THE SECRETS OF OUR SUCCESS

QUALITY OF LIFE STUDIES OF THE NCIC CLINICAL TRIALS GROUP

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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

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

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

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

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 QLR 2003, V12, pp 395-404

NCIC CTG QOL publications

- 30+ QOL publications since 1991
- 50+ manuscripts
- Methodological and clinical publications
- Latest = Osoba et al - Analysis and interpretation of HRQL data from clinical trials: basic approach of NCIC CTG EurJCa 2005, 41, pp280-287
- 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

What does a change in QOL scores mean?

- 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
    .....last 3 days.....last 7 days
    - Day 4 post chemo
    - Day 8 post chemo

When should we ask about QOL?

- 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
	p=0.001		

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

Pater et al QLR 1998, Vol 7, pp 273-278

Do QOL data give different information than toxicity data?

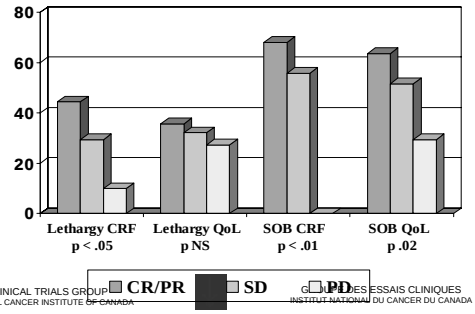
- *Butler et al - Determining the relationship between toxicity and quality of life in an ovarian cancer chemotherapy clinical trial. JCO 2004; 22(12):2461-8*
- *Paul et al - Methods of toxicity data collection: an evaluation of the relative effectiveness of the case report flow sheet, the patient symptom diary, and the quality of life questionnaire. Controlled Clin.Trials 12(5), 648. 1991.*

Does tumor response correlate w 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

Geels et al JCO 2000, Vol 18(12): 2395-405

MA.8: Proportion of Patients with Symptom Improvement by Response Category



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

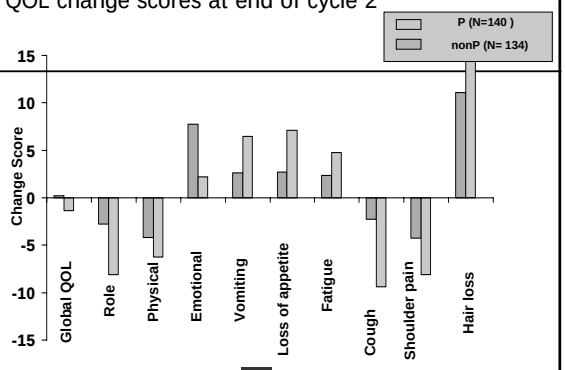
- *Osoba et al EurJCa 2005, 41, pp280-287*

NCIC CTG BR.14/ GemVin study

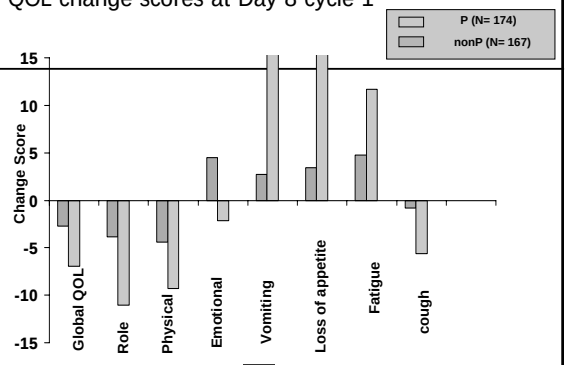
- Stage IV NSCLC
- Platinum based chemotherapy vs Gemcitabine + Vinorelbine
- Primary endpoint = global QOL
- Joint study of the National Cancer Institute, Naples and NCIC CTG

- *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

Variable	Improved		Stable		Worse	
	P	GemVin	P	GemVin	P	GemVin
Vomiting	16%	16%	19%	48%	65%	36%
Appetite	27%	28%	22%	37%	51%	35%
Cough	45%	38%	38%	34%	17%	29%
Dyspnea	37%	27%	36%	36%	27%	37%

Proportion of patients improved/stable/worse

Variable	Improved		Stable		Worse	
	P	GemVin	P	GemVin	P	GemVin
Global QOL	38%	39%	25%	23%	37%	38%
Physical F	23%	27%	31%	32%	45%	41%
Role F	27%	33%	25%	28%	48%	39%
Social F	32%	32%	27%	33%	41%	35%
Emotional F	44%	49%	23%	27%	37%	24%

Some Findings of QOL Analyses in NCIC CTG Trials

- 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

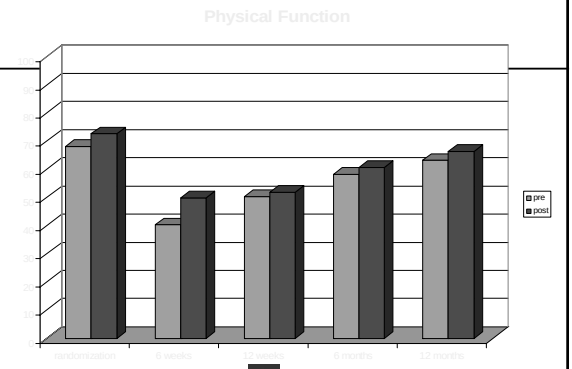
- Primary Outcome = Wound Complications
- 35% wound complications in pre-operative radiotherapy arm
- 17% wound complications in post-operative radiotherapy arm
- statistically significant difference, p=0.01
- study terminated at interim analysis

O'Sullivan et al Lancet 2003.

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

	Pre-op	Post-op	p-value
Fibrosis ≥ Grade 2	28%	56%	0.003
Edema ≥ Grade 2	7%	24%	0.01

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

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