Symptom Benefit Update

Michael Friedlander
Symptom Benefit – 10 years on!

• The 3rd Ovarian Cancer Consensus recommended the development of a specific instrument to measure symptom benefit that could be used in clinical trials. (2005)

Led to the formation of the SB working group GCIG
The primary aim of this study is to develop a better measure of the benefit of palliative chemotherapy rather than rely on objective response criteria alone and to include a measure of the subjective benefit of treatment. This may provide a better means to assess the potential value/impact of palliative chemotherapy in women with platinum resistant/refractory ovarian cancer.
Target Population

>18yrs

platinum resistant/refractory epithelial ovarian cancer

ECOG 0-3

 Able to commence treatment within 2wks of registration

Sufficient English language skills to complete QoL forms independently

During Trial

Stage1-100

• Complete 7 QoL forms
• 20 subjects will be asked to participate in additional QoL telephone interview

Stage2-400+

Determine the optimal number of QoL forms from Stage1

Data Collection

4 Treatment cycles or Disease progression
Publications- Stage 1


Primary Objective  To determine:

The criteria for defining a clinically significant subjective improvement and the optimal instrument/s to measure benefit

Secondary Objectives

- The proportion of women benefiting from palliative chemotherapy
- The time to symptom deterioration
- The proportion of women who receive treatment because they are (a) symptomatic, (b) have rising tumor markers alone, or (c) have imaging evidence of disease progression
- The percentage of patients who complete 4 or more cycles of treatment
- The most common, most severe and most noticed symptoms as perceived by patients.
- Develop a prognostic index
Stage 2

- MOST
- FACT-O
- EORTC QLQ C30
- EORTC OV28
- Expected and Perceived Benefits

These forms will be completed at Baseline and after each cycle until chemotherapy ceases.
Accrual Graph

Anticipated end of accrual, given current average rate continues: 26/07/2017
Planned end of accrual: 1/01/2014

- **Straight line target**
- **Target adjusted for predicted sites open**
- **Predicted accrual if current average rate continues**
- **Rate required to meet target from current actual**
- **Actual Accrual**

*GCIG MAY 12*
Trial Status

Closed to recruitment 31 December 2014

ANZGOG-0701 TOTAL ACCRUAL

ANZGOG: 144
ICORG: 72
AGO: 111
MITO: 83
CANADA: 56
GINECO: 172
NSGO: 32
UK: 174
JAPAN: 93
USA: 11

Total: 948
Quality of Life Research

Measuring what matters MOST: Validation of the Measure of Ovarian Symptoms and Treatment, a patient-reported outcome measure of symptom burden and impact of chemotherapy in recurrent ovarian cancer (ROC)

Purpose: Gynecologic Cancer Intergroup Symptom Benefit Study (GCIG-SBS) Stage 2 aimed to review, revise then validate the Measure of Ovarian Symptoms and Treatment concerns (MOST), developed in GCIG-SBS Stage 1 (MOSTv1, 35 items), and comprehensively document ROC symptom burden and benefit.

Methods: GCIG-SBS Stage 2 recruited patients with platinum resistant/refractory recurrent ovarian cancer (PRR-ROC) or potentially platinum sensitive ROC with ≥3 lines of prior chemotherapy (PPS-ROC≥3). Patients completed MOSTv1, QLQ-OV28 and FACT-O/FOSI at baseline and before cycle 3 of chemotherapy (pre-C3), and global assessments of change (MOST-Change) pre-C3. Clinicians rated patients’ cancer-related symptoms, performance status and adverse events. Internal consistency (Cronbach’s alpha), convergent and divergent validity (Spearman correlations), discriminative validity (effect sizes between groups classified by clinician-rated characteristics) and responsiveness (paired t-tests in patients expected to experience clinically meaningful change) were assessed.

Results: Of 948 recruits, 903 completed PROMs at baseline and 685 pre-C3. Baseline symptom burden was substantial, with few differences between PRR-ROC and PPS-ROC≥3. Eleven MOSTv1 items were excluded. MOSTv2 has 24 items and five multi-item scales: abdominal symptoms (MOST-Abdo), disease or treatment-related symptoms (MOST-DorT), chemotherapy-related symptoms (MOST-Chemo), psychological symptoms (MOST-Psych), and MOST-Wellbeing. Cronbach’s alpha were >0.80. Correlations confirmed concurrent and divergent validity. Discriminative validity was confirmed by effect sizes that conformed to a priori hypotheses. MOST-Abdo was responsive to improvements in abdominal symptoms and MOST-Chemo detected the adverse effects of chemotherapy.

