

The Measurement of Pain from Metastatic Bone Disease: Capturing the Patient's Experience

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Abstract Pain is prevalent for large numbers of patients with metastatic cancer, and this pain is often due to bone metastases. Despite the availability of effective pain treatments and various pain management guidelines, multiple studies document the undertreatment of pain in patients with cancer. The most frequently identified barriers to appropriate pain management are physician underestimation of the patient's pain, inadequate pain assessment, and patient reluctance to report pain. A first step toward reducing inadequate pain control in clinical practice is adequate assessment of cancer pain using validated pain measurement instruments. Using treatment for bone pain as an example, we discuss how patient satisfaction measures and self-report measures of pain and other symptoms, symptom interference with patient function, and related adverse effects can be combined with appropriate trial design to provide the information needed to choose the best possible treatment for bone pain. Symptom assessment needs to be done via standardized questionnaires, administered at appropriate times during the trial. The Brief Pain Inventory uses 11-point numerical rating scales to measure both pain severity and the resulting functional interference caused by pain. These severity and interference ratings can be further categorized as mild, moderate, or severe, as required to implement most pain management guidelines and define outcome expectations for clinical trials. Consistent pain measurement and standardized recording of analgesic use across clinical trials would enhance comparability and increase the chances that treatment decisions for management of bone pain could be evidence based. These and other considerations in the design of clinical trials are discussed.

Pain is prevalent for large numbers of patients with cancer (1–5). Pain is not limited to late-stage disease; it affects many patients earlier and intermittently during their disease. Although the pain that arises in late-stage cancer typically has multiple causes, including somatic, visceral, or neuropathic origins, bone destruction has been identified as a major cause of pain in 70% of patients with metastatic or recurrent disease (1) and up to 80% of patients with advanced breast or prostate cancer (6). Between 60% and 80% of patients with recurrent or metastatic cancer will need treatment for their pain (1).

Numerous guidelines for the management of cancer pain have been endorsed by governmental organizations, professional associations, and the WHO. Research studies evaluating the WHO guidelines for cancer pain relief (7, 8) indicate that most patients obtain good pain relief when the WHO protocol for oral analgesic medications is followed (9). Other pain management therapies can provide pain control when oral analgesics are not effective. Especially when pain is caused by

bone disease, a wide variety of nonanalgesic therapies are available to mechanistically treat the source of pain. These treatments include radiation therapy, radionuclides, interventional methods of stabilization (such as kyphoplasty and orthopedic intervention), and the use of bisphosphonates for regularization of bone metabolism.

Despite the availability of effective pain treatments, multiple studies document undertreatment of pain in cancer patients (1, 10, 11). A study completed by the Eastern Cooperative Oncology Group surveyed more than 1,300 outpatients with recurrent or metastatic cancer (1). Sixty-seven percent of the patients had pain or were being treated for pain with daily analgesics. Among the patients with pain, 42% were prescribed analgesics that were less potent than those recommended by WHO guidelines or other cancer pain management guidelines. In a more recent study, 60% of patients in a multicenter clinical trial did not receive analgesics of the potency recommended by current guidelines. There was considerable variation among the study sites, with inadequate treatment ranging from 15% to 67% (12).

Pain must be appreciated to be adequately treated, and pain of which the severity is underestimated will not be treated aggressively enough. One of the most important predictors of undertreatment of pain in the Eastern Cooperative Oncology Group study was the discrepancy between patient and physician in their estimates of pain intensity (1). Physicians typically underestimate the level of pain that patients reported on standardized questionnaires, especially when pain is severe. Inadequate pain assessment is a critical barrier to good pain control for patients with cancer. In another Eastern Cooperative

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Oncology Group survey, physicians completed a survey designed to assess their knowledge and practice of cancer pain management (4). The physicians ranked a list of potential barriers to pain management to indicate those that hindered pain treatment in their practice settings. The most frequently identified barrier was inadequate pain assessment: 76% of the physicians rated poor assessment as one of the top four barriers to good pain management. Patient reluctance to report pain, closely related to inadequate assessment, was the next most frequently cited barrier. A more recent survey of physicians in the Radiation Therapy Oncology Group found that poor pain assessment and patient reluctance to report pain continue to be identified as top barriers to optimal pain management (13). A first step toward reducing inadequate pain control in clinical practice is adequate assessment of cancer pain using validated pain measurement instruments.

