Evaluating the psychometric properties of the immunotherapy module of the MD Anderson Symptom Inventory (MDASI-Immunotherapy)

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Abstract

Immunotherapies have revolutionized the treatment of various cancers but little is known about their symptomatic toxicities. Assessing these symptoms are best accomplished by asking the patients themselves. However, some clinicians are suspicious of subjective reports as real scientific data. Demonstrating the validity of symptom tools mainly through the reduction of measurement errors has the potential impact of improving patient care if these tools are widely adopted. We present the psychometric properties of the MDASI-Immunotherapy in patients receiving various immunotherapies in early phase trials at a major cancer center. 282 and 88 patients completed the survey at baseline and after 9 weeks of treatment. The mean age of patients was 57 years, (SD=13.5), 58% were female, 79% identified as white, and 49% had at least some college education. Coefficient alphas for all the subscales were at least 0.70 (range: 0.72-0.93). Significant changes in the module items (95% CI: -0.57, -.09, p<.007) and interference (95% CI: -0.93, -.05, p<.03) were found. In conclusion, the MDASI- Immunotherapy is a valid, reliable and sensitive symptom assessment tool to measure symptomatic toxicities.

Key Words: Symptoms, Assessment, Validation, Cancer

Introduction

Patients with cancer experience disease and treatment-related symptoms that profoundly impact their quality of life and ability to function (Cleeland, 2007). Symptoms are further aggravated by newer cancer treatments such as immunotherapies that essentially interfere with the immune system. With this disruption in immune balance, a unique set of side effects referred to as immune-related adverse events (irAEs) have emerged. Because irAEs are classically autoimmune in nature and are often T-cell-mediated (Weber, Yang et al, 2015), the toxicities associated with immunotherapy may be caused by T cells indiscriminately attacking both tumor cells and normal cells.

Toxicities associated with immunotherapy are generally collected via tabulation of adverse events (AE), which are graded by clinicians. However, it is well known that clinicians typically underestimate the symptoms of toxicity of patients under their care (Basch, 2010;

Basch, Bennett et al, 2011). In order to accurately measure symptoms, we must rely on the use of patient-reported outcomes (PRO).

The patient symptom experience that is captured by patient-reported outcome (PRO) questionnaires administered during an oncologic clinical trial plays a critical role in how drug-approval agencies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency, evaluates the overall clinical risks and benefits of new therapeutic agents.

Symptom assessment requires psychometrically validated tools that are easy to use and quick to administer. The M. D. Anderson Symptom Inventory (MDASI) (Cleeland, Mendoza et al, 2000), was designed to assess the severity of common cancer-related and treatment-related symptoms that may better reflect the symptom experience of the cancer population. The MDASI assesses not only the intensity of cancer-related symptoms, but also the level of symptom interference with daily functioning. Symptoms specific to a particular cancer, treatment method, or treatment site can be added to the core MDASI. These "MDASI modules" include the 13 symptom and 6 interference items of the core MDASI, augmented by additional disease-specific or treatment-specific symptom items. MDASI modules have been developed for patients with brain tumors (Armstrong, Mendoza et al, 2006), head and neck cancer (Rosenthal, Mendoza et al, 2007), treatment-related heart failure (Fadol, Mendoza et al, 2008), lung cancer (Mendoza, Wang et al, 2011) and malignant pleural mesothelioma (Mendoza, Williams et al, 2019) among others. The number of additional module-specific symptom items is minimized to keep the MDASI concise and easy to use in clinical and clinical-research settings and to facilitate repeated measurement.

The goal of our study was to demonstrate the reliability and validity of an MDASI module specific to immunotherapy (MDASI-Immunotherapy). This module asks patients to describe symptoms related to cancer in general and to rate symptoms related specifically to immunotherapy as treatment.

Methods

Patients were recruited from the Departments of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center in Houston, Texas. To be eligible for this study, patients were required to be at least 18 years old, speak English, had a pathological diagnosis of cancer and are receiving immunotherapy as treatment. Patients were excluded if clinical research staff felt that they did not understand the intent of the study or could not complete the assessment measures. Patients completed the MDASI-Immunotherapy at baseline (before the initiation of immunotherapy treatment) and after 9 weeks of treatment. All patients provided written consent to participate. This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center in Houston, Texas.

