VALUE IN HEALTH 16 (2013) 789–796

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Development and Initial Validation of the NCCN/FACT Symptom Index for Advanced Kidney Cancer

Nan E. Rothrock, PhD[1,], Sally E. Jensen, PhD[1,2], Jennifer L. Beaumont, MS[1], Amy P. Abernethy, MD[3], Paul B. Jacobsen, PhD[4], Karen Syrjala, PhD[5], David Cella, PhD[1,6]*

[1]*Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA;* [2]*Department of Surgery, Division of Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, IL, USA;* [3]*Department of Medicine, Division of Medical Oncology, Duke University Medical Center, Durham, NC, USA;* [4]*Health Outcomes and Behavior Program, H. Lee Moffitt Cancer Center, Tampa, FL, USA;* [5]*Biobehavioral Sciences, Clinical Research Division, Fred Hutchinson Cancer Research Center and Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, USA;* [6]*Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA*

ABSTRACT

Objectives: There is a need for a brief symptom index for advanced kidney cancer that includes perspectives of both patients and clinicians and is consistent with the Food and Drug Administration's guidance for patient-reported outcome measures. This study developed and examined the preliminary reliability and validity of the new National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index 19. **Methods:** Fifty patients with advanced kidney cancer provided open-ended and survey responses ranking their most important symptoms. Responses were reconciled with published clinician reports of the most important symptoms. Ten experienced oncologists rated symptoms as disease- or treatment-related. Patients completed quality-of-life and performance status measures. **Results:** A 19-item index was produced from symptoms that were rated as most important by patients or clinicians. It includes three subscales: disease-related symptoms (DRS), treatment side effects (TSE), and general function and well-being (FWB). Internal consistency was good for the full instrument ($\alpha = 0.83$), the DRS subscale ($\alpha = 0.76$), and the FWB subscale ($\alpha = 0.78$) but lower for the TSE subscale ($\alpha = 0.59$). Convergent validity was demonstrated through correlations with the FACT-General. Patients with differing performance status were distinguished by the total score ($F_{2,47} = 17.37$; $P < .0001$), the DRS subscale ($F_{2,47} = 14.22$; $P < .0001$), and the FWB subscale ($F_{2,47} = 13.40$; $P < .0001$) but not the TSE subscale ($F_{2,47} = 1.48$; $P = 0.2380$). **Conclusions:** The National Comprehensive Cancer Network/FACT-Kidney Symptom Index 19 combines symptoms deemed most important by patients and clinicians. Preliminary evidence suggests that the total score and DRS and FWB subscales are reliable and valid as summary indexes. The TSE subscale may be least relevant given the advent of newer therapies.

Keywords: cancer, patient-reported outcomes, quality of life, symptoms.

Introduction

Every year in the United States, there are 64,770 new cases of kidney cancer, and an estimated 13,570 deaths [1]. Almost twice as many men than women are affected, with it representing about 5% of all new cancer diagnoses in men [1]. Approximately 25% to 30% of individuals with kidney cancer are diagnosed with metastatic disease [2]. For those treated for local disease, about 25% recur, typically with distant metastases [3]. Surgery is the primary treatment for early stage disease. Relative 5-year survival rates are significantly worse for distant (11%) and regional (63%) disease when compared with local disease (91%) [1]. Prior to 2005, the only available systemic treatment options for metastatic disease were cytokines, such as interleukin-2 and interferon-alpha. Since that time, several molecular-targeted therapies have been approved by the Food and Drug Administration (FDA) for metastatic kidney cancer, including sorafenib (Nexavar), sunitinib (Sutent), temsirolimus (Torisel), everolimus (Afinitor), bevacizumab (Avastin), pazopanib (Votrient), and axitinib (Inlyta) [4]. Newer targeted therapies offer promise for improved clinical outcomes [5]; however, cure remains an elusive goal [6].

Evaluating the clinical benefit of kidney cancer treatment must include an appreciation for health-related quality of life (HRQOL), including symptoms of disease and their impact on functioning and life enjoyment. Systemic therapies used for advanced disease contribute to declines in HRQOL. As patients are presented with second- and third-line treatment options, HRQOL associated with these options can be a useful guide when making treatment decisions [7]. Several HRQOL instruments have been used in kidney cancer research, including the EuroQoL five-dimensional questionnaire[8],

Conflict of Interest: No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the author(s) or on any organization with which the author(s) is/are associated.

* *Address correspondence to:* Nan E. Rothrock, Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, 625 N. Michigan Avenue, Suite 2700, Chicago, IL 60611, USA.

E-mail: n-rothrock@northwestern.edu.

1098-3015/$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2013.04.015

the Medical Outcomes Study short-form 36 health survey [9], the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 [10], the Renal Cell Carcinoma Symptom Index [11], and the Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index (FKSI) [12]. The FKSI was developed by using both patient and clinician input about the most important symptoms to assess during drug therapy for advanced kidney cancer. The 15-item instrument has demonstrated good internal consistency, test-retest reliability, convergent and discriminant validity, and responsiveness to change in clinical status [12]. It has been used as the primary patient-reported outcome measure for kidney cancer trials [13,14]. To reduce patient burden, a 10-item reliable and valid version of the FKSI was used in trials [12,14]. In an attempt to isolate disease-related symptoms, a 9-item subset of disease-related symptoms (DRS) was drawn from the FKSI-15 by a panel of clinical experts [15]. This DRS, also with good reliability and validity [12], was included as an outcome in clinical trials (e.g., [13,16]).