What Needs to be Assessed in Pain Clinical Trials

Pain measurement issues are critical in evaluating and comparing methods of pain treatment in clinical trials, allowing an evidence-based approach to the selection of the most effective approach to the management of the individual patient. When pain reduction is the primary outcome of the trial, the choice of appropriate assessment tools and design of the study is of utmost importance.

The need for common assessment approaches is well illustrated by the need to make comparisons among the multiple methods that can be used to treat bone pain. The ideal treatment for bone pain would provide good pain relief, be free of treatment-related adverse effects, reduce pain-related interference with activities and other pain-related symptoms (impaired mood, disturbed sleep, increased fatigue), act quickly (especially important for patients with a short life span), have a durable effect, reduce the need for opioid analgesics (because of the adverse effects of these drugs), and be reasonably priced. Finally, the patient's satisfaction with the treatment is an important consideration.

Of course, no treatment methods currently available can satisfy all these criteria. However, these criteria outline what types of information might be expected from a clinical trial (or more probably a set of clinical trials) of a treatment for bone pain, and the remainder of this article will discuss how self-report measures of pain and other symptoms, symptom interference with patient function, and related adverse effects can be combined with appropriate trial design to provide this type of information.

A trial with pain reduction as an outcome has several recognized obstacles to overcome. First, the severity of pain and the degree of pain relief can only be obtained by subjective report obtained from the patient, as opposed to more "objective" findings such as reduction of skeletal events (a common end point in bisphosphonate trials). Even so, patient self-report has often been discounted as too variable and too affected by personality factors to be used as an outcome measure. Second, pain can be affected by many other factors besides the treatment under examination. A patient with bone metastases, for example, is liable to have pain from preexisting comorbidities (e.g., arthritis) or other aspects of their cancer or treatment (e.g., therapy-related neuropathic pain). Pain may also arise from destruction or distortion of soft tissue in areas

adjacent to the bone lesion. It is often impossible for patients to differentiate pains coming from multiple sources. Every attempt to verify the mechanistic basis of the pain needs to be made. Finally, pain related to bone destruction is liable to be aggravated by activity level and to be at its worst only when challenged by activity.

Despite these obstacles, those whose major focus is to treat pain have become comfortable with self-report from analgesic studies as the primary clinical trial outcome variable. Those whose focus is treatment of cancer, however, are less likely to be comfortable with "pain" as a primary outcome.

Measuring Pain and Its Impact: Self-report Measures

Many adults with mild cancer-related pain function effectively with pain that does not seriously impair their daily activities. As pain severity increases, however, it typically disrupts many areas of life. Pain severity is thus the dominant factor determining the effects of pain on the patient and the urgency of the need for treatment. Accordingly, pain treatment guidelines often use a determination of pain severity as the primary item of information in specifying treatment (8, 14–16).

Pain assessment needs to be done via validated pain questionnaires administered at appropriate times during the trial. Although several measures of pain and its relief are available for clinical trial use, we will focus here on the Brief Pain Inventory (BPI; ref. 17), a short scale that measures both pain severity and functional interference caused by pain. The BPI is probably the most widely used pain questionnaire in trials that examine agents for the relief of both cancer pain and noncancer pain.

The BPI uses a numerical rating scale to capture both the severity of pain and the interference of pain with function (Fig. 1). Patients rate the severity of their pain at its "worst," "least," and "average" in the last week using an 11-point numerical rating scale with anchors of "no pain" and "pain as bad as you can imagine." They are also asked to rate their pain "now," at the time they complete the BPI. Using an 11-point numerical rating scale with anchors of "does not interfere" and "completely interferes," the BPI similarly assesses to what extent pain interferes with mood, walking, general activity, work, relations with others, sleep, and enjoyment of life. The BPI also asks patients to mark the location of their pain on a body drawing and includes other questions about pain treatment and the extent of pain relief. The BPI provides a list of descriptors to help the patient describe pain quality. A short form of the BPI is frequently used for regular pain assessment in clinical and research settings. The BPI short form uses a time reference of "in the last 24 hours" rather than "in the last week."

