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VALIDATION OF FACT/GOG-AD SUBSCALE FOR OVARIAN CANCER-RELATED ABDOMINAL DISCOMFORT: A GYNECOLOGIC ONCOLOGY GROUP STUDY

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Abstract

Objective—To evaluate the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Abdominal Discomfort (FACT/GOG -AD) Subscale for assessing abdominal discomfort in patients undergoing treatment for ovarian cancer.

Methods—A four item questionnaire was developed for use in Gynecologic Oncology Group (GOG) protocol 172. It was administered to patients with advanced ovarian cancer treated on this protocol with intravenous (IV) cisplatin/paclitaxel or a combination of intravenous and intraperitoneal (IP) cisplatin/paclitaxel (IV/IP) prior to randomization, before cycle 4, 3–6 weeks after cycle 6, and 12 months after cycle 6. The subscale was evaluated in patients receiving IV/IP therapy for internal consistency, concurrent validity, sensitivity to treatment differences, and responsiveness to abdominal discomfort grading.

Results—Internal consistency coefficients were 0.83 and 0.87 at baseline and pre-cycle 4 assessments, respectively; the average inter-item correlation was 0.61 at the pre-cycle 4 assessment. Item correlation with other scales ranged from 0.00 – 0.44. This Subscale was able to distinguish

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

PRÉCIS

This four item subscale reliably and validly assesses ovarian cancer-specific abdominal discomfort, and captures abdominal symptom responses to IV and IV/IP cisplatin/paclitaxel treatments.

those graded to have physician-rated abdominal pain compared to those without clinician-reported discomfort.

Conclusion—The four item AD Subscale reliably and validly assesses ovarian cancer-specific abdominal discomfort, and captures abdominal symptom responses to IV and IV/IP cisplatin/paclitaxel treatments.

Keywords

measurement tool; abdominal discomfort; self-assessment

INTRODUCTION

Abdominal symptoms are frequently associated with advanced epithelial ovarian cancer and can be related to disease, surgery or therapy [1]. Since this tumor type is highly responsive to first-line chemotherapy, abdominal symptoms may remit and quality of life (QOL) often improves as patients' respond to treatment [2,3]. This information has been described in the literature detailing responses to intravenous platinum-taxane combinations for first line therapy [3]. To date, little information has been available describing patient-reported outcomes associated with intraperitoneal (IP) chemotherapy, despite the fact that IP therapy has been studied in clinical trials for over 10 years.

A recent GOG trial demonstrated a significant progression-free survival (PFS) and overall survival (OS) for optimally debulked ovarian cancer patients who received IV/IP therapy, specifically noting a 65.6 month median survival as the longest survival reported to date from an advanced ovarian cancer randomized trial [4]. In this trial, although QOL differed between groups during active treatment, there was no treatment group difference 12 months post-treatment, and both treatment groups' QOL improved over time [5]. Despite the notable survival advantage associated with this treatment, it has not been fully embraced as the standard of care. Several reasons exist, including unique and higher grade toxicities and complications associated with IP compared to IV therapy [6]. It has been recognized that abdominal discomfort associated with IP therapy may not be adequately defined using the National Caner Institute common toxicity-criteria (NCI-CTC). Thus several GOG trials have used a modification of the NCI-CTC abdominal pain scale for objective assessment and scoring of this unique toxicity (Table 1). Using this scale, abdominal pain has been measured with three IP therapy trials [7], including the GOG 172 trial in which 11% of IV/IP patients had grade 3 or greater abdominal pain, compared to 1% in the IV study arm ($p<0.001$) [4]. In this study, 20 patients discontinued IP therapy for reasons that included abdominal pain [6], whereas no patients on the IV arm were reported to discontinue IV therapy for reasons that included abdominal pain.

