Journal of Palliative Care & Medicine
ISSN: 2165-7386

Jensen and Cella, J Palliative Care Med 2013, 3:3
DOI: 10.4172/2165-7386.1000145

Review Article Open Access

Use and Interpretation of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy Symptom Indexes in Palliative Research and Treatment: Special Considerations in Ovarian Cancer

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Abstract

Given the increasing importance placed upon Health-Related Quality Of Life (HRQOL) as an endpoint when evaluating advanced cancer treatment outcome, there is a need for improved measurement of clinically meaningful advanced cancer-specific symptoms that is sensitive to intervention-related changes and which reflects the symptoms considered most important to measure by both oncology clinicians and patients. In response to this need for improved HRQOL measurement, the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) advanced cancer symptom indexes were developed using rigorous, multi-step methodology that adheres to regulatory guidance for patient-reported outcome measures. Eleven NCCN-FACT advanced cancer-specific symptom indexes were produced, measuring the most important symptoms as determined by oncology clinicians and individuals with advanced cancer. In this review, we briefly describe the development of the NCCN-FACT scales, as well as their advantages over previously existing measures, including their brevity, clinical relevance, and greater regulatory acceptability. We review potential clinical and research applications for these scales in palliative medicine, as well as issues pertinent to interpretability. Finally, we present the NCCN-FACT-Ovarian Symptom Index-18 (NFOSI-18) and its precursor, the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Treatment Outcome Index (TOI) as an illustration of how findings from the NCCN-FACT symptom indexes can be used and interpreted in clinical practice. Given the preliminary status of research reporting the use of the NCCN-FACT symptom indexes, as well as their content overlap with precursor disease-specific measures from the FACT measurement system, we conclude with the recommendation that published clinical trial data using cancer-specific FACT measures can inform planning for future use of the NCCN-FACT symptom indexes in research and clinical practice.

Keywords: Health-related quality of life; Patient-reported outcomes; Ovarian cancer; Advanced cancer

Introduction

Interpretation of oncology clinical trials has become complicated by the frequent absence of a survival advantage associated with a new therapy, despite evidence suggesting there may be some value to treatment. Surrogate endpoints such as time to disease progression and progression-free survival may be improved with new treatments, but may not correlate with overall survival [1]. This can occur because the array of post-study treatments available to patients after they discontinue study medication may provide further benefit, because of uneven crossover after study treatment, or because these surrogate endpoints are actually not good surrogates for overall survival. Often, this begs the question of whether or not there is a value to the patient of extending time without disease progression. One can assess this value by asking patients about the effect that cancer is having upon their lives. This effect is typically estimated by asking about disease-related and treatment-related symptoms, and the effects that those symptoms have upon patients' function and well-being.

Cancer symptom assessment, whether symptoms of disease or treatment side effects, can provide an early indication of benefit that is directly relevant to patients' lives. Cancer symptom assessment can also predict long-term outcomes—including tumor response [2], disease progression [2-5] and survival [2,4-9]. Understanding the most important symptoms and related concerns associated with advanced solid tumors can be crucial to fully appreciating the value of new treatments. In this paper, we review an approach to efficiently measuring the most important symptoms and concerns of people being treated for advanced cancer, with special emphasis on ovarian cancer as a model disease that illustrates the importance of this assessment as a major component to determine treatment value.

Overview of the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy (NCCN-FACT) Indexes

Health-related quality of life (HRQOL) has increasingly become an accepted outcome in clinical trials; however, concern about the use and interpretability of multi-item, multi-dimensional HRQOL measures has led to some reluctance on the part of clinicians and regulatory agencies in the implementation of HRQOL assessment in clinical research and practice [10-13]. In response to the concerns about HRQOL measurement in clinical trials, the Food and Drug Administration Oncology Drug Advisory Committee's Quality of life Subcommittee stated that pharmaceutical company claims of improved HRQOL must be specific to the QOL domain measured, with the recommendation that assessment of specific symptoms serve as a starting point for improved measurement of HRQOL domains [14]. In recognition of the importance of assessing HRQOL and symptom improvement, particularly in the case of advanced cancer, recent research sought to improve upon existing validated cancer-related HRQOL and symptom

