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Palliative Care-Advancing Patient-Centered Evaluation: The NFOSI-18 in Advanced Ovarian Cancer Research

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Abstract

This study addresses the imperative for enhanced measurement of clinically significant symptoms in advanced cancer, focusing on Health-Related Quality of Life (HRQOL) as a pivotal endpoint in assessing treatment outcomes. The National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) advanced cancer symptom indexes were developed through a meticulous, multi-step methodology adhering to regulatory guidelines for patient-reported outcome measures. Eleven NCCN-FACT advanced cancer-specific symptom indices were designed to capture the most relevant symptoms identified by oncology clinicians and individuals with advanced cancer. This paper provides a succinct overview of the development of NCCN-FACT scales, highlighting their advantages over previous measures, including brevity, clinical relevance, and enhanced regulatory acceptance. We explore potential applications of these measures in palliative care, addressing interpretability-related concerns. Additionally, 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), to illustrate how results from NCCN-FACT symptom indexes can be employed and interpreted in clinical practice. Given the preliminary nature of research reporting the use of NCCN-FACT symptom indexes and their content overlap with precursor measures, we suggest that published clinical trial data using cancer-specific FACT measures can guide future utilization of NCCN-FACT symptom indexes in both research and clinical practice.

Keywords: Quality of life; Advanced ovarian cancer; Patient-centered evaluation; Clinical research; Symptom indices

Introduction

The challenge of interpreting cancer clinical trials arises from the frequent absence of a survival benefit associated with new medications, even when there are indications of potential treatment utility. While new therapies may improve surrogate endpoints like time to disease progression and progression-free survival, these may not align with overall survival [1]. Factors such as post-study therapies available to patients, unequal crossover following study therapy, or the inadequacy of surrogate endpoints as substitutes for overall survival contribute to this discrepancy. Evaluating cancer symptoms can provide an early indicator of benefit directly relevant to patients' lives, encompassing symptoms of the disease or side effects of therapy. Such symptom assessment can potentially predict future events, including tumor response, disease progression [2-5], and survival [6-9]. Understanding the worth of new treatments becomes crucial when considering the most significant symptoms and associated concerns in advanced solid tumors. Using ovarian cancer as a model, this study highlights the importance of symptom evaluation as a key component in determining treatment value. Although Health-Related Quality of Life (HRQOL) is increasingly recognized as a clinical trial outcome, clinicians and regulatory organizations have been hesitant to incorporate HRQOL assessment into clinical research and practice [10-13]. Concerns about the use and interpretability of multi-item, multi-dimensional HRQOL measures have been barriers. Addressing these concerns, recent research aimed to enhance validated cancer-related HRQOL and symptom measures. The goal was to develop clinically relevant, symptom-specific measures sensitive to intervention-related changes, reflecting the symptoms deemed most important by both oncology clinicians and patients, especially in advanced cancer cases. Patients ranked the most significant symptoms for 11 distinct forms of advanced cancer, while medical professionals determined whether these symptoms were primarily caused by the disease or therapy. The resulting advanced cancer symptom indices, developed through a multi-step approach, adhere to FDA recommendations on patient-reported outcomes. These indices offer clinically useful tools for evaluating the most significant symptoms across various advanced cancer types, ensuring content validity. By leveraging predecessor instruments with substantial content overlap, validity in other areas can be inferred. For example, using FDA-recommended methodology, the number of new questions added to previous FACT-specific questionnaires ranged from 0 to 4, with new material never exceeding 20% of the final index [14,15]. The constrained availability of curative treatment options in late-stage cancer emphasizes the importance of using patient-reported Health-Related Quality of Life (HRQOL) as an endpoint for treatment assessment. Therapeutic trials in advanced cancer focus on symptom management, functioning preservation, and HRQOL maintenance or enhancement. The NCCN-FACT symptom indices, developed through a meticulous process, offer a valuable tool for evaluating palliative therapy in advanced cancer.

NCCN-FACT symptom indexes: A novel approach

Clinical professionals and researchers now have a novel method for assessing patients' symptom-specific responses to therapy through the NCCN-FACT symptom indexes. These indexes provide a unique combination of clinical relevance and conciseness, making them particularly suitable for quick, clinically relevant, and change-

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sensitive HRQOL evaluations. Their shorter length (16 to 24 questions) addresses issues of patient burden, clinic workflow disruption, and interpretability, fostering easier adoption in clinical practice and research settings.

