

Assessment of Cancer-Related Neuropathy and Neuropathic Pain

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Key Words. Cancer • Neuropathy • Pain • Chemotherapy-induced neuropathy

Disclosures: Charles S. Cleeland: None; John T. Farrar: None; Frederick Hausheer: *Employment/leadership position:* BioNumerik Pharmaceuticals, KI Pharmaceuticals; *Intellectual property rights/inventor/patent holder:* BioNumerik Pharmaceuticals; *Ownership interest:* BioNumerik Pharmaceuticals..

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

ABSTRACT

Cancer-related neuropathic pain syndromes are common and serious complications of a patient's primary malignancy or its treatment, whether by surgery, radiation, or chemotherapy. They may compromise the patient's quality of life as well as their ability to receive effective treatment. In many patients, there may be more than one coexistent neuropathic pain syndrome, posing a diagnostic dilemma that, if unresolved, may result in the institution of therapies that are of limited scope or not targeted at the primary underlying pathophysiology. There is no single adequate diagnostic method that has been established to reliably diagnose or follow patients with cancer-related neuropathic pain

syndromes. Clinical assessment of cancer-related neuropathic pain poses some important challenges diagnostically as well as in defining a clear and reliable endpoint assessment in controlled clinical trials. Many different approaches have been applied to the development of assessment or diagnostic tools. Careful review of these methods has been helpful in developing a clearer vision for the future design and refinement of more reliable tools, and more importantly, validation of the clinical utility as well as the reliability of such tools when employed as endpoints in clinical trials focused on prevention, mitigation, or treatment of cancer neuropathic pain. *The Oncologist* 2010;15(suppl 2):13–18

INTRODUCTION

Neuropathy is an adverse change in sensory and/or motor function caused by toxic or physical nerve damage processes. Cancer-related neuropathy, whether a result of nerve damage produced by the tumor or by treatment, is a major adverse outcome for patients with cancer. Cancer-related neuropathy poses barriers to recovery of function

and treatment tolerability, and is a major and frequent cause of symptom distress in affected patients. In the case of chemotherapy-induced neuropathic pain, it can ultimately affect our ability to successfully treat the cancer itself. At times, neuropathy can produce high levels of pain and interfere with activities of daily living, but neuropathy can also cause severe sensorimotor dysfunction not identified

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by the patient as painful. Although the underlying pathophysiology is different, distinguishing neuropathic pain from nociceptive pain and other symptoms and signs of neuropathy is by no means a straightforward process.

Development of a more reliable systematic diagnostic assessment of cancer-related neuropathy is a critical need that will facilitate our ability to develop and evaluate much-needed targeted therapies. There is as yet no U.S. Food and Drug Administration (FDA)-approved treatment specifically for cancer-related neuropathy, and most agents that have been developed for neuropathic pain have been studied in patients with postherpetic neuralgia or peripheral diabetic neuropathy. Although the range of therapies currently in trials for cancer-related neuropathic pain confirms that there is no shortage of potential targets, the systematic evaluation of new therapies will require concerted, well-designed, multicenter trials using assessment methods that are standardized, validated, and robust enough to be used across many sites with minimal training of research staff. The diagnostic assessment of cancer-related neuropathic pain in clinical research studies must also be convenient, reliable, and practical for patients, who are the most reliable source of information on the efficacy and safety of any new medical intervention. We need to deploy and develop measures that rely on patient-reported outcomes—the patient's perception of the sensory and motor changes that they are experiencing.

In this article, we briefly outline the currently accepted measures of neuropathy and neuropathic pain. We discuss their commonalities and limitations, and we offer our thoughts on improvements to our current assessment strategies.

ASSESSMENT OF NEUROPATHIC PAIN

Pain, regardless of etiology, is ultimately expressed through processing in the brain that leads to a perception of the pain and results in a response. Nociceptive pain involves normal physiologic pain pathways, whereas neuropathic pain is thought to involve a dysfunction of the nervous system. And although we attempt to differentiate between nociceptive and neuropathic pain, we observe that these types of pain often coexist.

Given the common final pathway for pain perception, there are several types of pain measure currently used in the evaluation of neuropathic pain that are also used in nociceptive pain. These include pain intensity and frequency, the extent to which the pain interferes with activities, the physical and emotional distress experienced, and relief or global change experienced with time or medical intervention. The scales we use include word ratings and changes, numeric ratings, visual analogs, color, and graphical representa-

tions, all of which provide somewhat different information. There are a variety of methods for collecting data that take advantage of advancing technology, including pen-and-paper forms that are computer readable, voice-recognition software, and devices such as personal digital assistants. These data can be analyzed in multiple ways depending on the question to be answered. Summary data can include final pain levels, changes in pain scores as raw or percent pain scores, and analyses of responders.

Measures of pain include those that discriminate among types of pain and those that evaluate the change in pain over time. Once the type of pain has been established, the pain can be evaluated using questionnaires that are not specific to neuropathic pain, such as the McGill Pain Questionnaire [1] and the Brief Pain Inventory [2]. Both these measures have been shown to be sensitive to change in large trials in which the target population had pain identified as neuropathic. But these scales do not capture all the qualities of neuropathic pain.

Several other scales have been developed to try to differentiate neuropathic pain from nociceptive pain. Examples include the Leeds Assessment of Neuropathic pain [3], Pain ID [4], the Neuropathic Pain Symptom Inventory [5], the Neuropathic Trial Symptom Scale [6], and the Neuropathic Pain Scale [7]. Some of these scales include data from a physician examination of the patient. This component makes them more difficult to apply in a clinical trial setting. However, looking across several of these systems, a set of common descriptors emerges, including the sensations of pins and needles, heat or burning, impaired temperature sensitivity, numbness, and electric shock–like sensations; whether the pain becomes worse with touch; and whether the pain is present in the joints [8].