Levels of pain intensity. Categorizing a pain severity rating as "mild," "moderate," or "severe" is a crucial step in the assessment process and determines the urgency of treatment. The guidelines for cancer pain treatment from the WHO, the American Pain Society, the Agency for Health Care Policy and Research, and the National Comprehensive Cancer Network all recommend varying treatment approaches for these three categories of pain severity. The recent National Comprehensive Cancer Network pain management guidelines include a treatment algorithm that is based on the categorization of pain

Date: _____

Study ID: _____

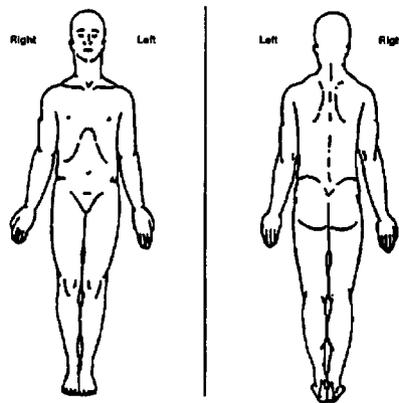
Hospital: _____

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain As Bad As You Can Imagine

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Fig. 1. The Brief Pain Inventory (short form). Copyright 1991, Charles S. Cleeland.

Date: _____

Study ID: _____

Hospital: _____

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
<input type="checkbox"/>										
No Relief										Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Does Not Interfere										Completely Interferes

B. Mood

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Does Not Interfere										Completely Interferes

C. Walking ability

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Does Not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Does Not Interfere										Completely Interferes

E. Relations with other people

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Does Not Interfere										Completely Interferes

F. Sleep

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Does Not Interfere										Completely Interferes

G. Enjoyment of life

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Does Not Interfere										Completely Interferes

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Fig. 1 continued.

as mild, moderate, or severe (14). For example, pain rated as severe is considered a pain emergency that mandates rapid titration of a short-acting opioid, along with prevention of common adverse effects of opioids and psychosocial support.

Thus, the implementation of cancer pain treatment guidelines necessitates the categorization of pain intensity. Mild, moderate, and severe pain can be defined as ranges of patient responses to a numerical rating of pain at its worst on an 11-point scale. The ranges for each category of pain severity are based on the degree of interference with function associated with each category. Both pain severity and pain interference can be obtained from the BPI (18).

Mild pain (1-4 worst pain) will most often call for a mild analgesic (acetaminophen or a nonsteroidal anti-inflammatory medication). Mild pain typically causes the least interference with function. Studies have shown that patients with mild pain, in terms of functional and affective interference, are more like patients with no pain than those with moderate or severe pain, both of which substantially disrupt function (18, 19). Because pain from bone metastases is rarely totally eliminated without significant adverse effects from opioids, especially at rest (20), reducing pain to the mild range may be a reasonable target for treatment or for a clinical trial. For instance, patients who end a trial with pain of ≤ 4 or ≤ 3 might be classified as trial "responders," allowing for a responder analysis of the data (12). Moderate pain (5-6 worst pain) and severe pain (7-10 worst pain) mandate aggressive analgesic intervention.

To fully understand the effect of a treatment for pain, additional measures are often added at certain points throughout the trial. A recent consensus on analgesic trial measurement suggested several measurement domains that need to be considered for inclusion in the trial (21). In addition to reported reduction in pain severity and improvement in pain relief, it is important to measure the effect of the treatment on other symptoms, which may increase if they are adverse effects of the treatment or decrease if they are linked to pain. Along with standard ratings of adverse events, a multiple symptom rating scale, such as the Rotterdam Symptom Checklist (22) or the M.D. Anderson Symptom Inventory (23), might be used for this purpose. An improvement in physical function might be expected with treatment and should be reflected in a decrease in the ratings of the interference items of the BPI. Some trials may include a specific measure of affective status, such as one of the versions of the Profile of Mood States (24).

Patient satisfaction scales. Recent recommendations for the conduct of clinical trials with pain as an outcome include having measures of both patient satisfaction and patient disposition (e.g., do the patients wish to continue treatment after the trial is ended?). Satisfaction scales are usually one or two items that have participants rate their satisfaction with the treatment. Satisfaction questionnaires may ask patients to rate how satisfied they are with their pain treatment on a five-point scale from "very satisfied" (1) to "very dissatisfied" (5; ref. 25). The scores are then classified into "adequate" (1-3) or "inadequate" (4-5) treatment. Alternatively, patients may be asked to indicate whether they believed the treatment improved their pain by rating their pain as "the same," "better," or "worse." The follow-up question relates to the first answer: if better, then how much better, "a lot," "some," or "a little"; or if worse, then how much worse, "much worse," "some," or "a little." Disposition can be covered by the end-of-trial

question, "If possible, would you continue taking this medication for pain relief?"