In the clinical setting, the assessment of abdominal discomfort has been made primarily by physicians using toxicity grading scales such as the pain scale in the NCI-CTC, or the modified abdominal pain scale used by the GOG (Table 1) upon which decisions to continue, dose-reduce or terminate treatment may be based. These grades, however, may not reflect the patient's perception of this adverse effect. A self-assessment tool enabling patients to score their experience with abdominal discomfort can provide additional information concerning the treatment effects from the patient's personal perspective.

Prior to initiating the GOG 172 trial, a search for brief, relevant measurement of the patient's experience with abdominal discomfort produced no available instrument, so one was created using input from expert clinicians in the GOG who summarized collective patient input from their experience. The four item abdominal discomfort subscale was incorporated into the trial with the Functional Assessment of Cancer Therapy-Ovary (FACT-O). The evaluation of

psychometric properties and performance of this four item scale, the FACT/GOG-Abdominal Discomfort (AD), is the subject of the current report.

METHODS

Patients and Treatment

GOG 172 sought to determine if an intense regimen of IV paclitaxel, IP cisplatin and IP paclitaxel could improve objective response, PFS or OS compared to standard IV cisplatin/ taxol in patients with advanced ovarian carcinoma. Secondary objectives, patient eligibility, and details of treatment administration and results were previously published [4,5]. Eligible patients were women with stage III epithelial ovarian cancer who had no residual disease greater than 1.0 cm in diameter after surgical staging, with a GOG performance status of 0 to 2 and adequate renal, hepatic and bone marrow function. All patients gave informed consent consistent with all federal, state and local requirements prior to receiving protocol therapy at participation institutions with prior Institutional Review Board approval of the protocol.

Patients were randomly allocated to receive 135 mg/m^2 IV paclitaxel over 24 hours followed by either 75 mg/m^2 IV cisplatin on day 2 (IV arm) or 100 mg/m^2 IP cisplatin on day 2 plus 60 mg/m^2 IP paclitaxel on day 8 (IP arm). Treatment was to be repeated every 21 days for 6 cycles. Toxicity was assessed according to the NCI-CTC. Cisplatin dose was reduced for grade 2 peripheral neuropathy. Treatment was held for grade 3 or 4 peripheral neuropathy. Treatment was not restarted until neuropathy resolved to grade 2 or less. If creatinine rose to greater than 2.0 mg/dl, creatinine clearance was measured. Treatment was held if creatinine clearance was less than 50 cc/min and could be resumed only when creatinine clearance was greater than > 50 cc/min. The GOG modified abdominal pain score was used to measure abdominal pain. The dose of IP drug was reduced for grade 2 abdominal pain for patients on the IP arm of therapy. Patients who experienced recurrent grade 2 abdominal pain after dose-reduction or patients who experienced grade 3 abdominal pain did not receive further study therapy. Patients who had a treatment delay of three or more weeks were removed from study.

FACT/GOG-AD Subscale

The Functional Assessment of Cancer Therapy-Ovarian (FACT-O) and the 11-item FACT-GOG/Ntx subscale (Neurotoxicity) were administered at each assessment interval. Patient-reported abdominal discomfort symptoms were assessed with the four item Abdominal Discomfort (AD) Subscale of the FACT/GOG-AD (Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group-Abdominal Discomfort). To form the subscale, two questions were contributed from the FACT-O scale (AD 1 & 2), and two were developed based on expert input and patient adverse event reports from previous IP chemotherapy studies (AD 3 & 4) (Table 2). The FACT-O is a 39-item self-report questionnaire [8] in the FACIT Measurement System consisting of two components, a general measure of QOL (FACT-G) and an ovarian cancer subscale, both which have been previously validated [8,9]. The AD Subscale was designed to measure discomfort potentially associated with advanced ovarian cancer, and potential response to treatment.

Each item in the AD Subscale was scored from 0 to 4 points where 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much. Consistent with FACIT scoring convention, the AD Subscale score was computed using proration when more than 50% of items were answered. Also consistent with FACIT scoring, a high score on the AD Subscale connotes better QOL: therefore a 0 score reflects extreme abdominal discomfort and a 16 reflects no discomfort at all.

