Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

Background

The NCI's Common Terminology Criteria for Adverse Events (CTCAE; http://ctep.cancer.gov/reporting/ctc.html) is a longstanding empirically developed "dictionary" or lexicon, designed for use in clinical trials to aid clinicians in detecting and documenting an array of adverse events (AEs) commonly encountered in oncology. An AE is any unfavorable sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or intervention that may or may *not* be considered related to the medical treatment or intervention under investigation. The AE may be either unexpected or expected.

An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE is graded on a scale of 1 (mild) to 5 (death related to AE). A grade 5 is not appropriate for some AEs, for which it is not an option. The reporting requirements for AEs are protocol-specific and are generally divided into two types. The first is the protocol-specific AEs to be addressed at designated evaluation intervals. The second is the pertinent positive clinical signs, symptoms, and laboratory results obtained as part of routine care of patients. The CTCAE is maintained by the NCI's Cancer Therapy Evaluation Program (CTEP). The CTCAE is currently in its fourth version.

There is growing awareness that collecting symptom data directly from patients using patient-reported outcome (PRO) tools can improve the accuracy and efficiency of symptomatic AE data collection. This is based on findings from multiple studies[1-11] demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings. For example, in a study of men with prostate cancer enrolled in a Phase II clinical trial, physician reporting was neither sensitive nor specific in detecting common chemotherapy symptomatic adverse effects[5].

In the field of pain management, it has long been recognized that only the patient can accurately report the onset, severity and duration of pain and its impact upon function. This principle extends to other symptoms, such as fatigue, erectile dysfunction, and xerostomia (dry mouth), which can be found in the CTCAE. The advantages of a PRO complement to the CTCAE can be found in the recent Trotti et al article[8].

Overview of the PRO-CTCAE

The NCI's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) system provides a web-based platform to collect patient reports of symptoms they are experiencing while undergoing treatment for the purpose of enhancing adverse event (AE) reporting http://outcomes.cancer.gov/tools/pro-ctcae.html). To date, 81 symptoms of the CTCAE (version 4) have been identified to be amenable to patient reporting. These symptoms have been converted to patient terms (e.g., CTCAE term "myalgia" converted to "aching muscles").

For symptoms like fatigue and pain, the PRO-CTCAE system will ask patients information about symptom frequency, severity, and interference with usual activities. For other symptoms like rash, questions will focus on the presence on the body. These items have undergone extensive qualitative review among experts and patients. The PRO-CTCAE electronic system provides an interface for patients, investigators, and clinicians in a secure web-based platform. This work is supported under contract with Memorial Sloan-Kettering Cancer Center (Principal Investigator: Ethan Basch, MD).

Objectives and Next Steps

The overall goal of the PRO-CTCAE initiative is to employ rigorous scientific methods to create a system for patient self-reporting of adverse symptoms in cancer trials that is widely accepted and used; generates useful data for investigators, regulators, clinicians and patients; and is compatible with existing adverse event reporting systems. In total, there are 126 questions that assess different attributes (e.g.,

frequency, severity, interference, presence of condition) of 81 symptoms that are represented in both the CTCAE (version 4) and MedDRA adverse event lexicons. These 126 questions have been extensively evaluated by cancer patients, using cognitive testing methods, to be clear, comprehendible, and measure the symptom of interest. Further, an electronic web-based system has been developed to provide interfaces to investigators, clinicians, and patients to collect and report patient-reported symptom data.

Next steps in the project include usability testing of the PRO-CTCAE software system, validation testing of the questions in a large cancer cohort, translations to Spanish and Japanese, feasibility testing of the PRO-CTCAE system in phase II and III clinical trials, and a study on alternate models to integrate patient and clinical reporting AE data for toxicity grading, drug modifications, and cancer care improvement. In the future, it is hoped that the PRO-CTCAE will be used in all cancer clinical trials.

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