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Received February 01, 2013; **Accepted** May 02, 2013; **Published** May 04, 2013

Citation: Jensen SE, Cella D (2013) Use and Interpretation of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy Symptom Indexes in Palliative Research and Treatment: Special Considerations in Ovarian Cancer. J Palliative Care Med 3: 145. doi:10.4172/2165-7386.1000145

measures to develop clinically-relevant symptom-specific measures that are sensitive to intervention-related changes and which reflect the symptoms considered most important to measure by both oncology clinicians and patients [15]. Patients provided input on the most important symptoms for 11 different types of advanced cancer and physician experts rated whether the symptoms were predominately disease-related or treatment-related. These results were reconciled with previously published indexes which measured the impost important symptoms to measure as determined by oncology clinicians. This multi-step process resulted in the development and initial validation of 11 advanced cancer symptom indexes that reflect the symptoms rated highest priority by patients and clinicians [15]. Figure 1 illustrates the methodological steps involved in the development of these advanced cancer symptom indexes.

In addition to providing clinically-meaningful tools for the assessment of the most important symptoms to measure across 11 different types of advanced cancer (Table 1), the development of these symptom indexes also demonstrates improved adherence to FDA guidance on patient-reported outcomes. It does this by ensuring content validity of the final questionnaire. Inferences regarding other aspects of validity can be drawn from the published performance of highly-related, precursor instruments that bear significant content overlap. For illustration, note in table 1 that the number of new items added to existing FACT-specific questionnaires based on the FDA-recommended approach, ranged from 0-4, with new content never exceeding 20% of the final index.

Use and Interpretation of NCCN-FACT Symptom Indexes in Palliative Oncology

The often limited availability of curative treatment options in advanced stage cancer highlights the importance of patient-reported HRQOL as an endpoint when evaluating the success of treatment. Among individuals with advanced cancer, HRQOL may be adversely affected by numerous physical and mental symptoms. As such, primary goals of clinical trials in advanced cancer involve symptom management, the preservation of functionality, and the maintenance or improvement of HRQOL. The emphasis on such endpoints in palliative interventions reinforces the need for psychometrically sound HRQOL assessment that yields clinically meaningful information, but also HRQOL measurement that reflects regulatory guidance in that it focuses specifically on the symptoms of importance for that condition. The rigorous multi-step methodology employed to develop the NCCN-FACT symptom indexes uniquely positions them for implementation in clinical research and practice involving palliative treatments for advanced cancer.

When to use the NCCN-FACT symptom indexes

The NCCN-FACT symptom indexes provide clinical providers and researchers with a new option for assessing patients' symptom-

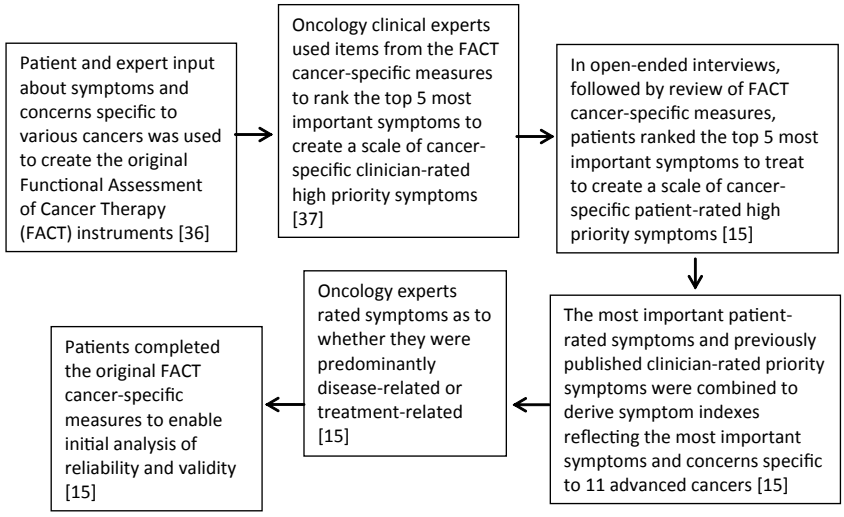

Figure 1: Multi-step methodological process involved in the development of the NCCN-FACT advanced cancer symptom indexes.