Conclusions: The MOSTv2 validly quantifies patient-reported symptom burden, adverse effects, and symptom benefit in ROC, making fit-for-purpose for clinical trials of palliative chemotherapy in ROC.
Further Analyses

• Defining MCID and Scoring
• Comparison with other Instruments
• Modification of MOST – fit for purpose
• MOST- in follow up – post chemotherapy
Potentially platinum sensitive ≥3 lines chemotherapy

- Baseline PF is an independent significant predictor of stopping chemotherapy early
  Chemotherapy was stopped early in 45/378 (12%) and they had median OS 3.4 months

- Baseline PF and GHS are independent significant predictors of short OS.

PF and GHS remained significant predictors of OS in multivariable models including Hb, ascites, neutrophil: lymphocyte≥5, platelets, log CA125, ECOG and BMI (p<0.007).
Median OS in the whole group 16.6 months.

Poster presentation at ASCO 2017: 3rd June, Gynecologic Cancer session 1:15-4:45pm Abstract ID 5575
Predictors of stopping chemotherapy early and short survival in patients with potentially platinum sensitive (PPS) recurrent ovarian cancer (ROC) who have had ≥3 lines of prior chemotherapy: The GCIG symptom benefit study (SBS).
Potentially platinum sensitive group $\geq 3$ lines chemotherapy

- Further planned analyses for this group:
- Identifying the “platinum resistant” subset included in PPS-ROC – “loose definition”
- Prognostic nomogram including HRQL

Manuscript in progress
Validation of the modified Glasgow Prognostic Score (mGPS) in recurrent ovarian cancer (ROC) – analysis of patients enrolled in the GCIG Symptom Benefit Study (SBS)

Methods

All assessments were performed prior to starting chemotherapy. The mGPS is a measure of systemic inflammation, based on serum levels of C reactive protein (CRP) and albumin, with scores ranging from 0 (least) to 2 (most). HRQL was measured with the EORTC QLQ C-30 and OV 28. X² tests for trend were used to examine the relationship between HRQL, PS and mGPS. Cox proportional hazards regression was used to assess associations between mGPS, HRQL, clinicopathological factors and overall survival (OS).
Conclusion

We validated the mGPS as an independent significant predictor of OS in ROC after adjusting for HRQL and clinicopathological factors. Higher mGPS is associated with lower HRQL independent of PS. The mGPS is inexpensive, simple to measure and would help predict patient outcomes in the clinic and in stratification of participants in clinical trials.
Platinum resistant/refractory group

Global health status, physical function, role function and abdominal/GI symptoms were independent predictors of overall survival

These factors were also significantly associated with early cessation of chemotherapy

Oral presentation at ASCO 2016
Currently in press – The Oncologist
Implications

• HRQOL scores identify the subset of patients with PRR-ROC who have a very poor prognosis
• More informative than ECOG PS
• Including baseline HRQOL together with clinical prognostic variables improves prediction of survival in patients with PRR-ROC
• Additional prognostic information could improve:
  – Stratification in clinical trials
  – Patient-doctor communication re prognosis
  – Clinical decision making
Other planned analyses

- Clinicians’ estimates of survival time – prognostic significance and accuracy
- Prognostic nomogram based on the whole group
- Cross cultural comparisons
- Symptom burden in patients with ROC
- Symptoms amenable to palliative intervention independent of chemotherapy - pain/insomnia/nausea/vomiting/anxiety/depression
- And ............
MOST-OPAL

Primary objectives: To

1. Investigate the utility of the MOST to detect early symptoms of recurrence during follow up and

2. Document the frequency, grade of adverse-effects of treatment and trajectory over time reported by women after completion of first line chemotherapy.

Survivorship Checklist - capture symptoms and adverse effects at clinical follow up as well as to identify subset of patients with anxiety and depression
871 patients recruited to date – recruitment closed November 2015

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MOST administered every 3 months after completion of chemotherapy for 2 years
GCIG  Symptom Benefit Committee- Ripple Effect on PRO’s in Ovarian Cancer Trials over the last decade

http://www.spyculture.com/tom-secker-ripple-effect/