Tailored for chemotherapy-treated patients with advanced cancer: The NCCN-FACT symptom indexes specifically target chemotherapy-treated patients with advanced (stages III and IV) cancer. Designed for clinical practice or trials focusing on the concentrated symptom experience of advanced disease patients, they offer a more efficient alternative to lengthier FACT cancer-specific measurements. While original FACT measures are preferable for assessing multidimensional HRQOL in advanced or early-stage cancer, the NCCN-FACT indexes cater to the unique needs of advanced cancer patients.

Regulatory compliance and sensitivity: Developed with consideration of FDA Patient-Reported Outcome (PRO) Guidelines, the NCCN-FACT symptom indexes align with regulatory frameworks, enhancing their acceptance in clinical research and filing. These indexes stand out as a suitable option for quantifying HRQOL when assessing the impact of novel medicines on essential symptoms across various cancer types. Notably, they exhibit exceptional sensitivity to FDA PRO Guidelines, especially in the context of ovarian cancer.

Contrasting approaches: FACT-O and QOL-OVCA: In contrast, currently available ovarian cancer-specific HRQOL assessments, such as FACT-O and QOL-OVCA, may not accurately reflect patients' prioritized symptoms due to limited direct patient input during their development. The EORTC-QLQ-OV-28, while considering ovarian cancer patients' assessments during development, may lack pertinence to women with advanced ovarian cancer or those receiving palliative care. This underscores the significance of the NCCN-FACT symptom indexes as a valuable tool for precise and clinically relevant HRQOL assessment in the context of advanced cancer treatment.

Importance of interpretability: Interpretability stands out as a crucial attribute for any measurement, impacting its utility and relevance. Similar to other FACT (Functional Assessment of Chronic Illness Treatment) surveys, the NCCN-FACT symptom indexes allow for the calculation of a total score, where higher scores indicate better outcomes. While an overall index provides clinical insights, a detailed examination of individual subscales (disease-related, treatment side effects, function, and well-being) offers a more nuanced understanding of how target symptoms.

Interpretability measures and future research: Given the novelty of the NCCN-FACT indexes, measures to ascertain their interpretability and significance are yet to be developed. Future research opportunities may include establishing significant change benchmarks, building on the work of Yost and Eton. A substantial change in NCCN-FACT indices is anticipated to be around 4-5 points. The challenge lies in interpreting NCCN-FACT symptom index scores in relation to the original FACT measure scores, especially for healthcare practitioners transitioning longitudinally from the original FACT measures to the more recent NCCN-FACT symptom indices.

Analyzing results of advanced ovarian cancer treatment: Ovarian cancer, the second most frequent and deadliest gynecologic malignancy in the U.S., necessitates a balanced approach considering both efficacy and safety in treatment decisions. Historically, the main goals included improving progression-free and overall survival rates while minimizing symptoms. Recent studies, however, emphasize optimizing Health-Related Quality of Life (HRQOL) as a crucial endpoint. The NFOSI-18 (NCCN-FACT Ovarian Symptom Index-18) serves as a valuable tool in evaluating treatment effectiveness.

NFOSI-18 development and validity: The NFOSI-18 was developed through a cross-sectional study involving 51 women with advanced ovarian cancer. Patient-rated priority symptoms were combined with clinician-rated priority symptoms, resulting in an 18-item symptom index. Initial reliability and validity assessments demonstrated strong results, with notable variations in scores based on performance status. While the NFOSI-18 and FACT-O (Functional Assessment of Cancer Therapy-Ovarian) are highly redundant, the NFOSI-18's brevity and focus on advanced ovarian cancer symptoms enhance its regulatory compliance. The NFOSI-18 differs from FACT-O in brevity, focus, and adherence to regulatory guidance. Notably, 14 questions from the NFOSI-18 are also present in the FACT-O Trial Outcome Index, providing reliable evidence for the NFOSI-18's expected performance. Despite its recent development, the NFOSI-18 demonstrates promise, with its validity extrapolated from its predecessor, the FACT-O Trial Outcome Index. In conclusion, the NCCN-FACT symptom indexes, particularly the NFOSI-18, offer valuable insights into evaluating the effectiveness of palliative treatment for advanced ovarian cancer, emphasizing the importance of a balanced approach that considers both clinical outcomes and patients' quality of life.