Cancer Type	NCCN/FACT Index Name	Number of items (New items)
Bladder	NCCN-FACT Bladder Symptom Index (NFBISI-18) [38]	18 (2)
Brain	NCCN-FACT Brain Symptom Index (NFBrSI-24)	24 (3)
Breast	NCCN-FACT Breast Symptom Index (NFBSI-16) [39]	16 (3)
Colon/rectum	NCCN-FACT Colorectal Symptom Index (NFCSI-19) [40,41]	19 (4)
Head and neck	NCCN-FACT Head and Neck Symptom Index (NFHNSI-22) [42]	22 (4)
Hepatobiliary	NCCN-FACT Hepatobiliary-Pancreatic Symptom Index (NFHSI-18) [43-,44]	18 (0)
Kidney	NCCN-FACT Kidney Symptom Index (NFKSI-19)	19 (2)
Lung	NCCN-FACT Lung Symptom Index (NFLSI-17) [45]	17 (2)
Lymphoma	NCCN-FACT Lymphoma Symptom Index (NFlymSI-18)	18 (2)
Ovary	NCCN-FACT Ovarian Symptom Index (NFOSI-18) [23]	18 (2)
Prostate	NCCN-FACT Prostate Symptom Index (NFPSI-17) [46]	17 (2)

Table 1: Overview of NCCN/FACT Symptom Indexes.

specific responses to treatment. The NCCN-FACT symptom indexes offer the unique combination of clinical relevance and brevity. Thus, they may be especially well-suited for situations and settings that require brief, clinically meaningful assessment of HRQOL that is also sensitive to change. Each index is between 16-24 items in length, which may help to overcome traditional concerns about implementation of HRQOL in clinical practice and research settings, including concerns about patient burden, interruption of clinic flow, and interpretability [15]. Minimizing patient burden may be of particular importance in the palliative context, given that patients may be more bothered by fatigue and other symptoms which could limit their ability to complete more lengthy HRQOL assessments. The brevity of the NCCN-FACT indexes highlights an improvement over the original FACT cancer-specific measures, which are longer in length and require more effort to complete.

The NCCN-FACT symptom indexes were developed specifically to measure the most important symptoms for patients with advanced (stages III and IV) cancer who are undergoing chemotherapy. Consequently, they are especially well suited for clinical practice or clinical trials which seek to assess the focused symptom experience of individuals with advanced disease, as well as the effect of disease and treatment on the symptom experience. In situations in which clinical providers and researchers seek to examine the multidimensional HRQOL experience of individuals with advanced cancer, or HRQOL in individuals with early stage cancer, the original FACT cancer-specific measures may offer a better alternative.

