Patient-Reported Outcomes (PROs) for GVHD prevention and treatment trials

Stephanie J. Lee, MD MPH
Fred Hutchinson Cancer Research Center
May 19, 2009
Financial Conflicts of Interest

• None
Patient-reported outcomes

• Quality of life, functional status, symptom burden
• Surveys, interviews or patient diaries
• Measure what people actually experience with a treatment approach
  – disease control
  – symptom improvement
  – side effects
Pros of PROs

• Data are complementary to physical exam findings and laboratory testing
• Primary source for much of clinician-reported symptom information in the chart
  – Best assessment of nausea, pain, anorexia
  – Only assessment of fatigue, impact of illness
• Provides the patient’s perspective of treatment benefit
Questions

• What are the requirements for PROs to be primary or supportive endpoints?
• What challenges will be encountered, especially for acute GVHD trials?
• In what circumstances can short-term PROs or QOL (rather than response or survival) be an endpoint for a GVHD prevention or treatment trial?
• Are there any validated PRO or QOL tools that can be used for acute GVHD trials, and what data support their validation?
FDA requirements

• “Clinical benefit” = Living longer or living better
• The amount and kind of PRO evidence to support a labeling claim is the same as that required for any other labeling claim
• “Intermediate” endpoints (e.g., symptoms) are not recognized for general claims (e.g., improved quality of life or activities of daily living) – need to show actual effects on the claim

FDA recommendations

• Capture current status and actual functioning
  – Not recall over a period of time
  – Not what a patient thinks they can do
• PROs suspect in unblinded studies
• Collect reasons for missing data
FDA “certification” of PRO tools

• Need a validated instrument in the study population to support the intended claim
  – A validated instrument that is modified in any way is considered a different instrument
  – If the study population is different, may need to repeat the validation – age, gender, race

• FDA will review instrument development and validation procedures
FDA instrument review

• Instrument creation
  – Patient interviews and focus group transcripts
  – Cognitive debriefing procedures, readability

• Validation
  – Questions and response options, recall period
  – Psychometrics: reliability, validity, sensitivity to change, clinically meaningful differences

• Study procedures
  – Mechanisms to ensure accurate data capture
  – Instrument formatting, method of data collection
Psychometric requirements

• Reliable – accurate measurement tool
• Valid – reflects endpoint of interest
• Sensitive to change – nimble enough to reflect differences achieved by treatment
• Clinically meaningful differences – recognized benefit by patient and clinician
Questions

• What are the requirements for PROs to be primary or supportive endpoints?
• What challenges will be encountered, especially for acute GVHD trials?
• In what circumstances can short-term PROs or QOL (rather than response or survival) be an endpoint for a GVHD prevention or treatment trial?
• Are there any validated PRO or QOL tools that can be used for acute GVHD trials, and what data supports their validation?
General challenges

• Difficult to collect PROs
  – Not available retrospectively or from other sources
  – Requires active patient cooperation – difficult if pts ill
  – Different versions for pediatrics, non-English speaking
  – Not a routine test you can just order

• Difficult to analyze and interpret PROs
  – Longitudinal statistical methods
  – Missing data are a big problem
  – Subjective not objective – open to bias
Acute GVHD & PROs

• Some GVHD is not symptomatic – liver
• Many symptoms and signs overlap with other common HCT toxicities
  – “noise” in PROs – conditioning regimen, drugs, infections, other complications
• Patients often quite ill - more work has been done with PROs in chronic GVHD because patients are more stable
Questions

• What are the requirements for PROs to be primary or supportive endpoints?
• What challenges will be encountered, especially for acute GVHD trials?
• In what circumstances can short-term PROs or QOL (rather than response or survival) be an endpoint for a GVHD prevention or treatment trial?
• Are there any validated PRO or QOL tools that can be used for acute GVHD trials, and what data supports their validation?
Clinical benefit

• Clear that patients with mod-severe acute GVHD, especially GI GVHD, are miserable
• PROs are unlikely endpoints for prevention trials – agents not that effective, change in rates too small, background noise too great
• Treatment trials - Prolonged disease-free survival is paramount
  – Similar survival, GVHD control plus:
  – Decreased symptoms (diarrhea, pain)
  – Decreased hospitalization days
  – Less side effects from treatment
MID

• Minimum Important Difference
• “The smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management”
• WIWI

Juniper EF et al, J Clin Epidemiol 1994; 47: 81-87
Sloan J, JCO 2002; 20: 4-6
Use of PROs to judge response

- If acute GVHD improves, by whatever gold standard is used for objective measurement, then patient-reported measures should improve too, unless
  - acute GVHD is not affecting how patients feel
  - the treatment toxicity outweighs the benefits of controlling acute GVHD
  - we’re asking patients the wrong questions
  - we think they are better, but they are not

- What factors best predict survival in patients with acute GVHD? Objective measures or PROs?
Gemcitabine and pancreatic cancer

