Introduction
Immunotherapy is a novel approach that shows great promise in the treatment of cancer. For example, immunotherapeutic agents approved for the treatment of nonsmall cell lung cancer include pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol-Myers Squibb), and atezolizumab (Tecentriq, Genentech). For lung cancer that has spread widely, the first-line treatment is pembrolizumab for patients with high levels of programmed death-ligand 1 (PD-L1), which is related to response to immune checkpoint blockade. In the KEYNOTE-024 trial, the response rate was 45.6%, compared with 26.0% for the chemotherapy group. Patients treated with the second-line pembrolizumab (KEYNOTE-010 trial) had a median overall survival duration of 12.2 months compared with 9.4 months in patients treated with docetaxel.[3] Finally, in the OAK trial, patients who received atezolizumab as a second-line treatment had a median overall survival duration of 13.8 months compared with 9.6 months for those treated with docetaxel.[4]

As the second-line treatment options for lung cancer, pembrolizumab, nivolumab, and atezolizumab all have better safety profiles than chemotherapy. Treatment-related adverse events (AEs) of any grade were reported in 63% of patients in the pembrolizumab group (receiving a dose of 2 mg/kg) compared with 81% in the chemotherapy group. The corresponding AE rates were 69% in the nivolumab group compared with 88% in the docetaxel group and 64% in the atezolizumab group compared with 86% in the docetaxel group. Very few patients discontinued treatment owing to treatment-related AEs. The percentages were 5% for pembrolizumab, 5% for nivolumab, and 1% for atezolizumab. In the first-line setting, the rate of treatment-related AEs of any grade was 73.4% for pembrolizumab compared with 90% for chemotherapy.[1]

Symptoms associated with immunotherapy are generally collected via tabulation of How to cite this article: Mendoza TR. Understanding the toxicity of cancer immunotherapies: Use of patient-reported outcomes. J Immunother Precis Oncol 2018;1:38-45.

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AEs, which are rated by clinicians and are known as clinician-reported outcomes (ClinROs). However, it is well known that clinicians typically underestimate the symptoms of patients under their care.5,6 Confounding the problem is the complex nature of assigning causality to AEs or determining whether an event is attributable to the investigational drug.7 Directly asking patients about their symptoms, known as patient-reported outcomes (PROs), provides more accurate information. Both ClinROs and PROs are subsumed under the much broader term of clinical outcome assessments (COAs). This article reviews the use of PROs, specifically pertaining to symptom burden in cancer patients. The review also discusses challenges in the use of PROs in patients undergoing immunotherapy and provides recommendations for future research.

Clinical Outcome Assessments

COAs are essential measures in assessing both the beneficial and detrimental impacts of cancer treatments. COAs include PROs, ClinROs, performance-reported outcomes (PerfOs), and observer-reported outcomes (ObsROs).

ClinROs are based on a report that comes from a trained health-care professional after observing a patient’s health condition. This report is based on the health-care professional’s clinical judgment or interpretation of observable signs, behaviors, or other physical manifestations that the clinician believes are related to a disease or condition.

PerfOs are based on a task that a patient performs according to the standardized instructions administered by a health-care professional. Examples include measures of finger dexterity or attention span.

ObsROs are those reported by someone other than the patient or a health-care professional. The observer could be a parent, spouse, or other nonclinical caregiver who can regularly observe and report on a specific aspect of the patient’s health.

Finally, PROs comprise any health status report that comes directly from a patient, without interpretation of the patient’s response by a clinician, a caregiver, or an observer. This review describes the use of PROs in cancer patients undergoing various treatment modalities and discusses how PROs can improve understanding of immune-related AEs.

Why Use Patient-Reported Outcomes?