Abdominal Discomfort Assessments

Patients were to complete the AD Subscale prior to randomization, prior to cycle 4, 3–6 weeks post cycle 6, and 12 months post cycle 6 by rating the accuracy of statements concerning signs and symptoms for the previous 7 days. An assessment cover sheet specifying the completeness and/or reasons for missing data was to be submitted at each scheduled time point even if the assessment was not completed. If a scheduled treatment cycle was delayed, the assessment was to be completed on the planned day of treatment. Patients taken off study prior to cycle 6 were encouraged to complete subsequent assessments. During treatment abdominal pain was clinically graded using a modification of CTC criteria, where 0 is considered no pain and 3 is considered pain so severe that pain confines the patient to bed and seriously interferes with daily activities.

Statistical Considerations

The objective of this report is to evaluate the psychometric properties of the FACT/GOG-AD Subscale for advanced ovarian cancer, created for this IV/IP study. Thus, patients allocated to the IV/IP arm represent the primary study sample.

Reliability—The standardized Cronbach's alpha coefficient was used to assess the internal consistency of the subscale. Coefficients are generally regarded as acceptable if they are above 0.7, good if above 0.8, and excellent if above 0.9 [11].

Construct Validity—Construct validity of the AD Subscale was examined for correlations among items, correlations between the subscale score (corrected for overlap) and its constituent item, and correlations between each item and other subscales using Spearman correlation coefficients since the item scores (scale: 0 to 4) are ordinal rather than continuous [11]. Pearson correlation coefficients were computed for relationships between the AD subscale score and other subscale scores.

Responsiveness to Change over Time—The sensitivity of the subscale to treatments was examined with paired t-test for the change in AD Subscale scores from baseline to pre-cycle 4 assessments among the patients who completed both baseline and pre-cycle 4 assessments in both arms. The sensitivity to different treatments was examined with the two-sample t-test by comparing the changes in AD subscale score from baseline to pre-cycle 4 assessments between the two arms. Given the potential for complications of IP therapy it was hypothesized that abdominal discomfort would spike during active treatment for those randomized to the IV/IP arm.

Sensitivity to Abdominal Discomfort Grading—To determine the extent to which patient-reported AD was reflective of clinically significant abdominal discomfort sufficient to warrant an adverse event report, FACT/GOG-AD scores of patients with AD Grade > 0 were compared to those of patients who never had pain or AD grade reporting of any severity at cycle 4.

RESULTS

Patient Characteristics

Between March l998 and January 2001, 415 eligible patients were randomly allocated to receive either IV (n=210) or IV/IP (n=205) chemotherapy in GOG 172. The majority of patients were white (90%), aged 50 or older (71%), having a performance status of 0 or 1 (94%). Psychometric results are reported only for patients on the IV/IP arm that completed the AD assessment prior to cycle 4.

Assessment Completion

Completion rates (assessments completed/patients alive at the scheduled points regardless of whether they were receiving protocol treatment) were 95 % (195/205) for baseline, 72% (144/199) prior to cycle 4, 80% (157/196) at 3~6 weeks post cycle 6 and 78% (137/176) at 12 months post cycle 6. Ninety-four percent of received questionnaires provided valid answers for all items, 3% (n=18) missed 1 item, and less than 4% (n=21) missed 2 or 3 items.

Documented reasons for not completing assessments included discontinuation of protocol treatment due to disease progression or treatment-related toxicity (2%), patients' lost to contact (3%), institutional error (neglecting to administer) (5%), patient refusal (2%), miscellaneous other (5%) and insufficient answers (3%).

Psychometric Properties of the AD Subscale

Six patients died prior to cycle 4. Of 199 living patients, 144 patients completed the QOL questionnaire with 138 having answered all four AD items prior to cycle 4. For the purpose of evaluating the psychometric properties of the Subscale, only assessments in which all 4 items were answered (accounted for 96% (138/144) of all received) were analyzed.