Finally, the NCCN-FACT symptom indexes were developed with special consideration of the FDA guidance on patient-reported outcomes [14] and thus offer potential advantage in terms of their acceptability in the regulatory setting. They provide a reasonable choice for measuring HRQOL in clinical research involving regulatory submission in the process of evaluating the effect of new treatments on the symptoms rated most important across cancer types. In ovarian cancer, for example, there is no other instrument or index that is more responsive to the FDA Patient-Reported Outcome (PRO) Guidance. Several valid and reliable ovarian cancer-specific HRQOL measures, including the Functional Assessment of Cancer Therapy-Ovarian Cancer (FACT-0) [16], and the Quality of Life Instrument—Ovarian Cancer Patient Version (QOL-OVCA) [17], are currently available. Although patients' input was included in the development of these measures, patients had no direct input in the selection of items included on the scale. Consequently, the FACT-O and QOL-OVCA may not fully reflect symptoms prioritized by patients and therefore do not meet the FDA regulatory standard. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module (EORTC-QLQ-OV-28) [18,19] did consider ovarian cancer patients' ratings of the relevance of each symptom or concern in the measure development phase. However, the measure was not developed specifically to reflect the concerns among women with advanced ovarian cancer and women with both early and advanced stage ovarian cancer provided relevance rankings of the symptoms/concerns during the measure development phase [18]. Thus, although the EORTC-QLQ-OV-28 may satisfy regulatory standards for the inclusion of direct patient input in selection of items, not all of the items included may be specifically relevant to women with advanced ovarian cancer or those receiving palliative treatment.

How to interpret the NCCN-FACT symptom indexes

Interpretability constitutes an important measurement characteristic that influences both the implementation of the measure as well as the meaningfulness of its results. In the case of the NCCN-FACT symptom indexes, as with all FACT/Functional Assessment of Chronic Illness Therapy (FACIT) [20] questionnaires, a total score can be obtained, and higher scores indicate better outcomes than lower ones. While this can be clinically informative at the level of the overall index, an examination of the specific subscales (e.g., disease-related, treatment side effects, and function and well-being) can yield more specific information about changes in target symptoms over time or in response to intervention. Given the NCCN-FACT indexes are new indexes, metrics to determine their meaningfulness or interpretability have not yet been established, but constitute an important area for future research. Based on the work of Yost and Eton [21], it is reasonable to anticipate that a meaningful difference for the NCCN-FACT indexes would be in the range of 4 - 5 points. This is consistent with the previously described differences in NCCN-FACT scores between Eastern Cooperative Oncology Group (ECOG) performance status groups [22], which exceed the range of 4 to 5 points [23].

Given that many clinical providers and researchers may have used the original FACT cancer-specific measures of HRQOL, the question may arise about how to interpret the NCCN-FACT symptom index scores in the context of the original FACT measure scores. This may be of particular importance to clinicians and researchers who have used the original FACT measures longitudinally in the past, but who wish to transition to using the newer NCCN-FACT symptom indexes. Due to the fact that the newer NCCN-FACT scales include items not originally part of their original FACT counterpart, the NCCN-FACT symptom index scores cannot be directly calculated from the original FACT measures. However, comparable scores using the original FACT measures can be pro-rated to make them comparable to the NCCN-FACT measures using this established formula: (number of items in NCCN-FACT measure) x [(sum of NCCN-FACT item responses)/(number of NCCN-FACT items completed) if more than 50% of the NCCN-FACT items are completed [24].

In order to illustrate the application of the NCCN-FACT symptom indexes when evaluating the effectiveness of palliative treatment for advanced cancer, we have provided the following example related to the NCCN-FACT Ovarian Symptom Index-18 (NFOSI-18) [23] for use as a potential outcome measure in evaluating the effectiveness of chemotherapy for advanced ovarian cancer.

Applying the NFOSI-18 to Evaluate Treatment Outcomes in Advanced Ovarian Cancer

Ovarian cancer is the second most-common gynecologic cancer in the United States, as well as the most deadly [25], with nearly three-fourths of women presenting with advanced stage (stage III-IV) disease [26]. The goals of treatment for ovarian cancer have historically included increasing progression-free and overall survival and minimizing symptom burden due to disease and treatment. However, recent research examining clinically-meaningful patient-centered outcomes has increasingly focused on maximizing HRQOL as an important end-point [27]. With a greater emphasis on HRQOL, research has increasingly noted the impact of disease and treatment on HRQOL. Given that certain clinical benefits of treatment for ovarian cancer may compromise HRQOL, decision-making regarding treatment often involves a consideration of the balance between efficacy and safety, or benefit and harm. Alternatively, a clinical benefit from therapy may also improve HRQOL, essentially increasing the value of that therapy beyond the clinical measures of response, disease-free survival, progression-free survival and overall survival. Consequently, ovarian cancer provides a relevant context in which to review the application

of the NFOSI-18 to evaluate treatment outcomes in advanced ovarian cancer.