Despite a growing consensus that global measures of treatment satisfaction should be included in clinical trials (21, 26, 27), little research that clarifies the meaning or validity of such measures has been done. Jensen et al. (28) reported the validity of global satisfaction ratings as assessing something other than pain intensity or change in pain intensity and therefore supported the use of such measures, as recommended by experts in the field of pain assessment in clinical trials (21). The predictors of satisfaction in the context of an analgesia clinical trial included treatment regimen, age, worst pain experienced, pain interference with functioning, morphine equivalent dose taken, and number of opioid-related symptoms (e.g., nausea and fatigue). All of these were associated with satisfaction with the overall performance of the study medications at day 1. These findings indicate that the study participants considered more than one factor when estimating their satisfaction with the study medications and that the changes produced by the treatment (e.g., decreased pain and opioid-related symptoms) mediated, in part, the effects of treatment on treatment satisfaction.

Concurrent Symptoms and Treatment Adverse Effects

Cancer patients with pain usually have symptoms other than pain that need to be assessed and treated. The disease itself often produces fatigue, weakness, cachexia, and cognitive deficits. Cancer treatments frequently cause nausea, vomiting, fatigue, and other physical, cognitive, or affective symptoms. The negative side effects of analgesic medications may include constipation, nausea, fatigue, and sedation. Common symptoms of cancer and cancer treatment significantly impair the daily function and quality of life of patients. Thus, it is important to assess symptoms routinely and develop appropriate treatment plans.

A checklist of potential concurrent symptoms, such as the M.D. Anderson Symptom Inventory, can be used to assess the presence and intensity of symptoms (23). The M.D. Anderson Symptom Inventory consists of a core list of symptoms that are common across all cancer diagnoses and treatments, plus modules of additional symptoms that can be included for patients who are at risk for symptoms not highly prevalent in oncology patients in general (e.g., because of a particular cancer or treatment regimen). The core M.D. Anderson Symptom Inventory consists of 13 symptoms: pain, fatigue, nausea, sleep disturbance, emotional distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling. Each symptom is rated on a 11-point scale, with 0 being "not present" and 10 being "as bad as you can imagine."

Innovative Trends in Pain Assessment

Recent developments in computer and communications technology offer new opportunities for the assessment of patients' pain and other symptoms. Handheld computers and other electronic recording devices have been used to assess pain within patients' home and work environments (29). Given that memory for pain and other symptoms is often poor, the real-time assessment of symptoms can provide accurate data

about symptom patterns and changes over time. However, not all patients are comfortable using handheld computers or other small automated devices. In addition, patients have to remember to use the devices every day and to transmit the symptom data to their health care providers. The development of telephone interactive voice response technology provides an option for frequent sampling of a patient's pain and other symptoms. With this technology, the patient receives a computer-generated telephone call and makes responses using the telephone keypad. Electronically administered questionnaires may cut down on missing data, a major problem with the frequent assessments that are required, especially early in the trial when latency to effect is important to capture.

Trial Design: Important Considerations

A recent review by the Cochrane Database (30) examined clinical trials of bisphosphonates for pain relief from bony metastases. Thirty randomized controlled studies were evaluated. For each of several outcomes, few studies had usable data. When pain relief was measured (in only eight studies), treatment groups showed benefit at 4 and 8 weeks. Although there seemed to be ample evidence to support the effectiveness of bisphosphonates in providing some pain relief for bone metastases, there was insufficient evidence to recommend these agents for immediate effect or as first-line therapy. Problems that made it difficult to compare trials included inconsistency in pain measurement and its timing and nonstandardized recording of analgesic use. Although it is not mentioned in this review, agreement about what constitutes "bone pain" would also be extremely useful. Consistency across trials would obviously enhance comparability and increase the chances that treatment decisions could be evidence based.

When pain is the primary outcome variable for a clinical trial, either between the agent under investigation or the agent and a comparator, several design features need to be considered. Once the instruments for assessment are determined, rules need to be established a priori that define the success or failure of the trial. Often, a regulatory authority such as the Federal Drug Administration will be involved in an agreement about the adequacy of these rules. In very large trials, marginal group differences may be statistically significant, although these differences may be of little or no clinical significance for patients. It is important to justify what a minimally important difference will be in the context of the trial. There are several methods of setting the minimally important difference, which are beyond the scope of this presentation, but one rule of thumb is that the difference between groups on pain severity at the end of trial should be in the range of half a SD of the pain scores of both groups at trial baseline (31). Alternatively, the minimally important difference might be set by change seen in prior trials with the same or similar painful conditions. Another alternative is to define a "responder" to the trial, with a responder being defined as having achieved a prespecified reduction in pain and the final test being the proportion of responders in each arm of the trial. With bone pain from cancer, few treatments will provide total relief or totally eliminate the need for analgesics, so the definition of a "responder" needs to be set realistically.

