

Integrating Pain Metrics into Oncology Clinical Trials

Charles S. Cleeland¹, Ann O'Mara², Martin Zagari⁴, and Carole Baas³

Abstract

Cancer-related pain is highly prevalent and often severe, and as a result is often one of the defining experiences for patients with malignancy. Patients and patients' families almost always live with the ever-present reality that cancer treatment and progression may be accompanied by pain. For patients nearing the end of life, most fear that their final days will be spent living with the terrible effects of the disease, the most important of which is pain. Despite this, there is far less systematic research on the mechanisms of cancer-related pain or on the development of new agents to reduce or eliminate pain in cancer patients compared with research to combat the disease itself. Further, even when the focus of research is treatment of the tumor, the effects of anticancer treatments on pain are often under-reported in publications and other forums. To illustrate the relative drought in the cancer pain control area, there have been no new drugs approved for cancer-related pain in recent years. A number of methodologic and logistical challenges that hinder the ability to assess pain response in clinical trials are discussed in this article. Possible ways to address these challenges are also discussed. *Clin Cancer Res*; 17(21); 6646–50. ©2011 AACR.

Introductory Note

At the 2010 Conference on Clinical Cancer Research, co-convened by Friends of Cancer Research and the Engelberg Center for Health Care Reform at the Brookings Institution, participants explored 4 pressing challenges in the field. Articles summarizing the panel's recommendations on each of these topics are featured in this issue of Clinical Cancer Research (1–4).

The Need to Integrate Measures of Pain in Cancer Clinical Trials

As more effective drug products become available to treat cancer, survival rates for many types of cancers have improved. Patients are not only living longer with cancer, but they are also living longer with symptoms associated with both cancer and its treatment. Cancer-related pain and other symptoms, such as fatigue, disrupted sleep, and psychosocial distress, have a significant impact on functioning and health-related quality of life (5–8). With the

availability of more effective treatment options, oncology product development programs are targeting add-on, second-line, or advanced disease indications in addition to first-line therapy. As a result, in addition to including objective measures such as overall survival and tumor response, oncology clinical trials are also targeting improvements in patient-reported cancer-related symptoms.

Cancer-related pain is a frequently reported and distressing symptom associated with many malignancies. A recent systematic review indicates that approximately half of patients with solid tumors have pain, and that, of those with pain, one third report pain that is moderate to severe (9). Analgesics are the mainstay of therapy in treating cancer-related pain (10). However, chemotherapeutic agents that demonstrate evidence of pain reduction or of a delay in the onset of pain in addition to meeting standards of efficacy could provide a significant treatment benefit for the patient. As a result, some oncology clinical trials have included measures of pain in study designs (11–13). However, the number of patients enrolled in oncology trials that examine pain as an outcome is a fraction of those receiving care, even in the setting of a clinical trial, resulting in a paucity of quality of evidence of treatment effects on cancer pain. Carefully designed trials with cancer pain relief as a primary or secondary outcome are required in patients with well-defined disease and pain.

Adequately Measuring Subjective Pain in Clinical Trials

Adequately and reliably measuring and interpreting subjective endpoints such as pain can be challenging. Randomized clinical trials in oncology from 1996 through 2001

Authors' Affiliations: ¹Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, Texas; ²Palliative Care Research and Community Oncology Prevention, and ³Physical Sciences in Oncology, National Cancer Institute, National Institutes of Health, Bethesda Maryland; and ⁴Health Economics and Outcome Research, Amgen Inc., Thousand Oaks, California

Corresponding Author: Charles S. Cleeland, Department of Symptom Research, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1450, Houston, TX 77030. Phone: 713-745-3470; Fax: 713-745-3475; E-mail: ccleeland@mdanderson.org

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have included at least 125 different pain outcome measures (14). Different pain outcome measures may evaluate different aspects of pain, such as pain intensity, pain interference (the extent to which pain interferes with daily living), or pain relief. The most commonly used scale is a numeric rating scale, where patients typically rate their pain from 0 to 10, with 0 representing no pain and 10 corresponding to worst pain imaginable. Other scales (verbal descriptor scales) use graded adjectives (mild to severe) to represent increases in severity. Finally, the visual analog scale may be used in acute (postoperative) pain studies, where patients indicate on a line their pain intensity. Other domains that might be assessed include the degree to which pain interferes with physical and emotional function. The Brief Pain Inventory (BPI) is an example of a measure that samples both severity and interference, as well as the degree to which trial participants believe a therapy has helped their pain (15). Measures of pain relief are similar to those for pain intensity, except that patients are asked to rate how much relief they have experienced relative to their previous pain levels following some intervention. Some pain metrics provide a more qualitative assessment of cancer pain, such as the McGill Pain Questionnaire (MPQ) which scores sensory, affective, evaluative, and miscellaneous pain (16). The pain metrics listed above, and others, are described in detail in a systematic review of 164 studies of cancer pain comprising over 35,000 adult cancer patients (17). This report discusses the utility, validity, and reliability of these measures and provides recommendations for selecting the appropriate pain measure depending on the situation. More recently, consensus reviews both in the United States and Europe indicate that, at a minimum, a numeric rating scale of pain severity is acceptable as a unidimensional measure of pain, and is quite easy to implement in most clinical trials (18, 19). Thus, despite the subjective nature of pain, reliable methods exist to measure pain and the challenge now is to integrate these methods into clinical trials in a way that results in meaningful improvements for patients suffering from cancer pain.