Overview of the NFOSI-18

The NFOSI-18 was developed as part of a larger cross-sectional study (described earlier) that developed symptom indexes for 11 different types of advanced cancer. Fifty-one women with advanced ovarian cancer rated the most important symptoms when treating advanced ovarian cancer and ten gynecologic oncologists rated whether these symptoms were predominately disease-related or treatment-related [23]. The reconciliation of the patient-rated priority symptoms with earlier published clinician-rated priority symptoms resulted in an 18-item symptom index for advanced ovarian cancer. The NFOSI-18 demonstrated good preliminary reliability, with the full scale internal consistency reliability (16 items with data) α=0.80, and subscale reliability ranging from α=0.55 (Treatment side effects) to α=0.64 (Function and Well-Being) [23]. Preliminary validity for the NFOSI-18 was also good, with significant differences in scores between performance status groups as measured by the ECOG measure of performance status [22], such that poorer performance status was associated with lower NFOSI-18 scores [23]. Although future research is needed to establish standards for clinically meaningful difference and change on the NFOSI-18, the differences in the NFOSI-18 scores between ECOG performance status groups exceeded the range of 4 to 5 points discussed in previous research to establish standards for clinically meaningful differences in measures from the FACIT measurement system [21,23].

The NFOSI-18 is highly redundant with the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) [16] HRQOL measure. Prior to the production of the NFOSI-18, the most common clinical trial endpoint in advanced ovarian cancer clinical trials was the 26-item FACT-O Trial Outcome Index (TOI). Table 2 compares item content between the NFOSI-18 (built to respond to the U.S. FDA PRO Guidance on content validity), and the FACT-O TOI (built to be more inclusive of HRQOL considerations beyond the most important symptoms and concerns). Most (n=14) NFOSI-18 items are also in the TOI, suggesting that published data on the TOI would provide good and related evidence for the likely performance of the NFOSI-18 in future trials. Thus, while the NFOSI-18 offers several advantages over the FACT-O, such as its brevity, focused symptom measurement for advanced ovarian cancer, and enhanced satisfaction of regulatory guidance, its recent emergence compels us to infer much of its validity from its very similar precursor, the TOI.

The TOI of the FACT-O includes the items on the Physical Well-being scale (7 items), the Functional Well-being scale (7 items), and the Ovarian Cancer Subscale (12 items). As mentioned, it is the most frequent clinical trial outcome measure in use in this setting. Its overlap with the NFOSI-18 (Table 2) enables one to inform planning for future research using the NFOSI-18 as an endpoint. An examination of published studies reporting on outcomes using the FACT-O TOI now follows.

FACT-O TOI Clinical Trial Outcomes

Combination chemotherapy

A recent prospective phase II randomized clinical trial examined

Item	Included in NFOSI-18	Included in FACT-O TOI
I have a lack of energy	Yes	Yes
I have pain	Yes	Yes
I feel ill	Yes	Yes
I have cramps in my stomach area	Yes	Yes
I feel fatigued	Yes	No
I am bothered by constipation	Yes	No
I have swelling in my stomach area	Yes	Yes
I have control of my bowels	Yes	Yes
I worry that my condition will get worse	Yes	No
I am sleeping well	Yes	Yes
I have nausea	Yes	Yes
I am bothered by hair loss	Yes	Yes
I am bothered by side effects of treatment	Yes	Yes
I have been vomiting	Yes	Yes
I am bothered by skin problems	Yes	No
I am able to get around by myself	Yes	Yes
I am able to enjoy life	Yes	Yes
I am content with the quality of my life right now	Yes	Yes
Because of my physical condition, I have trouble meeting the needs of my family	No	Yes
I am forced to spend time in bed	No	Yes
I am able to work (include work at home)	No	Yes
My work (include work at home) is fulfilling	No	Yes
I have accepted my illness	No	Yes
I am enjoying the things I usually do for fun	No	Yes
I am losing weight	No	Yes
I have a good appetite	No	Yes
I like the appearance of my body	No	Yes
I am able to feel like a woman	No	Yes
I am interested in sex	No	Yes
I have concerns about my ability to have children	No	Yes

Table 2: Item-level comparison of NFOSI-18 and FACT-O.