- 1° endpoint: “Clinical benefit response”
  - pain "index" which includes pain intensity scoring and analgesic consumption
  - Karnofsky performance status
  - one secondary measure: weight change
- Clinical benefit: 24% vs. 5% (p=0.002)
- Survival also better
  - Longer median survival (30%, 1.3 mo, p=0.003)
  - 1 year survival: 18% vs. 2%

Burris HA et al, JCO 1997; 15: 2403-13
Questions

• What are the requirements for PROs to be primary or supportive endpoints?
• What challenges will be encountered, especially for acute GVHD trials?
• In what circumstances can short-term PRO or QOL (rather than response or survival) be an endpoint for a GVHD prevention or treatment trial?
• Are there any validated PRO or QOL tools that can be used for acute GVHD trials, and what data support their validation?
Instruments

• MOS SF-36
  – Medical Outcome Study, Short Form – 36
  – 36 items, 6 minutes
  – 8 subscales, 2 summary scores
• FACT-BMT
  – Functional Assessment of Cancer Therapy
  – BMT module
  – 37 items, 6 minutes
  – 4+1 subscales, 1 summary score
• MDASI
  – MD Anderson Symptom Inventory
  – 13 symptom items, 6 interference, 5 minutes
  – 2 summary scores (symptom severity and interference)
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

- **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports ................................................................. □ 1 .............. □ 2 ................... □ 3

- **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf ................................................................. □ 1 .............. □ 2 ................... □ 3

- Lifting or carrying groceries ................................................................. □ 1 .............. □ 2 ................... □ 3

- Climbing **several** flights of stairs ................................................................. □ 1 .............. □ 2 ................... □ 3

- Climbing **one** flight of stairs ................................................................. □ 1 .............. □ 2 ................... □ 3

- Bending, kneeling, or stooping ................................................................. □ 1 .............. □ 2 ................... □ 3
<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

<table>
<thead>
<tr>
<th>Item</th>
<th>Not Present</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Your pain at its WORST?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Your fatigue (tiredness) at its WORST?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Your nausea at its WORST?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Your disturbed sleep at its WORST?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Your feelings of being distressed (upset) at its WORST?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cleeland CS et al, Cancer 2000; 89: 1634-40
NHLBI T Cell Depletion (TCD) trial

- N=410, ex vivo TCD vs. csa/mtx, 1995-2000
- PROs collected
  - baseline, d100, 6 mos, 1 yr, 3 yr
  - FACT-BMT, SF-36, CES-D
- Similar trajectory for both groups, although 2x more acute grade III-IV GVHD in non-TCD (37% vs. 18%, p<0.0001)

Altmaier EM et al, BBMT 2006; 12: 648-655
FACT-BMT

No difference between arms in RCT

III-IV acute GVHD (n=105)
73 non TCD
32 TCD

0-II acute GVHD (n=291)
124 non TCD
167 TCD
Dana-Farber analysis

- N=96, 1999-2004
- PROs collected
  - Baseline, 6 mos, 12 mos
  - SF12, FACT-BMT
- Grade II-IV acute GVHD associated with worse QOL at 6 months
- Chronic GVHD associated with worse QOL at 12 mos

Lee SJ et al, 2006, BMT 38: 305-310
Acute and chronic GVHD

No acute or chronic GVHD (NN) —
No acute, Yes chronic GVHD (NY) ...
Both acute and chronic GVHD (YY)

p=0.01 NY vs YY
p=0.006 NN vs YY

Trial Outcome Index (TOI) score

month after HSCT

0 6 12
MD Anderson analysis

- N=125
- Symptom assessments
  - Baseline, 6-20 follow-ups
  - MDASI
- Grade I-IV acute GVHD associated with greater symptom burden days 22-100 than no acute GVHD

Williams L et al, 2009, BBMT 15: abs #49
Graft source or GVHD prevention studies

- CTN 0201 RCT, G-PB vs. BM in URD (n=550)
  - FACT-G-BMT, SF36 baseline, 6 mo, 12 mo

- CTN 0402 RCT, Rapa/Tac vs. Mtx/Tac (n=312)
  - No PRO
Acute GVHD Treatment studies

- **MSC RCT, placebo-controlled**
  - steroid-refractory treatment (n=280, closed)
    - FACT-G-BMT treatment day 0, 30, 100, 180
    - “additional efficacy endpoint”
  - initial treatment (n=184, closed) – no PRO

- **CTN, initial treatment**
  - 0302 Randomized, phase II – no PRO
  - 0802 RCT, pred vs. pred/MMF (n=372, not open yet) – no PRO, discussion about adding MDASI

- **BDP RCT, placebo-controlled**
  - Initial treatment of GI GVHD (n=166, not open yet)
  - MDASI collected weekly to day 80
  - “Additional endpoint”
Steph’s Recommendations

• Very narrow PRO goals if FDA approval sought
  – Focus on symptoms
  – Avoid composite endpoints or broad domains
• Have a validated instrument in hand before Phase II
• Do a test run in the Phase II study
Conclusions

• Treatments that improve patients’ experiences with acute GVHD, either through prevention or successful treatment, should be considered for FDA approval.

• There are daunting methodologic barriers to proving, by FDA standards, that a treatment improves symptoms or QOL related to acute GVHD.