The iterative development of these brief, symptom-focused indexes occurred prior to the FDA's *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* [17]. Consequently, they do not explicitly ensure content validity in a manner consistent with the *Guidance*. For example, although the FKSI-15 development did use patient input for item generation and review for clarity and readability, this does not strictly meet the recommendation of the FDA *Guidance*, which identifies the centrality of patient involvement in final selection and content through qualitative research methodology. The *Guidance* also emphasizes reaching saturation in item generation. A more explicit open-ended questioning, prior to presenting a list of previously identified items, might help ensure that an instrument would meet this requirement.

The National Comprehensive Cancer Network (NCCN) embarked on an effort to develop and validate symptom indexes for advanced cancer treatment by using a methodology [7] that includes both patient and expert clinician input regarding relevant symptoms with an emphasis on the patient's perspective. Consequently, we developed the NCCN/FACT-Kidney Symptom Index (NFKSI) for advanced kidney cancer in accordance with the FDA *Guidance*, and examined its preliminary reliability and validity.

Methods

The present study was part of a larger study that sought to develop 11 symptom indexes for different types of advanced cancer by using a multistep process [7]. First, patients with advanced kidney cancer answered open-ended questions to identify their highest priority cancer symptoms. Next, patients' responses were combined with results from previous surveys of oncology clinicians to create a symptom index including the most important patient- and oncology clinician-rated symptoms specific to advanced kidney cancer. Next, expert oncologists rated the identified symptoms as predominantly disease- or treatment-related. This was used to create subscales within the measure. Finally, initial validation analyses were conducted on data collected from patients.

Patient Participants

Adult patients with stage III or IV kidney cancer receiving care at one of four NCCN member institutions or a community cancer support organization in 2005 and 2006 were eligible for participation. Participants had received at least two cycles of chemotherapy or 1 month of noncyclical chemotherapy to ensure that patients would have some experience with treatment-related symptoms and had no other primary malignancy (excluding nonmelanoma skin cancer) in the previous 5 years. NCCN accrual sites included Duke Comprehensive Cancer Center in Durham, NC; Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago, IL; H. Lee Moffitt Cancer Center & Research Institution in Tampa, FL; Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance in Seattle, WA; and NorthShore University Health System in Evanston, IL, which at the time was affiliated with the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. A private, nonprofit social service organization, Cancer Wellness Center of Northbrook, IL, also served as an accrual site. All participants as judged by their treating physician and study staff had sufficient cognitive ability to provide informed consent and were fluent in reading and speaking English. All participants provided informed consent in accordance with institutional review board and Health Insurance Portability and Accountability Act (HIPAA) guidelines prior to participating and completed all measures at one time point. Participants received $50 in exchange for their participation.

Patient Procedures

After providing basic demographic information, patients completed a two-part survey. First, patients were asked to "Please think of the full range of your experience receiving drug treatment for your illness. Please tell me what you think are the most important *symptoms* or *concerns* to monitor when assessing the value of drug treatment for your illness." This open-ended prompt was intended to identify concepts not currently included in the Kidney Cancer Symptom/Concern Checklist (Checklist). Patients were asked to rate each of the identified symptoms on a scale from 0 (not important to you) to 10 (extremely important to you). Second, patients were provided the Checklist and asked to identify the 10 most important symptoms and write in additional symptoms. Then, patients were asked to reduce their list of top 10 symptoms down to the 5 "very most important" symptoms. The Kidney Cancer Symptom/Concern Checklist [12,18] consists of 26 symptoms identified by expert clinicians to be related to cancer in general and specific to kidney cancer. To control for potential response bias due to item order, four versions of the Checklist presenting symptoms in different order were administered.

Patients next completed the FACT-General (FACT-G) [19] and the FKSI-15 [12] with duplicate items administered only once. The FACT-G total and subscales (Physical Well-being [PWB], Functional Well-being [FWB], Emotional Well-being [EWB], and Social Well-being [SWB]) were used in analyses. Higher scores on all FACT instruments indicate better QOL. Patients completed the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) [20], which assesses performance as fully ambulatory without symptoms (0), fully ambulatory with some symptoms (1), requiring less than 50% of awake time to rest (2), requiring more than 50% of awake time to rest (3), or bedridden (4).

Analysis of Patient Data

Frequency distributions were analyzed from the patient-generated symptom list. Symptoms/concerns that were identified by at least 10% of the sample were retained for further consideration. If a treatment-related symptom was identified by 20% or more of the patients, it was retained in the final instrument. Identified symptoms were analyzed to determine whether they were already represented on the Checklist. If not, they were reviewed further to select an item from the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system to include in the final instrument. FACIT items were used where the patient-generated content matched an existing item because they had already been tested for comprehension, validity, and translatability.

Frequency distributions of patients' five most important Checklist symptoms/concerns were created. A "write-in" symptom was