Some trials have used a composite end point, such as a specified reduction in pain coupled with a reduction in opioid

analgesics. There are a few examples of successful trials using such end points, but they need to be approached with caution; often, as reviewed earlier, there is substantial practice-to-practice variation in prescription of analgesics, making stabilization or reduction of analgesics as an end point problematic.

Another approach to trials where bone pain is an outcome is similar to studies that use skeletal-related events as an outcome. Patients with mild or no current bone pain, but who are at risk for developing bone pain, are enrolled. Stable bone pain (e.g., two or more assessments where moderate to severe pain is present) becomes an "event" defining "failure" of the agent for preventing bone pain. This design allows broader recruitment of patients and provides information about how long patients might be expected to be free of significant bone pain if they are treated.

Finally, timing of assessments is critical, especially when testing methods for the reduction of bone pain. Many of these patients have limited survival, and thus rapidity of onset is a major positive factor for a given treatment. Although not all measures need to be given frequently, daily use of pain severity scales and estimates of pain relief (in percentages), whether obtained by calls from research nurses, pain diaries, or one of the more recent electronic methods, can capture the onset of pain relief and help determine when the maximal effect of the treatment has been achieved.

Open Discussion

Dr. Suva: Are there any data across patients, for example, patients who have bone pain from cancer versus other skeletal abnormalities?

Dr. Cleeland: Yes, those comparisons have been made. As you might expect, you are going to get significantly more interference from pain from the bone metastasis patients compared with a group with moderate to severe osteoarthritis.

Dr. Clohisy: The same thing is true in mice. If you give them different types of pain and then you look at the amount of narcotics that they need to get the same level of function, bone pain requires many more narcotics than arthritis pain or neuropathic pain.

Dr. Smith: If you were designing the next bisphosphonate trial of the bone-targeted therapy trials, is it preferable to have an event-driven analysis, as was done in many of the previous trials, or to take patients with pain and look at change in pain?

Dr. Cleeland: It's a lot easier to do the latter. I've been doing these event-related trials for a long time; you need large numbers of patients, and you have to wait a long time. The regulators, at least in the United States, are more interested in symptom-related primary outcomes as opposed to skeletal events. It's important to have pain as a primary outcome.

Dr. Bruland: Are you suggesting that targeting analgesics to bone might be a way of improving their effect by a selective action on the neurons themselves?

Dr. Cleeland: Yes, absolutely.

Dr. Cook: You mentioned the difficulty with the mortality in estimating the pain over time. This is more of a problem the sicker the patients are. It's difficult to interpret those means after, for example, 2 years of follow-up when you have a potentially small subset.

Dr. Cleeland: It's often difficult to interpret after 6 months of follow-up. One of the problems has been regulatory, because

you have to show a sustained benefit. That's a battle that has to be fought with the Food and Drug Administration.

Dr. Cook: One strategy that people use in quality-of-life analyses is to give a utility to a particular score on a quality-of-life scale, accumulate those over time, and look at quality-adjusted life-years. Have you thought of that approach in the context of pain analysis?

Dr. Cleeland: Yes, we have. We work under a larger umbrella, which I call symptom burden, and we are trying to translate symptom burden into something like quality-adjusted life-years.

Dr. Weilbaecher: If we are just focusing on pain and not treating the cancer, we are missing the bigger picture. By using better bone pain parameters, could we look at the impact of these ancillary therapies on actual disease progression?

Dr. Cleeland: Yes, and symptoms as well. One of my soapboxes is to attach very simple multiple-symptom scales to

treatment protocols so that we gather data. Bisphosphonates, for example, are multi-action agents with inflammatory components. Why aren't we tracking the symptoms of patients taking bisphosphonates so that we're learning something?

Dr. Coleman: The issue of standard response criteria is extremely important, and I wonder what it's going to take to get those defined. We have had the Unio Internationale Contra Cancrum criteria for 30 years. Why can't that happen for pain?

Dr. Cleeland: We're getting close.

Dr. Coleman: We want them to be simple.

Dr. Cleeland: We want them to be very simple. There is a disenchantment with this notion of global quality of life because it has surplus meaning. We are trying to use the term "symptom burden." However, it is difficult to get people to agree on what a reduction in symptom burden is, but not impossible, because we have done it with pain.