Several factors have contributed to the emergence of PROs in clinical research and practice. First, the National Institutes of Health, as part of its Roadmap Program, spent a considerable amount of money and resources to increase the measurement precision of patient self-report questionnaires.8 Second, the US Food and Drug Administration (FDA) has issued guidance for the pharmaceutical industry, aptly named “PRO measures: Use in medical product development to support labeling claims.” This document describes how self-report measures are to be used for making claims about the effectiveness of therapeutic agents for regulatory approval.9 Third, the National Institutes of Health convened a State-of-the-Science Conference on Symptom Management (http://consensus.nih.gov) to review the current state of knowledge, provide recommendations, and identify potential future projects to help patients with cancer by treating their pain, depression, and fatigue.10 A key issue identified at this conference was the need for refinement and use of symptom-report measures. Finally, having observed the lack of patient voices in AE reporting, the National Cancer Institute proposed the development of the PRO version of the Common Terminology Criteria for AEs (PRO-CTCAE).11

In a more practical sense, PROs systems such as those assessing symptoms coupled with clinician feedback were found to be useful in managing symptoms and improving outcomes. In a randomized two-group trial of patients with lung cancer who had undergone thoracotomy, those assigned to a group in which clinicians responded to alerts generated when prespecified symptoms reached a predetermined symptom severity threshold had a greater reduction and more rapid decline of symptoms than those in the control group in which no alerts were generated.12 More recently, in a two-group randomized trial of patients with advanced solid tumors, Basch et al.13 reported that the group with symptom monitoring coupled with alerts had fewer emergency room visits, showed improved health-related quality of life (HRQOL), continued their chemotherapy longer, and had improved survival compared with the usual care group.

Which Patient-Reported Outcomes to Use?

Most people typically associate PRO with HRQOL, which includes many aspects of a patient’s health and functioning. HRQOL is a multidimensional concept measuring at least four different constructs: physical function (e.g., daily activities, self-care), psychological function (e.g., emotional or mental state, mood), social role function (e.g., social interactions, family dynamics), and disease-related or treatment-related symptoms (e.g., pain, nausea).14

As previously mentioned, symptoms are a subset of a larger domain of patient perceptions about HRQOL. Most HRQOL measures include questions that evaluate the severity of at least some symptoms. Some of the most commonly used HRQOL measures, such as the Medical Outcomes Study Questionnaire Short Form-36,15 the Functional Assessment of Cancer Therapy,16 and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire,17 assess symptoms (e.g., pain, fatigue, shortness of breath). HRQOL measures also cover other dimensions of patient perception, such as social support. However, if immune-related AEs are the
primary interest, the focus should be symptoms, including measures of symptom severity and its functional impact. Symptoms can be thought of as the patient report most proximal to the physical and psychological perceptions of cancer progression and the immediate effects of oncologic therapies on these perceptions.[18]

The measurement of symptoms is perhaps best illustrated conceptually by introducing the concept of symptom burden, which, in cancer, is the subjective counterpart of tumor burden and is similar to the concept of disease burden. Symptom burden includes not only the severity of each of the patient’s symptoms but also the effect of these symptoms on how the patient functions. Therefore, symptom burden could be defined as the combined impact of all symptoms (related to disease, therapy, or both) on the ability of people to function as they did before the onset of the disease or therapy.[18] Although the term “symptom burden” has most often been used for cancer, it has also been applied to the study of other chronic illnesses such as diabetes,[19] asthma,[20] and HIV infection.[21]

Many multisymptom inventories can be used to identify prevalent and distressing symptoms across various cancers and treatments. Some of the most commonly used multisymptom assessment tools include the MD Anderson Symptom Inventory (MDASI),[22] the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire,[17] the Rotterdam Symptom Checklist,[23] the Symptom Distress Scale,[24] the Memorial Symptom Assessment Scale,[25] the Edmonton Symptom Assessment Scale,[26] and the Symptom Monitor.[27]

