Issues For Design of Acute GVHD Treatment Trials

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Basis for NDA/BLA Approval

• Demonstration of efficacy with acceptable safety in adequate and well-controlled studies (21 CFR 314.126)
• Ability to generate product labeling that
  – Defines an appropriate patient population for treatment with the drug
  – Provides adequate information to enable safe and effective use of the drug
Demographic Factors Potentially Predictive for Response

- Patient age (Adult vs Pediatric)
- Degree of histoincompatibility (MRD vs MUD vs Haplo)
- Source of cells (BM vs PBSC vs UCBT vs PB)
- Preparative regimen (ablative vs NMA)
- GVHD Prophylaxis (TCD vs CNI/MTX vs CNI/MMF)
- Grade of GVHD
- Prior Treatment
  - Newly diagnosed
  - Steroid-refractory
  - Treatment-refractory
Who is Steroid-Refractory?

Table 2  Definition of steroid-refractory acute graft-versus-host disease

<table>
<thead>
<tr>
<th>Definition</th>
<th>All centers</th>
<th>Adult</th>
<th>Combined</th>
<th>Pediatric</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not resolved</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26</td>
<td>9</td>
<td>12</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Days of treatment&lt;sup&gt;b&lt;/sup&gt; (days)</td>
<td>5.5 (3–14)</td>
<td>6 (3–14)</td>
<td>5 (3–14)</td>
<td>10 (3–14)</td>
<td>0.72</td>
</tr>
<tr>
<td>Daily steroid dose&lt;sup&gt;b&lt;/sup&gt; (mg/kg)</td>
<td>2 (1–15)</td>
<td>2 (2)</td>
<td>2 (1–15)</td>
<td>5 (2–14)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Not improved</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>45</td>
<td>25</td>
<td>16</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Days of treatment (days)</td>
<td>5 (2–14)</td>
<td>5 (3–14)</td>
<td>6 (2–14)</td>
<td>4 (2–14)</td>
<td>0.66</td>
</tr>
<tr>
<td>Daily steroid dose (mg/kg)</td>
<td>2 (1–20)</td>
<td>2 (1–10)</td>
<td>2 (1–10)</td>
<td>12.5 (2–20)</td>
<td>0.051</td>
</tr>
<tr>
<td><strong>Progressed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>63</td>
<td>29</td>
<td>22</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Days of treatment (days)</td>
<td>3 (1–14)</td>
<td>3 (2–7)</td>
<td>3 (1–14)</td>
<td>3 (2–7)</td>
<td>0.98</td>
</tr>
<tr>
<td>Daily steroid dose (mg/kg)</td>
<td>2 (1–24)</td>
<td>2 (1–15)</td>
<td>2 (1–24)</td>
<td>5 (2–20)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Overall threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Number</td>
<td>83</td>
<td>37</td>
<td>31</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Daily steroid dose (mg/kg)</td>
<td>2 (1–24)</td>
<td>2 (1–15)</td>
<td>2 (1–24)</td>
<td>5 (2–20)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<sup>a</sup>Number of centers responding. Some centers included more than one category in their definition.

<sup>b</sup>Median (range).

(Hsu et al, 2001)

Van Lint et al, 1998: Progression or “no response” after MP 2 mg/kg x 5 days as assessed by day-180 TRM (16% vs 46%, p=0.007)
Phase I Study Endpoints

• The drug or biologic may limit the choice of endpoint
• Endpoint can be toxicity
  – Maximal tolerated dose
  – Target level of toxicity (See Dr. Thall’s talk)
  – Dose limiting toxicities of interest vary with the investigational therapy, the expected level of toxicity of standard therapy, and the patient population
    ♦ Acute regimen-related toxicity ♦ Acute GVHD
    ♦ Infusion/administration events ♦ Chronic GVHD
    ♦ Graft failure ♦ Other CTCAE toxicities
    ♦ Infections
Phase I Study Endpoints

• The drug or biologic may limit the choice of endpoint
• Endpoint can be toxicity
  – Maximal tolerated dose
  – Target level of toxicity
• Endpoint can be activity
  – Optimal biological dose
  – Pharmacokinetically-guided dose
Efficacy Requirements

• Regular approval
  – Clinical benefit or established surrogate
• Accelerated Approval (21 CFR 314 Subpart H and 21 CFR 601 Subpart E)
  – Uses a surrogate endpoint reasonably likely to predict clinical benefit
  – Requires subsequent confirmation of benefit
• Clinical Benefit
  – Quantity of life
  – Quality of life
Published Endpoints for Acute GVHD Treatment Trials

- PubMed search for Acute GVHD, Treatment
- Nine randomized trials identified
- Primary endpoints:
  - Overall survival at Day 180
  - Response (PR+CR) but not defined
  - Response (PR+CR) (PR is dec in ≥ 1 grade, CR not defined)
  - Response (Dec in ≥ 1 grade on day 42)
  - Response (Dec in ≥ 1 stage on day 42) (2)
  - Response (Dec in ≥ 1 stage on day 14)
  - Alive in CR at 6 weeks
  - Response scores according to the following scale: 0 = worse, 1 = no change, 2 = improved, and 3 = resolved
Quality of Life

• Multidimensional measure of how patient feels and functions

• Advantages
  – Recognized clinical benefit in symptomatic pts

• Disadvantages
  – Difficult to define (what is important to all?)
  – Difficult to measure (validate the scale)
  – Difficult to analyze (attrition is not random)
  – Difficult to interpret (what size effect?)
  – Difficult to maintain scientific integrity
    (who completes the forms, toxic drug, heterogeneity)
Patient-Reported Outcomes

• Multidimensional measure of symptoms specific to the disease (EPIC – bladder function, bowel function, sexual function, hormonal symptoms)

• Advantages
  – Records only signs and symptoms
  – Completed by patient
  – Useful when survival change not expected

• Disadvantages
  – All the disadvantages as with QOL
  – Needs symptomatic patients at baseline

• Is this applicable to acute GVHD treatment?
Issues Regarding GVHD Treatment Trials

- What are the sources of heterogeneity in the transplant population that impact the responsiveness of acute GVHD and how do we manage these?
- Are the response criteria for acute GVHD treatments suitably established?
- What endpoints denote clinical benefit?
- What endpoints are reasonably likely to predict clinical benefit?
- How do we assess clinical benefit endpoints statistically in the face of competing risks?
Speakers for Afternoon Session

**GVHD Treatment Trial Design and Endpoints**
Amin Alousi, MD, U T MD Anderson Cancer Center, Houston, TX
Dan Weisdorf, MD, University of Minnesota, Minneapolis, MN
Paul Carpenter, MD, Fred Hutchinson Cancer Research Center

**Patient-Reported Outcomes**
Stephanie Lee, MD, MPH, Fred Hutchinson Cancer Research Center