Relevant Endpoints in Supportive Care Trials

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What is a “Relevant” Endpoint?

• Relevance must relate to the goals of the trial
• Most trials are intended to alter how future patients are treated, i.e., they are “pragmatic,” and intend to be “practice changing.”
• Thus, a relevant endpoint is one that will form a valid basis for future decisions
  – Decision-makers are both care providers and patients, so endpoints must be relevant to both
What is Special About Supportive Care Trials?

• The goal of these trials is by definition to relieve symptoms or to prevent a complication that could lead to morbidity

• This talk will focus on the former type of trials, i.e., symptom control trials
  – Will not consider febrile neutropenia studies, studies with growth factors, etc.
What is Special About Symptom Control Trials?

• Relevant endpoints are by definition symptoms

• The requirement that endpoints form a valid basis for future decisions means, therefore:
  – There must be a way of collecting information on symptoms that meets standard criteria of reliability and validity
What is Special About Symptom Control Trials?

– The method of collection must also “work” in the context of a clinical trial
  • This will be the focus of the remainder of the presentation; namely, our (NCIC CTG’s) experience in collecting data on symptoms in supportive care clinical trials
Symptom Assessment in NCIC CTG Trials

• Vast amount of data from QOL questionnaires that have individual questions on symptoms and/or have modules or checklists eliciting symptom data
  – Largely untapped though publications on:
    • Specific symptoms - fatigue
    • Relationship between toxicity assessment and QOL symptoms
Fatigue in patients with cancer: results with National Cancer Institute of Canada Clinical Trials Group studies employing the EORTC QLQ-C30

Palliative Effect of Chemotherapy: Objective Tumor Response Is Associated With Symptom Improvement in Patients With Metastatic Breast Cancer

By Paul Geels, Elizabeth Eisenhauer, Andrea Bezjak, Benny Zee, and Andrew Day

Symptom Assessment in NCIC CTG Trials

• Trials that have focused on symptoms as the study endpoint
  – Nausea and vomiting (many studies)
  – Pain
  – Multiple symptoms

• Will briefly discuss major lessons learned from studies in each of these areas
Assessment of Nausea and Vomiting

• When we first began studying emesis, “objective” measures were still employed.
• Patient diaries soon replaced observation of emetic episodes.
• Two key observations:
  – Validity of patient reported outcomes
  – Utility of simple questions
Assessment of Nausea and Vomiting

• Validity
  – Correlation of diary reports with patient preference in double blind crossover trials

• Utility of single question assessment
  – QOL questions more sensitive (in terms of p values) than diaries to differences between regimens
Effect of Cancer on Quality of Life

FIGURE 1. Distribution of treatment differences by preference with respect to nausea.
Assessment of Nausea and Vomiting

• Validity
  – Correlation of diary reports with patient preference in double blind crossover trials

• Utility of single question assessment
  – QOL questions more sensitive (in terms of p values) than diaries to differences between regimens
Effects of altering the time of administration and the time frame of quality of life assessments in clinical trials: an example using the EORTC QLQ-C30 in a large anti-emetic trial


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Table 4. Impact of varying time and recall period of assessment on differences in global quality of life between patients who did and did not receive dexamethasone in addition to 5-HT3 antagonists.

<table>
<thead>
<tr>
<th>Period assessed</th>
<th>Difference in change in global quality of life from baseline*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1–3</td>
<td>13</td>
<td>0.005</td>
</tr>
<tr>
<td>Days 4–7</td>
<td>9</td>
<td>0.013</td>
</tr>
<tr>
<td>Days 1–7</td>
<td>7</td>
<td>0.163</td>
</tr>
</tbody>
</table>

*The larger the number the greater the difference, on a scale of 100, in favor of the dexamethasone group.

Difference in day 1-3 diary nausea = 10; p = 0.003
Difference in day 1-3 QOL nausea = 17; p = 0.001
Assessment of Pain

• Reliable and valid instruments for collecting data on pain clearly exist, and they “work” in the context of multicentre clinical trials
  – As in the case of nausea and vomiting, simple QOL questions perform very well in comparison to more intensive data collection through diaries
Assessment of Pain

• However, collecting reliable data on medications can be problematic in large scale multicentre trials
  – Patients are ambulatory, so self-reporting in diaries is necessary
    • Patients don’t always know the names of their drugs
      – A particular problem in multinational trials
    • It is difficult to construct a diary method for reliably collecting patient-initiated variations in dose and schedule
Assessment of Pain

• Collecting accurate data on analgesic use is, however, critical to using pain relief as an outcome measure since in most circumstances this is really a composite outcome, i.e.,
  – Less pain with the same dose of analgesics
  – The same pain with a lower analgesic dose
Assessment of Pain

• Accurate data on analgesic use can also be required for eligibility assessment
  – “Stable pain for the past week” means no change in analgesic dose
Multiple Symptoms

• In some settings, several symptoms may be the target of a single intervention, for example, palliative chest irradiation
  – Dyspnea, cough, hemoptysis, pain, etc.

• Determining in these circumstances which of two interventions is superior requires the investigators to generate a single outcome measure from these symptoms
Multiple Symptoms

• There are several possible approaches to doing this:
  – Ask the patient or physician to name a single target symptom
    • The most severe
    • The most likely to be affected by the intervention
Multiple Symptoms

- Evaluate changes in all symptoms, but create an overall outcome by:
  - Summing them
  - Creating a weighted average
  - Defining “responses” in terms of whether one or more symptoms were relieved by a certain amount

- Etc

- No one approach is necessarily the best, but something must be defined before the analysis begins
RANDOMIZED PHASE III TRIAL OF SINGLE VERSUS FRACTIONATED THORACIC RADIATION IN THE PALLIATION OF PATIENTS WITH LUNG CANCER (NCIC CTG SC.15)

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Apparent Extent of Palliation

Percent Palliated

- Index Improved
- Pain Improved
- Grade 2-3 Pain
- QOL Physical
- 50% of Symptoms
- All symptoms

Bar chart showing the apparent extent of palliation for different categories.
Conclusions

• By definition, conducting symptom control clinical trials requires accurate measurement of relevant symptoms
• Eliciting information on symptoms through self report can be very effective
• However, getting the right information to be able to assess the right, i.e., the truly relevant, outcome is not always easy