The Challenge of Incorporating Pain Metrics into Oncology Clinical Trials

In 2009, the U.S. Food and Drug Administration (FDA) "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" was published (20). The guidance describes how FDA reviews patient-reported outcome (PRO) measures that are used to support claims in approved product labeling. The guidance defines a PRO as any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else. The guidance notes that, like other endpoints in a clinical trial, a PRO measure must be well-defined and reliable and show evidence that it is an adequate measure of the specific concept it was designed to measure. Based on the FDA PRO Guidance principles, symptoms known only to the

patient, such as cancer-related pain, are best evaluated by a self-reported measure. The measure should be comprehensible, interpretable, and appropriate for the target population. In addition to selecting the actual pain measure, based on the FDA PRO Guidance, it is also important to consider how the pain measure will be incorporated in the clinical trial. The endpoint model describes the relationship of all endpoints, both PRO and non-PRO, in a clinical trial (e.g., primary, coprimary, or secondary). The endpoint model is critical in the implementation of the pain measure in the clinical trial.

Although the FDA PRO Guidance lays out general principles for developing PRO measures and endpoints, it is not specific to the issue of pain measurement in oncology. There are many uncertainties and methodologic challenges to consider in incorporating pain endpoints in oncology clinical trials. For example, if a sponsor plans to include pain as an efficacy endpoint in a pivotal trial, the sponsor will need to determine whether pain should be used as a primary or coprimary endpoint as opposed to a secondary endpoint. If pain is an endpoint, the endpoint model must be constructed to appropriately interpret study results with consideration for the impact of treatment on tumor burden in addition to pain. The sponsor must find some way to measure and differentiate between "cancer-related pain" and "treatment-related pain" (e.g., chemotherapy-induced peripheral neuropathy) in the context of the proposed trial. In addition, the sponsor must determine how to design the trial to include the appropriate frequency of pain assessment in order to answer the trial question but not burden patients. Specific enrollment criteria, including level of pain, also need to be considered for pain palliation trials, and there is no firm definition of what constitutes "significant pain."

In addition to these issues, sponsors must also address analgesic use by patients within the trial. Analgesic use must be monitored, and it may be difficult to differentiate pain relief provided by the analgesic from pain relief provided by the cancer treatment. Additionally, it may be hard to adequately measure and compare pain severity and pain relief when patients enrolled in the trial are taking different baseline and rescue analgesics. Because of these issues, the sponsor will need to use a pain endpoint that includes assessments of both pain and analgesic use.

There are statistical considerations for including pain as an efficacy endpoint in oncology clinical trials as well. For example, a pain palliation trial must include a placebo arm, and blinding will most likely not be possible. Therefore, the sponsor will need to find or develop strategies to minimize unblinding in palliation trials. The sponsor will also need to find strategies to minimize missing data, particularly when data are self-reported.

Potential Scenarios for Adding Pain Metrics to Chemotherapy Clinical Trials

In order to explore specific examples of how pain metrics could be introduced into a clinical trial and how those

metrics could serve as decision-making criteria for the regulatory approval process, we present here 3 hypothetical clinical trial scenarios in which changes in pain or use of analgesics might be an outcome. In 2 of the scenarios, pain progression or palliation are assessed as secondary outcomes in a clinical trial of a new chemical entity, whereas in the third scenario pain palliation is a primary outcome for a new agent designed to reduce pain when the agent is added to an approved, second-line therapeutic. For these scenarios, metastatic castration-resistant prostate cancer (CRPC) is used as an example because large numbers of CRPC patients have significant pain for long periods of time (21). In addition, pain has been used in the past as a trial outcome for CRPC patients, and some trials with this patient population have used pain relief as a primary endpoint (22, 23). Although CRPC is used as an example here, these scenarios can be generalized to other cancer types. The design and measurement challenges may be addressed differently depending on the scenario. These scenarios are not intended to reflect regulatory thinking.

