THE SECRETS OF OUR SUCCESS
QUALITY OF LIFE STUDIES OF THE NCIC CLINICAL TRIALS GROUP
Andrea Bezjak, MDCM, MSc, FRCPC
Chair, NCIC CTG QOL Committee

Outline of the Presentation
• Can we consider NCIC CTG QOL activities a success?
• What has NCIC CTG done to ensure success in QOL assessment?

Take-Home Messages
• QOL is a meaningful and measurable outcome in clinical trials
• QOL data have been “value added”
• NCIC CTG has established a benchmark of excellence in QOL in clinical trials

What the talk is not about
• Convincing “non-believers” that QOL is worthwhile measuring in clinical trials

NCIC CTG QOL committee - History and Structure
• QOL committee formed in 1987
• Founding chair David Osoba
• First QOL assessment in a trial in 1988
• Structure of committee:
  - 16 committee members – diverse expertise, background, professional and geographic representation

National Cancer Institute of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe des essais cliniques
• A research organization funded by NCIC
• Mission = to develop and conduct clinical trials aimed at improving the treatment and prevention of cancer
• IND and Phase III program
• Central office + investigators across Canada
**Function of the QOL committee**

Site liaisons:
- QOL committee representatives to a disease site group
- Role = consultation and advice regarding QOL
- QOL coordinator for each trial:
  - Formulating the design of the QOL aspect of the study
  - Objectives of QOL measurement/hypotheses
  - Choice of instrument
  - Timing of administration
  - Analysis
  - Publication

**QOL in NCIC CTG Trials**

- QOL has been an endpoint in:
  - 51 completed trials
  - 20 current trials
- Only 2 phase III trials originating in CTG did not have QOL as an endpoint (MA.12, SC.17)
- QOL questionnaires used:
  - Primarily EORTC QLQ-C30
  - Also a variety of other QOL questionnaires as appropriate for the research question

**Evidence for Success of NCIC CTG QOL activities**

- Site Reviews
- Peer-reviewed grants
- Publications
- New knowledge related to QOL
- Studies that have influenced practice
- International Reputation

**NCIC CTG Site Reviews**

- 5 yearly reviews for grant renewal
  - Fall 1998, Winter 2004
  - Also NCI US 5 yearly reviews (last in 2003)
- QOL committee rated as excellent to outstanding at each of the reviews

**Peer-Reviewed Grants**

- 3 sequential NCIC/CIHR grants for a series of projects to examine:
  - The way patients want QOL information presented
  - Whether QOL information would change the treatment decision to have adjuvant treatment
  - How do pts perceive QOL vs toxicity information
  
  Brundage et al. OLR 2003, VI2, pp 395-404
NCIC CTG QOL publications

- 30+ QOL publications since 1991
- 50+ manuscripts
- Methodological and clinical publications
- Bezjak et al - QOL in ovarian cancer patients (OV.10) JCO 2004 Nov 15; 22(22): 4595 - 4603
- Duncan et al - QOL, mucositis and xerostomia from RT for head and neck cancers (HN.2) Head Neck 2005 In Press

New knowledge related to QOL

- What does a change in QOL scores mean?
- When should we ask about QOL?
- Do QOL data give different information than toxicity data?
- Does tumor response correlate w QOL response?
- How to analyze and interpret data?

What does a change in QOL scores mean?

Subjective Significance Questionnaire

- Five questions added to end of EORTC QLQ C30
  - "Since the last time you completed this questionnaire, has there been a change in your physical condition"
  
    Very much worse – moderately—a little worse—no change— a little better—moderately better—very much better

  - Emotional state
  - Ability to enjoy social life
  - Physical comfort
  - Overall quality of life

Results :

- Moderate correlation with differences in QOL domain scores (Spearman 0.38-0.5)
- Clear relationship between magnitude of SSQ differences and magnitude of QOL changes
  - "No change" = mean change of QOL score <5
  - "A little change" = mean change score 5-10
  - "Moderate change" = 10-20
  - "Very much change" = >20

Osoba et al JCO 1998, Vol 16, pp 139-144

When should we ask about QOL?

SC.11 study of Chemo-related Nausea/Vomiting

Question = Does timeframe (3 vs 7 days) and day of administration (day 4 vs day 8) affect pt reports of QOL?

Methods = randomized pts to 2 different wordings of questionnaire and 2 different days of administration

- How much did you have
  - Day 4 post chemo
  - Day 8 post chemo

- Last 3 days......last 7 days

SC.11 QOL Results

- Change in Global QOL from baseline last 3 days last 7 days
  - Day 4 post chemo -8.4 -5.6
  - Day 8 post chemo -1.2 -10.3 p=.001

- Both timeframe and day of administration affected reported QOL
- Strongest effects occurred when questionnaire administered at time of maximal symptoms

Do QOL data give different information than toxicity data?

- Butler et al - Determining the relationship between toxicity and quality of life in an ovarian cancer chemotherapy clinical trial. JCO 2004; 22(12):2461-8


Does tumor response correlate with QOL response?