Comparative study on platinum-sensitive recurrent ovarian cancer: A recent prospective phase II randomized clinical study addressed platinum-sensitive recurrent ovarian cancer, comparing outcomes between docetaxel plus carboplatin and docetaxel alone followed by carboplatin. Overall survival remained consistent, but the combination arm exhibited significantly longer progression-free survival, increased neurotoxicity, and more neutropenia. Surprisingly, the sequential arm had a lesser impact on Health-Related Quality of Life (HRQOL). Specifically, the FACT-O TOI demonstrated a milder effect in the sequential arm compared to the combination arm throughout the study. Notably, the TOI in the combination arm decreased by 4.9 points, while it increased by 1.4 points in the sequential arm from baseline to trial completion. Although the median time to TOI worsening showed no difference across groups, these findings underscore the importance of balancing treatment benefits and HRQOL implications in clinical decision-making.

Intraperitoneal (IP) vs. intravenous (IV) treatment in advanced ovarian cancer: Survival benefits were observed in women with advanced ovarian cancer receiving intraperitoneal (IP) treatment. However, a significant reduction in FACT-O TOI scores was noted in the IP group before cycle four and three to six weeks post-treatment compared to the intravenous (IV) group. Despite improved progression-free and overall survival with IP chemotherapy, patients in the IP group reported more physical, functional, and ovarian cancer-specific issues during and immediately after treatment than those in the IV group. Both groups showed TOI improvement over time, with no differences at one year, except for the IP group prior to cycle four. This highlights the necessity of considering both potential survival benefits and short-term HRQOL impairments in treatment decision discussions.

Exploring innovative biologic medicines: The pursuit of therapeutic advancements for advanced ovarian cancer, considering limited curative options, has led to the exploration of innovative biologic medicines. ZD1839, an oral epidermal growth factor receptor tyrosine kinase inhibitor, was tested in Phase I studies for advanced ovarian cancer and other solid tumors. The results indicated a decline in the total TOI median from baseline, emphasizing the importance

of evaluating HRQOL alongside safety and tolerability when assessing innovative medicines. Future trials using the NFOSI-18 as an HRQOL outcome measure in trials involving innovative biologic therapy may provide valuable insights into the TOI changes among ovarian cancer patients.

Discussion

In the realm of advanced ovarian cancer treatment evaluation, the NFOSI-18 emerges as a valuable tool for researchers and clinical practitioners. Noteworthy advantages, such as its brevity, targeted assessment of key symptoms specific to advanced ovarian cancer, and enhanced compliance with FDA regulatory guidelines, make it particularly appealing. Its potential applications span clinical settings, where minimizing patient and provider burden is crucial, and clinical research, where strict adherence to regulatory instructions is essential. The NFOSI-18's patient-centered approach distinguishes it from previous Health-Related Quality of Life (HRQOL) measures for ovarian cancer, as patients actively contributed to item development and selection by prioritizing the most significant symptoms alongside medical professionals.

Conclusion

The primary limitation of existing research on the NFOSI-18 lies in its preliminary nature. Despite this drawback, leveraging published results involving item subsets common to both the FACT-O and NFOSI-18 can guide the development of future studies utilizing NFOSI-18 as a specific Health-Related Quality of Life (HRQOL) measure for advanced ovarian cancer. Redundancy with the well-established FACT-O, utilized in numerous studies, underscores the potential validity and interpretability of the NFOSI-18, with room for further enhancement through additional research applications. To bolster the reliability of NFOSI-18, more studies incorporating its usage are essential. While recognized for their brevity, further investigations are required to assess whether modifications are necessary to minimize patient burden in both clinical research and therapeutic settings. Currently, limited data exists on the widespread utilization of NCCN symptom indices in clinical practice, both nationally and internationally. As these measures gain more prominence, their increased application in clinical and research settings is anticipated. Ongoing evaluations of these measures should focus on their adaptability to change, generalizability across diverse patient populations, and applicability across various administration contexts (e.g., clinical trials versus clinical practice). Regular updates to the scales are imperative to ensure their relevance and alignment with evolving symptom profiles resulting from emerging treatment and supportive care strategies.

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Conflict of Interest

Author declares no conflict of interest.

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