Measures

At the time of patient enrollment, research staff asked study participants to complete self-administered questionnaires, answered questions, and assisted with completion of survey forms as needed. Patient demographic information (e.g., sex, age, marital status, education level, and employment status) was collected during the initial clinic visit using a general survey questionnaire.

A study-specific clinician checklist was used to collect medical background information from hospital records, including treatment, presence of metastases, and cancer diagnosis, location, and staging.

Eastern Cooperative Oncology Group performance status (ECOG PS) was used to estimate disease severity (Oken, Creech et al, 1982). ECOG PS is a physician-rated measure of functional ability, ranging from 0 (fully active; able to carry on all predisease performance without restriction) to 4 (completely disabled; cannot perform self care; totally confined to bed or chair).

The MDASI-Immunotherapy asks patients to rate the severity of disease-related and treatment-related symptoms during the past 24 hours. Each symptom (pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, numbness or tingling, rash, diarrhea, pain the abdomen, swelling in the hands and legs, headache, night sweats and fever and/or chills) is rated on an 11-point scale ranging from 0 (not present) to 10 (as bad as you can imagine). Patients also rate the degree to which symptoms interfered with various aspects of life during the past 24 hours. Each interference item (general activity, mood, normal work [including both work outside the home and housework], relations with other people, walking ability, and enjoyment of life) is rated on an 11-point scale ranging from 0 (did not interfere) to 10 (interfered completely). To create the MDASI-Immunotherapy, we added seven symptoms - rash, diarrhea, pain the abdomen, swelling in the hands and legs, headache, night sweats and fever and/or chills. Selection of these immunotherapy-specific symptom items was based on literature review and clinician input.

Scoring the MDASI-Immunotherapy. The ratings in the MDASI-Immunotherapy module can be averaged into several subscale scores: mean *severity* (13 core symptom items plus the immunotherapy-specific items), mean *core* (13 core symptom items only), and mean *interference* (interference items only). The interference items can further be broken down into mean activity-related interference (work, general activity, and walking ability) and into mean mood-related interference (relations with people, enjoyment of life, and mood).

A more sensitive characterization of symptoms for a given cohort may use a subset of the most severe symptoms reported by that group. Symptom items may be used individually or in subsets without summary scoring if specified *a priori*. Specific symptom items can also be used based on the expected (i.e., prespecified) outcome. For example, we hypothesized that cancer patients undergoing immunotherapy who developed pneumonitis would experience worsening shortness of breath.

Statistical analysis

All statistical analyses were conducted using Statistical Package of the Social Sciences (SPSS) software version 24. Means, standard deviations (SDs), ranges, and 95% confidence limits (CL) were computed for all symptoms and subscales. Statistical significance was set using a two-tailed alpha level of 0.05.

Reliability of the MDASI-Immunotherapy: Reliability refers to the extent to which the items in a scale are measuring the same concept. Cronbach coefficient alphas were computed to estimate the internal consistency reliability of the three MDASI-Immunotherapy subscales: the core subscale (13 MDASI symptom items), the severity subscale (core plus immunotherapy-specific items), and the interference subscale (six interference items). The criterion for good internal consistency (reliability) requires a Cronbach alpha value of 0.70 or higher (Nunnaly and Berstein, 1994).

Validity of the MDASI-Immunotherapy: Known-group validity comparisons were made for the MDASI-Immunotherapy subscales relative to ECOG PS scores. We performed

independent t-tests to demonstrate ECOG group differences on the subscales. The tool should be able to discriminate between patients with good versus poor performance status.

Results

Of the 282 patients with assessments at baseline, 88 patients also completed the Week 9 assessment. The mean age was 57 years (SD=13.5). About 58% were female, 79% identified as White and 49% had at least some college education. The largest cancer diagnoses were breast (26%) and lymphoma/myeloma (21%).

Reliability: Coefficient alphas for all the subscales were at least 0.70 (range: 0.72-0.93).

Validity: Known group validity shows that patients with poor vs good ECOG performance status was significantly different on the severity subscale ($p<.05$, effect size=0.45 SD) and interference subscale ($p<.05$, effect size=0.5).

Conclusion

The MDASI-Immunotherapy is a valid and reliable instrument for assessing the severity of symptoms and their interference in cancer patients receiving immunotherapy.