Internal Consistency

The standardized Cronbach's coefficient (Cronbach's alpha) was calculated to evaluate the internal consistency of the four item AD Subscale, and was 0.83 at baseline and 0.87 prior to cycle 4, indicating very good internal consistency, especially for a 4-item scale.

Construct Validity

The construct validity of the AD Subscale was assessed by calculating the Spearman rank correlation coefficient among items and between constituent items and the scores of the remaining 3 items in the subscale. The average inter-item correlation was 0.61; item-total correlations (corrected for overlap) ranged from 0.64 – 0.83. Item correlations with other scales (including the FACT-G, PWB, SWB, EWB, FWB, Ovarian Subscale, Trial Outcome Index (TOI) (Physical, Functional and Ovarian subscales), and NTX subscale) ranged from 0.00 – 0.44, Table 3. Within this range of relatively modest correlations, the strongest were with the Physical Well-being Subscale and the TOI.

Sensitivity to Abdominal Discomfort Grading

There were 23 patients in the IV/IP arm who were graded to have at least mild abdominal pain at cycle 4 by their physicians (modified CTC AD grade >0). The FACT/GOG-AD scores of these patients were compared to those (n= 81 IV/IP patients) who never had pain or AD grade reporting of any severity at cycle 4. The average FACT/GOG-AD score of the patients who had clinician-reported abdominal discomfort (AD grade >0) was 10.36 (SD=3.55). In contrast, the average FACT/GOG-AD score of those without clinician-reported abdominal discomfort was 13.06 (SD=3.15). This difference of almost 1.0 SD represents a large effect and one considered to easily exceed the minimum important difference [11].

Responsiveness to Change over Time

Sensitivity includes an ability to detect clinically relevant differences that may exist after patients received treatments and between patients receiving different treatments. Abdominal discomfort in general was expected to improve as patients' respond to therapy. IV/IP patients were anticipated to experience more frequent and more severe abdominal symptoms than IV-only patients; thus, IV-only patients were considered a reference group for evaluating the Subscale's sensitivity to treatment differences. Abdominal discomfort Subscale scores are presented in Table 4. As expected, baseline scores were similar since patients on both regimens

were chemotherapy-naïve. After 3 cycles of chemotherapy, both arms reported significant improvement in abdominal discomfort. The analysis of patients who provided baseline and cycle 4 responses showed the improvement in AD is 2.4 points ($p<0.001$) in IV-only arm and 1.5 points ($p<0.001$) in IV/IP arm. The average change (two arms combined) in AD score is 2 points (SD=3.88) corresponding to an effect size of 0.52. In comparison with IV/IP patients, IV-only patients reported significantly more improvement in abdominal discomfort (IV-IP of AD changes is 0.91, 95% CI: 0.04 ~ 1.78; $p=0.04$). This difference diminished after treatment completion and no longer existed by one year follow up [5].

DISCUSSION

Abdominal discomfort is a key outcome when evaluating treatments for advanced ovarian cancer. Both the disease and the treatment can cause abdominal discomfort. In the case of IP therapy administered shortly after optimal debulking surgery, much of this discomfort is likely to be treatment-induced. The FACT/GOG-AD Subscale was developed to assess patient-reported abdominal discomfort. Development of this measure was pursued in the GOG 172 randomized phase III setting because of investigator speculation that abdominal pain would be a primary complaint among the IV/IP treatment arm patients. This patient-reported outcome measure could be central to the interpretation of ovarian cancer clinical trial results given that a psychometrically sound patient-reported outcome measure is likely to have greater reliability and validity than common toxicity criteria measurement [12]. Further, this has the potential to serve as a meaningful clinical measure to document the patient's experience of abdominal discomfort.

The evaluation of this Subscale's psychometric properties demonstrated that it is a reliable and valid instrument. Moreover, the Subscale exhibited excellent capability to detect treatment differences and response to treatment, features essential for successful application to clinical research. Specific to this trial comparing IV versus IV/IP treatment, the FACT-GOG/AD demonstrated a more rapid, and significant improvement in abdominal discomfort for patients in the IV-only arm after receipt of three chemotherapy cycles [5]. However, to avoid misinterpreting the results, it is worth re-iterating that overall both treatment groups' abdominal discomfort improved over time and converged 12 months after the last cycle of therapy where the greater spike in improvement occurred for the IV-only patients prior to cycle 4 [5].