HRQOL as a secondary outcome in women with recurrent platinum-sensitive ovarian cancer randomized to either docetaxel in combination with carboplatin or single agent docetaxel followed sequentially by carboplatin [28,29]. Although there was no difference in overall survival, there was significantly longer progression-free survival, more neurotoxicity, and more neutropenia in the combination arm [28]. However, the sequential treatment had significantly less impact on HRQOL outcomes. Specifically, the sequential arm had less impact on the FACT-O TOI over the course of the trial, compared to the combination arm [29]. In the combination arm, the TOI decreased by 4.9 points from baseline to study end, whereas in the sequential arm, TOI increased by 1.4 points. There was however, no difference between groups in median time to TOI deterioration [29]. These findings highlight a trade-off between better progression-free survival and greater toxicity and poorer HRQOL in the combination chemotherapy arm. Given that there was no significant difference in overall survival between the combination and sequential chemotherapy strategies, the TOI findings may inform treatment decision-making. This magnitude of change in the TOI from baseline to study end in each treatment arm may help to inform planning of future clinical trials utilizing the NFOSI-18 as a HRQOL outcome measure.

Intraperitoneal chemotherapy

Intraperitoneal (IP) chemotherapy confers a survival advantage to women with advanced ovarian cancer [30-32]. Although a phase III randomized trial found that intravenous (IV) paclitaxel plus IP cisplatin and paclitaxel significantly increased progression-free and overall survival when compared to IV-onlypaclitaxel and cisplatin [30], the FACT-O TOI was significantly worse in the IP group compared with the IV group before cycle four (10 point difference) and three to six weeks after treatment (7 point difference) [33]. Patients receiving IP therapy reported significantly and clinically meaningfully more physical, functional, and ovarian cancer-specific problems during treatment and shortly after, compared to IV-treated patients [33]. Of note, with the exception of the IP group prior to cycle four, both groups reported improved TOI over time, with no differences between the IP arm and the IV arm at one year [33]. Specifically, the TOI improved from 70.0 (baseline) to 83.2 (12 months) in the IV arm and from 64.5 (baseline) to 82.2 (12 months) in the IP arm. These findings highlight the fact that discussions about treatment decision-making must balance the potential survival advantages of IP chemotherapy with the short-term HRQOL decrements associated with it. Moreover, magnitude of differences in TOI scores between treatment arms, as well as longitudinally over time, may provide guidance when planning future clinical trials that measure HRQOL outcomes using the NFOSI-18.

Novel biologic therapies

Although improvements have been made the in surgical and chemotherapeutic treatment strategies for women with advanced ovarian cancer, the limited availability of curative treatment options has prompted a search for alternative therapeutic agents, such as novel biologic therapies. Among the novel biologic therapies under development and investigation, the selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 was examined in two Phase I trials among individuals with advanced ovarian cancer, as well as other advanced solid tumors [34]. ZD1839 acts by disrupting signaling pathways that are important in tumor growth [35]. LoRusso et al. report that in both Phase I trials of ZD1839, the median TOI for participants with advanced ovarian cancer deteriorated from baseline over time, although this was not the case for other solid tumor types in the trial [34]. Specifically, in the European/Australian trial, the overall TOI median deterioration from baseline was -4.50 [34]. The small number of ovarian participants in the U.S. trial limits interpretability of TOI change over time. These findings highlight the importance of examining HRQOL in addition to safety and tolerability when examining novel therapies. The magnitude of change in the TOI among ovarian cancer participants may provide context for the future use of the NFOSI-18 as a HRQOL outcome measure in trials examining novel biologic therapies.