Case 1: Pain progression

In this scenario, a chemotherapeutic agent that may prevent pain progression in addition to treating HRPC is being tested relative to placebo in chemotherapy-naïve patients. This blinded, randomized trial will enroll patients with the following pain medication use profile: patients who have received no more than 1 day of opioids in the previous 14 days, or patients who have received no more than 6 days of nonopioids in the prior 14 days. Presumably, these are patients whose pain required episodic rather than more continuous treatment.

This trial could use a patient-reported outcome assessment with a 0-to-10 numerical rating scale. Data collection would occur daily for 4 weeks and every 12 weeks thereafter until disease progression is confirmed, and subsequent analysis will attempt to determine if a single daily pain assessment is representative of the pain experienced by patients. The time to pain progression in this scenario is defined as an increase in the worst daily pain of more than 2 points as measured by the numerical rating scale, by the initiation of opioid analgesic use in those patients who had not taken opioids for cancer-related pain at the study's initiation, an increase in opioid use to more than 3 days over a 14-day period in patients who had used opioids as needed prior to the study, or the start of bone-directed radiotherapy for pain palliation. The time to pain progression will serve as a secondary outcome for the purposes of seeking regulatory approval for this new agent.

Case 2: Pain palliation

This scenario adds pain metrics to a clinical trial being run on a second-line chemotherapeutic agent in combination with prednisone in patients with hormone-refractory prostate cancer (HRPC) who have experienced failure of taxane-based therapy. While overall survival will

be the primary endpoint, pain progression and pain response will be important secondary endpoints. This trial is designed as a randomized, open-label multicenter study with one arm consisting of the new agent combined with prednisone and the other arm consisting of mitoxanthrone and prednisone. The patient population will have experienced documented disease progression during or within 6 months after prior hormone therapy and taxane therapy.

In this trial, pain and neuropathy might be assessed using the MPQ, which measures important neurosensory symptoms that patients might not describe as pain, such as numbness, as well as pain severity, and records analgesic use quantified as an analgesic score derived from a patient-kept analgesic diary. Pain will be assessed prior to every treatment cycle and at the end of the study with the goal of determining if pain and analgesic use assessment should be part of the inclusion criteria for the study.

Case 3: Pain palliation with product add-on

The third scenario is designed to use pain metrics to assess the efficacy of a medication designed to ameliorate pain in combination with an approved chemotherapeutic. In this trial, patients with stable baseline pain and analgesic use who have relapsed after first-line therapy will be randomized to receive second-line therapy in combination with either the new pain palliation drug candidate or placebo. In this trial, the primary endpoint will be the extent of permanent pain palliation as measured using a combination of the BPI short form (BPI-SF) and an analgesic log. Secondary endpoints will assess whether patients receiving drug, as opposed to placebo, have a longer time to pain progression or have less pain-induced interference with their ability to walk, work, and sleep.

This study will attempt to answer a number of questions relating to pain metrics, including how to define minimum, maximum, and stable pain, and how to define stable analgesic use in the context of which analgesics are used, such as nonsteroidal anti-inflammatory drugs or long-acting opioids. This scenario also calls for determining the optimal frequency for pain assessment and quantifying the degree and duration of pain reduction and analgesic use that is clinically meaningful.

Conclusions and Next Steps

Cancer-related pain is arguably the physical ailment most feared by cancer patients (24, 25). Yet while clinical trials designed to assess the efficacy of new therapies for cancer include a variety of measures to assess a patient's physical response to therapy, these trials often do not include pain as either a primary or secondary outcome. Furthermore, clinical trials in oncology often fail to assess other symptoms or aspects of quality of life. Especially with patients who have more advanced disease, simple PRO measures of additional symptoms, such as fatigue, sleep disturbance,

gastrointestinal function, and mood impairment, add significantly to what patients and providers can expect of treatments (26).

As discussed in the PRO Guidance, PRO measures of symptom reduction can be direct indicators of treatment benefit, but barriers still exist to including pain endpoints in trials. In addition to the methodologic challenges discussed above, sponsors face logistical challenges in measuring pain in oncology trials. There is a high degree of uncertainty regarding what pain measurement endpoints the FDA will accept and what changes they will find clinically meaningful. This level of uncertainty, coupled with the expense associated with the measurement of pain in clinical trials, can make sponsors reluctant to measure pain palliation or prevention in oncology. Increased dialogue between the FDA and sponsors is recommended early in product development to plan the most efficient path forward for PRO measurement. The development of an oncology-specific pain-measurement guidance that details the standards for trial design, the number of trials required to incorporate pain measurements into labels, the pain instruments that FDA will

accept, and standards for statistical analysis, as well as other methodologic issues, would greatly benefit the cancer community. Such a guidance would facilitate the incorporation of pain relief into oncology trials with the ultimate result of cancer patients not only living longer but experiencing a higher quality of life.

Disclosure of Potential Conflicts of Interest

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