References

1. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med* 1994;330:592–6.
2. Cleeland CS, Gonin R, Baez L, Loehrer P, Pandya KJ. Pain and treatment of pain in minority patients with cancer. The Eastern Cooperative Oncology Group Minority Outpatient Pain Study. *Ann Intern Med* 1997;127:813–6.
3. Cleeland CS. Undertreatment of cancer pain in elderly patients. *JAMA* 1998;279:1914–5.
4. von Roenn JH, Cleeland CS, Gonin R, Hatfield AK, Pandya KJ. Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. *Ann Intern Med* 1993;119:121–6.
5. Portenoy RK, Thaler HT, Kornblith AB, et al. Symptom prevalence, characteristics and distress in a cancer population. *Qual Life Res* 1994;3:183–9.
6. Janjan N. Bone metastases: approaches to management. *Semin Oncol* 2001;28:28–34.
7. World Health Organization. *Cancer Pain Relief*. Geneva: World Health Organization; 1986.
8. World Health Organization. *Cancer Pain Relief and Palliative Care*. Geneva: World Health Organization; 1996.
9. Grond S, Radbruch L, Meuser T, Sabatowski R, Loick G, Lehmann KA. Assessment and treatment of neuropathic cancer pain following WHO guidelines. *Pain* 1999;79:15–20.
10. Vainio A, Auvinen A. Prevalence of symptoms among patients with advanced cancer: an international collaborative study. *J Pain Symptom Manage* 1996;12:3–10.
11. Zenz M, Zenz T, Tryba M, Strumpf M. Severe undertreatment of cancer pain: a 3-year survey of the German situation. *J Pain Symptom Manage* 1995;10:187–91.
12. Cleeland CS, Portenoy RK, Rue M, et al. Does an oral analgesic protocol improve pain control for patients with cancer? An intergroup study coordinated by the Eastern Cooperative Oncology Group. *Ann Oncol* 2005;16:972–80.
13. Cleeland CS, Janjan NA, Scott CB, Seiferheld WF, Curran WJ. Cancer pain management by radiotherapists: a survey of Radiation Therapy Oncology Group physicians. *Int J Radiat Oncol Biol Phys* 2000;47:203–8.
14. Benedetti C, Brock C, Cleeland C, et al. NCCN practice guidelines for cancer pain. *Oncology (Williston Park)* 2000;14:135–50.
15. Jacox A, Carr DB, Payne R, et al. Management of cancer pain: adults. *Cancer Pain Guideline Panel. Agency for Health Care Policy and Research. Am Fam Physician* 1994;49:1853–68.
16. American Pain Society. *Principles of analgesic use in the treatment of acute pain and cancer pain*. 5th ed. Glenview (IL): American Pain Society; 2003.
17. Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, editors. *Issues in pain measurement*. New York: Raven Press; 1989. p. 391–403.
18. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain* 1995;61:277–84.
19. Wang XS, Cleeland CS, Mendoza TR, et al. The effects of pain severity on health-related quality of life: a study of Chinese cancer patients. *Cancer* 1999;86:1848–55.
20. Mercadante S. Malignant bone pain: pathophysiology and treatment. *Pain* 1997;69:1–18.
21. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003;106:337–45.
22. de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990;62:1034–8.
23. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer* 2000;89:1634–46.
24. McNair DM, Lorr M, Droppleman LF. *Manual for the Profile of Mood States*. San Diego: Educational and Industrial Testing Service; 1992.
25. Ware JE, Jr., Snyder MK, Wright WR, Davies AR. Defining and measuring patient satisfaction with medical care. *Eval Program Plann* 1983;6:247–63.
26. Wright JG. Outcomes research: what to measure. *World J Surg* 1999;23:1224–6.
27. Wu CL, Naqibuddin M, Fleisher LA. Measurement of patient satisfaction as an outcome of regional anesthesia and analgesia: a systematic review. *Reg Anesth Pain Med* 2001;26:196–208.
28. Jensen MP, Mendoza T, Hanna DB, Chen C, Cleeland CS. The analgesic effects that underlie patient satisfaction with treatment. *Pain* 2004;110:480–7.
29. Lewis B, Lewis D, Cumming G. Frequent measurement of chronic pain: an electronic diary and empirical findings. *Pain* 1995;60:341–7.
30. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database Syst Rev* 2002;2:CD002068.
31. Norman GR, Sloan JA, Wyrrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003;41:582–92.

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