+MTX vs FK+Sirolimus for GVHD Prophylaxis after HLA-id sib PBSCT

- Endpoint – GVHD-free survival
- Monitoring rules: mucositis and VOD
  - Stopped for excessive VOD
  - Risk found to be predominantly in patients receiving BuCy conditioning
  - Re-opened with restriction to TBI-based conditioning
Why Does Conditioning Regimen Matter?

- Affects GVHD risk and timing (myeloablative vs reduced intensity vs minimal intensity)
- Affects risk of other events (early morbidity and mortality)
- Variable interaction with treatments to be tested
- BUT............
  - Results of GVHD prophylaxis tested with a particular regimen are often extrapolated to other regimens without further evaluation
ISSUES IN DESIGNING GVHD PREVENTION TRIALS

- Heterogeneity of patients
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- Heterogeneity in GVHD assessment and treatment philosophies
- Multiple competing risks
Interobserver Variability

- Stratification on center helpful to address institutional differences in approach – but not individual differences

- Blinding
  - Desirable
  - Expensive
  - Difficult (impossible?) when drug levels must be monitored or when therapies affect levels of other drugs

- Independent observers
  - Expensive
  - Logistically difficult

- Collection of primary data – allows computation of grade by predetermined algorithm, external review
Treatment before reaching primary endpoint

- BMT CTN 0302: Treatment for Grades B-D AGVHD
  - Required enrollment within 24 hours of starting corticosteroids
  - MANY patients ineligible because of corticosteroid therapy for Grade A AGVHD, including stage 1 skin only
    - What we *do* is different from what we *say* we do
- Prevention trials that have Grade B-D or IV-IV AGVHD as an endpoint may be compromised by treatments initiated for lesser degrees of GVHD
  - 0402: Primary endpoint includes Grade II-IV AGVHD or treatment for Grade I GVHD
  - Stratification by center
ISSUES IN DESIGNING GVHD PREVENTION TRIALS

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TIMELINE OF TRANSPLANT

Complications:
- Secondary tumors
- Acute and/or chronic GvHD
- Viral infections (CMV, VZV, PCP)
- Bacterial (IP)
- Infections (VOD)
- Mucositis

Blood & Marrow Changes:
- PBSC/BM harvests in ABMT
  - Collect & freeze gcsf
  - eg: DHAP and GF and PBSC

Supportive Therapy:
- Antibiotics
- Nutrition
- Antiemetic factors
- Growth factors

BMT Process:
- Donor search or obtain autologous stem cells
- Chemo
- XRT

Donor search or obtain autologous stem cells
Red cell transfusions
Platelet transfusions

Time Line:
- Primary diagnosis and treatment
- Relapse and salvage therapy
- Marrow failure
- Disease remission
- Disease recurrence
- Continuous complete remission (cure)

Disease State:
- High-dose myeloablative therapy
- Continuous complete remission (cure)
HOW DO COMPETING RISKS AFFECT ABILITY TO DO CLINICAL TRIALS IN HCT?

- Complicates the primary endpoint
  - How do you treat patients who die before they have a chance to get the primary endpoint?
  - May make final result unclear
- Impairs ability to attribute toxicities to intervention
  - May lead to reporting many adverse events
- May be increased by intervention even if GVHD is decreased leading to overall adverse result
Impact of Competing Risks of Choice of Endpoint

- Acute GVHD – may be decreased at the cost of increasing other toxicities
  - Need to ensure that the therapy does "no harm", i.e., unacceptable increases in adverse events, infections, non-relapse mortality, recurrent malignancy
- Survival – impacted by many things other than GVHD – unlikely to be able to show a benefit
Simulation Study using Multistate Models: What if AGVHD was decreased with NO impact on the rate of relapse or other causes of TRM?
1459 patients with acute leukemia in CR1

<table>
<thead>
<tr>
<th></th>
<th>Relapse</th>
<th>TRM</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real</td>
<td>17%</td>
<td>20%</td>
<td>65%</td>
</tr>
<tr>
<td>No AGVHD</td>
<td>18%</td>
<td>11%</td>
<td>72%</td>
</tr>
<tr>
<td>50% ↓ in AGVHD</td>
<td>17%</td>
<td>16%</td>
<td>69%</td>
</tr>
</tbody>
</table>
Primary Objective
To compare the rates of 114-day Grades II-IV acute GVHD-free survival between study arms

Rationale: Considers potential effects on both acute GVHD and TRM in primary endpoint

- 80% power to detect an increase in GVHD-free survival 114 days from randomization from 60 → 75%
- Sample size n = 312 patients
Summary

- Transplant outcomes are influenced by many patient, disease and treatment factors – these must be considered for their potential confounding of evaluation of GVHD regimens
- There is considerable variability in GVHD assessment and treatment approaches – blinding, stratification on center are important
- GVHD is an important barrier to successful BMT outcome but not the only one
  - Improved survival requires better therapies to prevent GVHD AND to prevent and treat other transplant-related complications and disease recurrence
  - A good GVHD prevention strategy must decrease GVHD without excessively increasing other causes of morbidity and mortality BUT cannot be expected to substantially improve survival by itself