- MA.8 = Doxo vs NLB+Doxo in metastatic breast ca
- Conventional QOL analysis:
  - Baseline QOL predictive of survival
  - QOL improved over time, for pts who remain on chemo
- Added value of QOL data:
  - Symptom response correlated to tumor response
  - PR = greatest improvement of baseline symptoms
  - Stable disease = improvement of baseline symptoms
  - Progression = no improvement


How to analyze and interpret data?

- Have a primary QOL research question
- Report the proportion of pts who have improved, remained stable or worsened
- Avoid complex statistical modelling

- Osoba et al EurJCa 2005, 41, pp280-287

NCIC CTG BR.14/GemVin study

- Stage IV NSCLC
- Platinum based chemotherapy vs Gemcitabine + Vinorelbine
- Primary endpoint = global QOL
- Joint study of the National Cancer Institute, Naples and NCIC CTG

- Gridelli et al JCO 2003 21(16): 3025-34

QOL change scores at end of cycle 2
QOL change scores at Day 8 cycle 1

Proportion of patients improved/stable/worse

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improved P</th>
<th>Stable P</th>
<th>Worse P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global QOL</td>
<td>38% GemVin</td>
<td>25% GemVin</td>
<td>37% GemVin</td>
</tr>
<tr>
<td>Physical F</td>
<td>23%</td>
<td>31%</td>
<td>45%</td>
</tr>
<tr>
<td>Role F</td>
<td>27%</td>
<td>25%</td>
<td>48%</td>
</tr>
<tr>
<td>Social F</td>
<td>32%</td>
<td>27%</td>
<td>41%</td>
</tr>
<tr>
<td>Emotional F</td>
<td>44%</td>
<td>23%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Baseline QOL is an independent predictor of survival
- ME.7, SC.8, SC.9
QOL returns to pretreatment levels and higher by 12 months after adjuvant chemo
- MA.5, BR.10
Nausea (even 1-2 episodes) impairs QOL
- SC.8, SC.9
Certain patient characteristics predict for greater chemo-induced nausea and vomiting
- SC8, SC9, SC11

Some Findings of QOL Analyses in NCIC CTG Trials

QOL was more sensitive to toxicity than toxicity criteria
- MA10
Patient age affects the degree to which fatigue is a dose limiting toxicity
- MA11
Focusing on relief of one symptom is insufficient
- SC.12
Palliation is different depending on how you measure it
- SC.15, PA.1

Studies that have influenced practice
NCIC CTG SR.2
Preop vs postop Radiotherapy for Extremity
Soft Tissue Sarcomas

- Primary Outcome = Wound Complications
- 35% wound complications in pre-operative radiotherapy arm
- 17% wound complications in post-operative radiotherapy arm
- statistically significant difference, p=0.01
- study terminated at interim analysis


SR.2 Function/Quality of Life Measures

- Toronto Extremity Salvage Score (TESS)
  - disease-specific physical disability with demonstrated reliability and validity: patient-based (Davis, 1994)
- Musculoskeletal Tumor Society Rating Scale (MSTS)
  - disease-specific clinical impairments, clinician-based (Enneking, 1987)
- Short-Form 36 (SF-36)
  - generic; patient-based health status measure (Ware, 1993)

Davis et al, JCO 2003

SR.2 Early results - Summary

- there is a statistically significant disadvantage to pre-operative radiotherapy in the early stages of recovery following limb preservations for STS
- as time increases from surgery, the TESS (physical disability), MSTS (clinical measures) and SF-36 bodily pain scores are similar for both treatment groups

SR.2 - Radiation morbidity two years post treatment

<table>
<thead>
<tr>
<th>Effect</th>
<th>Pre-op</th>
<th>Post-op</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis ≥ Grade 2</td>
<td>28%</td>
<td>56%</td>
<td>0.003</td>
</tr>
<tr>
<td>Edema ≥ Grade 2</td>
<td>7%</td>
<td>24%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Effects are confounded by maximum radiation dose and larger field size in the post-operative arm. QOL data beyond 1st yr reflect worse function in patients with late RT morbidity

Value Added from QOL analyses - SR.2

- Helped interpret the clinical impact of treatment complications
- Wound complications didn’t impact on functioning/QOL as much as late fibrosis/edema did
- Clinical practice changed to pre-op RT on basis of QOL data that emerged from ongoing F/U
International Reputation

- For seamless integration of QOL within the clinical trials process
- For high rates of compliance
- For clinical emphasis on QOL analysis and interpretation
- For the publication record

QOL Compliance

- A real-time monitoring process to record and report submission rates of questionnaires
- Lack of compliance with baseline QOL completion = major protocol violation
- Compliance continues to be excellent
  - Baseline = 95-100%
  - On treatment = 80-95%
  - In long-term follow-up = 60-70%

What has NCIC CTG done to ensure success in QOL assessment?

- Is what is the “secret” of our success?
- What issues should others consider?

Take-Home Messages

- QOL is a meaningful and measurable outcome in clinical trials
- QOL data have been “value added”
- NCIC CTG has established a benchmark of excellence in QOL in clinical trials

The founding father of NCIC CTG QOL

THE SECRETS OF OUR SUCCESS

QUALITY OF LIFE STUDIES OF THE NCIC CLINICAL TRIALS GROUP

Andrea Bezjak, MDCM, MSc, FRCPC
Chair, NCIC CTG QOL Committee