Relevance of FACT-O TOI Outcome Findings to the NFOSI-18

Substantial overlap in item content between the NFOSI-18 and FACT-O TOI, and anticipated similarities in the range of what constitutes a clinically meaningful difference between the NFOSI-18 and other measures in the FACIT measurement system suggests good potential for cross-walk between these two measures of ovarian-cancer HRQOL. Thus, we anticipate that the published clinical trial FACT-O TOI outcomes can play a useful role in the future application of the NFOSI-18 in several important ways. First, an examination of between-group and within-group differences in FACT-O TOI scores over time provides a useful metric with which to set expectations for HRQOL differences by group and time when implementing the NFOSI-18. Second, the magnitude of change observed in published trials utilizing the FACT-O- TOI can also be of assistance when addressing questions of power calculation and sample size when planning for future trials that use the NFOSI-18 to measure HRQOL outcomes. Third, the difference in NFOSI-18 scores across performance status groups provides preliminary evidence to support the NFOSI-18's ability to detect a magnitude of change or difference consistent with published findings on FACT-O TOI outcomes. Thus, as research begins to incorporate the NFOSI-18 for use as a measure of HRQOL in advanced ovarian cancer, the relevance of the FACT-O TOI findings to the NFOSI-18 may assist clinical researchers in study design and planning involving the use of the NFOSI-18.

Conclusion

The NFOSI-18 offers clinical providers and researchers a new tool for measuring patients' response to treatment for advanced ovarian cancer. The benefits of the NFOSI-18 include its brevity, targeted measurement of the most important symptoms specific to advanced ovarian cancer, and enhanced adherence to FDA regulatory guidance. As such, it may be particularly appealing for use in clinical settings in which the minimization of patient and provider burden is critical, as well as clinical research in which conforming to regulatory guidance is essential. Another important distinction between the NFOSI-18 and existing measures of HRQOL in ovarian cancer is its patient-centeredness, given that patients—in addition to clinicians—played a role in item development and selection by ranking the most important symptoms. The primary limitation of the NFOSI-18 is the preliminary nature of research reporting on its use. However, given its redundancy with the FACT-O, which has been used in a number of published studies, we believe that published findings using item subsets common to both the FACT-O and the NFOSI-18 can be used to assist in the development of future research utilizing the NFOSI-18 as an advanced ovarian cancer specific HRQOL measure. Future research using the NFOSI-18 will further enhance its validation and interpretability. Additionally, although the NFOSI-18 and other NCCN symptom indexes are considered brief in nature, additional investigation needs to determine whether refinement is warranted to further reduce patient burden in both clinical research and clinical treatment contexts. Presently, little information exists regarding the extent to which the

NCCN symptom indexes are employed in clinical practice settings both in the U.S. as well as internationally. It is anticipated that as the awareness of these measures increases, so will their use in both clinical and research contexts. Therefore, ongoing evaluation of their responsiveness to change, generalizability to more diverse patient samples, and generalizability across administration contexts (e.g., clinical trials versus clinical practice) constitute important future steps to further develop and establish the psychometric properties of these measures. Finally, given changes in symptom profiles as new treatment and supportive care interventions emerge, it will be imperative to periodically update the scales to ensure that they continue to reflect the current priority symptoms.

Acknowledgements

Support for the study was provided by grants from the following pharmaceutical companies: Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Centocor, Cell Therapeutics, Inc., Clovis Oncology, Genentech, GlaxoSmithKline, Eli Lilly and Company, Merck & Co., Novartis, Ortho Biotech, Pfizer, Sanofi-Aventis and Takeda Pharmaceuticals. The contents represent original work. No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the author(s) or upon any organization with which the author(s) is/are associated.

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