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

Definition	*All centers*	*Adult*	*Combined*	*Pediatric*	*P*
Not resolved					
Number[a]	26	9	12	5	
Days of treatment[b] (days)	5.5 (3–14)	6 (3–14)	5 (3–14)	10 (3–14)	0.72
Daily steroid dose[b] (mg/kg)	2 (1–15)	2 (2)	2 (1–15)	5 (2–14)	0.09
Not improved					
Number	45	25	16	4	
Days of treatment (days)	5 (2–14)	5 (3–14)	6 (2–14)	4 (2–14)	0.66
Daily steroid dose (mg/kg)	2 (1–20)	2 (1–10)	2 (1–10)	12.5 (2–20)	0.051
Progressed					
Number	63	29	22	12	
Days of treatment (days)	3 (1–14)	3 (2–7)	3 (1–14)	3 (2–7)	0.98
Daily steroid dose (mg/kg)	2 (1–24)	2 (1–15)	2 (1–24)	5 (2–20)	0.01
Overall threshold					
Number	83	37	31	15	
Daily steroid dose (mg/kg)	2 (1–24)	2 (1–15)	2 (1–24)	5 (2–20)	0.003

[a]Number of centers responding. Some centers included more than one category in their definition.
[b]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
    - ♦ Infusion/administration events
    - ♦ Graft failure
    - ♦ Infections
    - ♦ Acute GVHD
    - ♦ Chronic GVHD
    - ♦ Other CTCAE toxicities

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