In the past decade, much effort has gone into the development of the Patient-Reported Outcomes Measurement Information System (PROMIS). This National Institutes of Health-funded initiative, which is based on item response theory, led to the development and testing of a large bank of items that correspond to many different symptoms across various chronic diseases, including cancer. One of its deliverables was a computerized adaptive testing system that allows for efficient, psychometrically robust assessment of PROs in clinical research.[28] Many people consider PROMIS to be a major advance in the development of PROs because of its item banking and methodical item response theory approach, but much work is still needed to provide enough evidence for clinicians to use these PRO measures in clinical practice. The most recent effort in the development of PROs specifically addressing symptomatic effects of treatment is the PRO-CTCAE. The validated PRO-CTCAE consists of 124 items reflecting 78 symptomatic AEs, and each AE is assessed relative to one or more attributes, specifically presence or absence, frequency, severity, and/or interference with usual or daily activities.[29] The PRO-CTCAE captures a full range of symptomatic treatment effects across a full range of cancer treatment modalities. Frequency, severity, and interference with daily activities are scored using a 0–4 rating scale (i.e., frequency: 0 indicates never, 1 rarely, 2 occasionally, 3 frequently, and 4 almost constantly; severity: 0 indicates none, 1 mild, 2 moderate, 3 severe, and 4 very severe; and interference with daily activities: 0 indicates not at all, 1 a little bit, 2 somewhat, 3 quite a bit, and 4 very much). The response options for the presence or absence are 0 for no or 1 for yes. The recall period for all items is the past 7 days. Intended to complement the CTCAE, the PRO-CTCAE is primarily used to describe and elucidate the toxicity profile of an investigational agent. The PRO-CTCAE has been shown to be feasible to use in large multicenter trials;[30] however, because the PRO-CTCAE was only recently developed, work remains to be done to determine clinically meaningful differences in PRO-CTCAE scores.

As Kirkova et al.[31] pointed out, many multisymptom instruments are appropriate for clinical use, and the choice of instrument depends on the intended purpose (research, clinical practice, or targeted symptoms). On the basis of our own work, we described the use of the MDASI in longitudinally designed correlative studies following different cohorts of patients undergoing various therapies. The MDASI is a brief (<5 min), psychometrically validated, multisymptom assessment tool developed for use with cancer patients who either are undergoing or have completed a variety of cancer therapies.[18,22] The 13 MDASI core symptoms comprise physical symptoms (fatigue, pain, nausea, vomiting, poor appetite, numbness/tingling, dry mouth, shortness of breath), psychological/affective symptoms (sadness, distress, disturbed sleep, drowsiness), and a cognitive symptom (difficulty remembering). Symptoms are rated over the previous 24 h on an 11-point scale ranging from 0 (“not present”) to 10 (“as bad as you can imagine”). Several MDASI modules that include the 13 core symptoms and additional symptom items relevant to the disease or treatment of interest (e.g., MDASI-Head and Neck,[32] MDASI-Brain Tumor[33]) have been psychometrically validated.

**Symptom Severity is Predictive of the Development of Radiation-Induced Pneumonitis**

Concurrent chemoradiation therapy for locally advanced nonsmall cell lung cancer was found to be associated with the development of clinically significant radiation-related pneumonitis. In a study of 152 patients with nonsmall cell lung cancer treated with concurrent chemoradiation, the MDASI was administered before the start of chemoradiation and then weekly up to 6 months after therapy was completed. After controlling for the effects of sex, age, and radiation dose/volume, the authors found that increases in the severity levels of shortness of breath and coughing were associated with high-grade radiation-related pneumonitis at 6 months after therapy completion.[34] Figure 1 shows the symptom development trend by grades of radiation pneumonitis.
Symptom Severity and Symptom Interference Predict Survival in Advanced Lung Cancer

In a study in which we followed 94 patients with advanced-stage nonsmall cell lung cancer, we collected symptom data with the MDASI before and after the first cycle of chemotherapy.[35] We found that moderate-to-severe levels of cough (ratings ≥5 on a 0–10 scale) at baseline predicted poor overall survival. In addition, increases in fatigue and shortness of breath from baseline to the end of the first chemotherapy cycle predicted poor overall survival. In a separate cohort of patients with advanced-stage nonsmall cell lung cancer, we found that patient-reported symptom interference with daily activities, as measured by the MDASI, added prognostic information to Eastern Cooperative Oncology Group performance status and cancer stage in the prediction of overall survival.[36]