This four item subscale effectively captured clinically meaningful data for patients with advanced, optimally debulked ovarian cancer treated with platinum and paclitaxel, and therefore represents a valuable tool in combination with other QOL instruments in detecting response to treatment via reduced abdominal symptom burden, treatment response differences (IV vs. IV/IP), as well as toxicities or complications stemming from treatment (e.g., IP administration). It is important to note that the AD subscale responsiveness to differences in IV versus IV/IP chemotherapy was comparable to that of the FACT-G, Ovarian subscale and FACT-O TOI [5], while contributing additional content to the domain of abdominal discomfort. Therefore, this Subscale may be an effective and efficient means to gather patient-reported abdominal discomfort in the context of treatment for ovarian cancer, and the addition of two items to the FACT-O does not appear to contribute to patient burden or missing data. Its usefulness to assess abdominal discomfort in other patient populations and/or treatment regimens, however, remains to be validated.

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TABLE 1

MODIFIED ABDOMINAL PAIN SCORE

Grade		Performance
0	No Pain	
1	Mild Pain	Narcotic Analgesia not required; pain causes minimal interference with daily activities and lasts for less than 72 hours
2	Moderate Pain	Narcotic Analgesia required; pain causes moderate interference with daily activities and lasts longer than 72 hours
3	Severe Pain	Narcotic Analgesia required; pain confines patient to bed and causes severe interference with daily activities.

Table 2

FACT/GOG-AD Subscale Items

AD1:	I have pain
AD2:	I have cramps in my stomach area
AD3:	I have pain in my stomach area
AD4:	Stomach pain interferes with daily functioning

Table 3

Correlation Coefficients Among AD Items and Between Each Item and the Subscale Score (N = 138): Pre Cycle 4 data

	AD1	AD2	AD3	AD4	AD Subscale score
AD1	1.00	0.72	0.63	0.66	-
AD2	-	1.00	0.59	0.57	-
AD3	-	-	1.00	0.49	-
AD4	-	-	-	1.00	-
AD Subscale Score	0.83*	0.76*	0.64*	0.67*	-
TOI	0.32	0.40	0.43*	0.22*	0.35*
PWB	0.32	0.40	0.44*	0.26	0.36*
SWB	0.05	0.14	0.09	−0.00	0.10
EWB	0.07	0.19	0.20	0.06	0.15
FWB	0.21	0.26	0.35	0.13	0.28
OV	0.30	0.36	0.32	0.18*	0.27*
NTX	0.31	0.34	0.31	0.26	0.37

Spearman correlation coefficients for inter-items correlation

Pearson correlation coefficients for between items and subscale scores

*Corrected for overlapping items

Table 4

Abdominal Discomfort Subscale Score

Assessment points	No.	IV Mean ± S.D.	No.	IV/IP Mean ± S.D.	Difference Mean ± S.E.
Baseline (pre-randomization)	197	11.7 ± 3.5	195	11.0 ± 3.7	0.7 ± 0.36
Prior to cycle 4	173	14.0 ± 2.9	144	12.6 ± 3.3	1.4 ± 0.35
Change from baseline[1]	168	2.4 ± 3.65	139	1.5 ± 4.11	0.91 ±0.44

Note: Higher score indicates less abdominal discomfort.

[1] Overall effect size for change in AD score from baseline to cycle 4 is 0.52 (pooled analysis of patients who provided baseline and cycle 4 responses). Patients in IV arm experienced significantly more improvement in AD from baseline to pre cycle 4 assessment. Baseline to cycle 4 change scores were significantly different between groups (p=.04). This difference diminished after treatment completion and no longer existed by one year follow up (ref JCO Feb 1, 2007).