Symptom Burden in Hematopoietic Stem Cell Transplantation Recipients

We used the blood and marrow transplantation module of the MDASI (i.e., MDASI-Bone Marrow Transplantation) in 192 patients who had undergone hematopoietic stem cell transplantation to assess symptom severity and symptom interference with daily activities. Data were collected at 20 time points from the day of stem cell infusion to 100 days after hematopoietic stem cell transplantation. Symptom severity and symptom interference with daily activities were calculated using the arithmetic average of MDASI-Bone Marrow Transplantation items for symptom severity or symptom interference with daily activities. Those who had acute graft-versus-host disease (GVHD) had higher symptom severity and greater symptom interference with daily activities than patients without GVHD[37] [Figures 2 and 3]. As depicted in the figures, symptoms are initially expected to increase but will eventually decrease over time. These changes in symptoms can be reliably and validly measured using MDASI-Bone Marrow Transplantation. It is worth noting the commonality between GVHD and immunotherapy. GVHD is one of the major complications of allogeneic hematopoietic stem cell transplantation.[38] For both GVHD and immunotherapy, symptoms are reported because of the immune response.

We have also shown that long-term collection of symptom data is feasible. In a study of patients with chronic myeloid leukemia, symptoms were assessed via the MDASI-Chronic Myeloid Leukemia every 2 weeks for 1 year using an interactive voice response system. Compliance was excellent: 80% of patients completed at least 50% of assessments and 51% of patients completed 80% of the assessments.[39]

Symptom Burden in Patients with Head and Neck Cancer

In a prospective study,[40] we examined the pattern of patient-reported symptoms during radiation therapy and concurrent chemotherapy for patients with head and neck cancer so that future symptom interventions and clinical investigations could be more effectively designed. A cohort consisting of 149 patients completed the head and neck module of the MDASI weekly during radiation therapy-based treatment. Overall symptom severity (P < 0.001) and symptom interference with daily activities (P < 0.001) became progressively worse over the treatment course and were worse for those receiving concurrent chemotherapy (P < 0.001). Fatigue, drowsiness, lack of appetite, mouth and throat mucus, and problems tasting food were more severe for those receiving concurrent chemotherapy. By the end of 6–7 weeks of treatment, about 67% of patients experienced high symptom
burden. Multivariate analysis showed that low patient baseline performance status and receipt of concurrent chemotherapy were associated with increased symptom burden. In conclusion, the study identified the pattern of both local and systemic symptoms, and the degree of symptom interference with daily activities was temporally distinct, marked by increased magnitudes and shifts in individual symptom rankings, as well as identifiable symptom clusters.

**Patient-Reported Outcomes in Patients in Early-Phase Trials**

In 52 patients with advanced cancer enrolled in phase I clinical trial of the first-in-human true human monoclonal antibody, MABp1, patients completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, a PRO measure, at three time points over the course of the trial. The PRO measure was able to capture longitudinal changes in symptoms over time. PRO assessments at baseline and week 8 showed significant improvements on day 1 of cycle 3 in social (P = 0.025), emotional (P = 0.032), and role function scores (P = 0.006). Fatigue (P = 0.0084), pain (P = 0.025), and appetite loss (P = 0.020) also improved. Patients reported a significant improvement in global quality-of-life scores, from 4.8 to 5.4 (P = 0.021). These results indicate that PRO changes can be observed in patients in phase I clinical trials undergoing treatment with monoclonal antibodies.

In a recent cross-sectional study, George et al. explored symptom patterns and patient clusters based on symptom severity and examined associated factors. The researchers approached 248 patients in phase I clinical trials and only two patients declined to participate. Patients in a phase I clinical trial reported less dyspnea (P < 0.001) and vomiting (P < 0.029) than did patients who were not enrolled, but the patient groups did not differ in terms of other symptoms. The researchers also assessed the relationships among sleep quality, symptom burden, and mood in patients with advanced cancer who were enrolled in early-phase clinical trials. Results showed that sleep quality was poor among most patients, and poor sleep was associated with an increased likelihood of high symptom burden and symptom-related interference with daily activities [Figure 4].

**Feasibility of Obtaining Multiple Baseline Symptom Assessments and Frequent Assessments in Patients in Phase I Clinical Trial Settings**

In a recent study of cancer patients enrolled in phase I clinical trials at MD Anderson, 37 patients receiving immunotherapy were assessed daily for about 2 weeks before beginning treatment and twice per week for 4–6 weeks before the end of cycle 2 or disease progression. Patients were given the option to respond on paper, through an interactive voice response system, or electronically through web-based platforms. Most patients preferred responding electronically. With 15 potential maximum baseline assessments, the mean was 10.2 and the standard deviation was 2.8. The median number of baseline assessments was 11 with a mode of 12 from eight patients. With 22 potential maximum on-treatment assessments, the mean was 11.8, standard deviation 6.1, median 13, and mode 15.

**Patient-Reported Outcomes in Immunotherapy**

Although multiple ongoing clinical trials are testing the safety and efficacy of immunotherapy, either singly or in combination with other forms of therapy, patient-reported symptom data related to new immune-based oncology treatments are lacking. Although a few studies reported HRQOL associated with immunotherapy, symptom-focused PROs are more relevant, owing to their proximity to the effects of immunotherapy. This information is vital for clinicians because it indicates the patient’s ability to tolerate the intended oncologic therapies and allows for improved patient-centered care. Because the FDA is also concerned about how cancer patients feel and function, in addition to prolonging survival of cancer patients, the role of symptom PROs is even more critical in drug development, especially for newer immunotherapeutic agents. However, the lack of symptom data collected over time for patients undergoing treatment with immunotherapy hinders our understanding of these changes in symptoms and their associated interference with daily functions.

**Potential Issues in the Incorporation of Patient-Reported Outcomes in Immunotherapy Studies**

Issues of practicability, ease of administration, level of patient (assessment) burden, and interpretability are paramount in optimizing the use of PROs in immunotherapy studies. Immunotherapy is known to prolong survival...
in many cases, but the patient’s experience and function with this survival benefit are less clear. PROs focusing on symptom burden will improve understanding of the impact of immunotherapy. Many symptom measures are available to suit a variety of needs but require critical thinking about how they will be used. We can ask similar questions to those used for other treatment modalities. Will the treatment reduce symptoms that are present (e.g., shortness of breath in lung cancer) or prevent symptoms normally expected to occur (e.g., neuropathy from certain cancer treatments)? Will the treatment have rapid effects on symptoms, requiring repeated assessments over a short period, perhaps daily or three times per week? Or will the treatment have more gradual effects on the symptom, such as the pain reduction associated with palliative radiotherapy? If the effects on symptoms are rapid, repeated use of a brief and easily administered symptom measure is probably the best choice, whereas if symptoms change more gradually, assessment should be less frequent and might include additional symptom items.

Selection of symptom items for the assessment in immunotherapy poses another challenge. Many symptom measures, including the MDASI, were further improved by including items specific to the disease or treatment. For example, the head and neck module of the MDASI included items such as difficulty swallowing and problems with mouth sores to underscore the nature of cancer affecting the head and neck region. However, a comprehensive list of symptoms associated with immunotherapy has yet to be uncovered. Although the list of immune-related AEs provides a good indication of the symptomatic effects of immunotherapy, we need to ask the patients themselves via qualitative interviewing, a well-accepted approach favored by regulatory agencies.

Conclusions

COAs, especially PROs, are gaining widespread use in oncology research. PROs that specifically focus on symptom burden have improved understanding of both the benefits and the detrimental effects of cancer therapies on various types of cancer. We have seen the impact of different treatment modalities, such as radiation, chemotherapy, and hematopoietic stem cell transplantation, on how patients feel and function in several longitudinal studies of patients with chronic myeloid leukemia, head and neck cancer, and lung cancer. We have also seen how early changes in shortness of breath and coughing observed in nonsmall cell lung cancer patients are associated with the development of radiation-induced pneumonitis. Regulatory agencies such as the FDA are increasingly interested not only in prolonging survival of cancer patients but also in how these patients feel and function while undergoing cancer treatment. Understanding patient’s experiences is best accomplished by directly asking them about their symptoms with the use of PROs. Many studies involving the use of immunotherapeutic agents have started to incorporate PROs in the study design. However, many of these studies are still in their infancy. Many issues involved in symptom assessment have yet to be resolved, such as frequency of administration and adequacy of the chosen symptom list to cover both known and unknown effects of immunotherapy. These areas offer a potentially rich agenda for future research.

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