Ultimately, however, the choices we make across all these dimensions must serve the goal of making a diagnosis, deciding on a treatment, and following the course of treatment. Nociceptive and neuropathic pain may have different etiologies and require different interventions for effective therapy. Although differentiating these two components can be difficult, it is important that we make the effort, as can be illustrated with the example of breast cancer. With breast cancer, the causes of pain include surgical outcome, tumor spread, bony metastasis to the spine, and chemotherapy. The interplay of nociceptive and neuropathic is exemplified by a bony metastasis to the spine that causes local nociceptive pain and can push on a nerve, causing the shooting, tingling, numbing sensations that define neuropathic pain. The etiology of these symptoms dictates that the best treatment is to shrink the tumor with chemotherapy and to reduce the local nerve inflammation by the coadministration of potent corticosteroids. Treatment of

neuropathic pain caused by the administration of a chemotherapeutic agent requires a completely different strategy. Furthermore, several commonly used medications have been reported to produce peripheral neurotoxicity, and they may confound the diagnosis and management of patients who are subsequently treated with neurotoxic chemotherapy. In many cases, patients must endure a degree of neuropathic pain in order to receive the appropriate level of cancer treatment, or because it poses a diagnostic dilemma and the appropriate treatment for the pain is not clear. The inability to reliably diagnose and monitor neuropathic pain is clearly a large unmet medical need.

In order to properly clinically assess neuropathic pain, we need evidence that is diagnostically reliable (i.e., with high sensitivity and specificity), associated with either a well-characterized permanent or reversible pathologic insult to the patient's nervous system. The best approach to this assessment can be achieved through structured coalescence of neuropathic symptoms in questionnaires and evidence from an examination. Although we are aware of the potentially neurotoxic adverse events relating to the primary cancer, surgery, radiation, or chemotherapy, the symptoms remain largely subjective with few objective findings. The challenge is similar to that posed by the reliable assessment and quantification of the severity, frequency, and degree of patient symptoms and impairment resulting from nausea/emesis and depression by the use of carefully designed and validated patient questionnaires. When the exact cause is unclear, we can sometimes assess the patient's response to drugs like gabapentin, pregabalin, or duloxetine. Response to these agents suggests at least a component of neuropathic pain. We can also use quantitative electrophysiological techniques to assess neurologic dysfunction, which can help us infer that the patient has neuropathic pain. There are several different methods to measure potential nerve dysfunction, including nerve conduction and electromyography, quantitative sensory testing, skin biopsy for nerve ending staining, selective nerve root blocks, provocative nerve testing, routine imaging for etiology, and functional brain imaging. None of these have been validated in cancer pain and they are not in widespread use because of the need for physician expertise, special resources that may be limited to certain centers, or a lack of patient compliance (e.g., nerve conduction velocity [NCV]). None have been used as a primary endpoint assessment for neuropathic pain in adequate, well-controlled clinical trials to assess neuropathic pain in cancer. In addition, of the many neuropathic pain scales, only a few actually assess the location of the pain, which is an important neurological clue. Other important diagnostic clues include the frequency of the pain and whether it is spontaneous or in-

duced, and the character of the pain in terms of the patient's actual reported symptoms or interference with the activities of daily living.

ASSESSMENT OF CHEMOTHERAPY-INDUCED NEUROPATHY

With our continued improvement in the treatment of cancers, some of the side effects of the cancer therapy have become more common causes of chronic pain. Chemotherapy-induced peripheral neuropathy (CIPN) is a subset of the larger cancer-related neuropathic pain syndromes, and is perhaps one of the most well-studied areas [9]. CIPN is largely a subjective constellation of symptoms associated with anatomic distribution and some degree of functional impairment—of which pain is an essential part to characterize—that are reported by the patient to the physician. For CIPN, the major purposes of the assessment are threefold: (a) to make the diagnosis of CIPN and discern if there are any other coexisting neuropathic components, (b) to determine the severity of the patient's symptoms and their degree of functional impairment resulting from the CIPN component, and (c) to reliably measure the patient's response to a treatment intervention over time. The primary treatment of CIPN is to stop the neurotoxic treatment that has caused it and allow recovery of nerve function, if possible. This is a difficult decision for a patient who is responding to their cancer treatment yet is experiencing severe impairment in their quality of life as a result of CIPN.

A nonexhaustive initial search of the U.S. National Institutes of Health's clinical trials database, www.ClinicalTrials.gov, uncovered a list of compounds ranging from vitamins to newer biologics that are being investigated for the potential prevention and treatment of CIPN. Many are reported to be promising, but the prospect of evaluating such a list of candidates is challenging without better methods to more reliably diagnose and assess the response to treatment interventions. The question of assessment then becomes one of how we can effectively do clinical research on neuropathic pain in multi-institutional settings where we may have the opportunity to look at agents that will be either of protective benefit or treatment benefit to patients. We need to work on more innovations to address this problem; the major focus should be on developing a reliable, noninvasive, convenient, and easy to administer diagnostic test that reliably helps the physician to identify and quantify the presence and severity of CIPN, as well as reliably monitors the patient's response to any treatment intervention for CIPN, including controlled clinical trials.

Although quantitative tests of sensory and motor dysfunction are available, for example, the vibration perception threshold and NCV testing, they are not routinely used to make treatment decisions for CIPN for several reasons

[9]. First, no adequate controlled studies have been published using quantitative measurements as the primary endpoint for CIPN because a correlation between quantitative measurements and clinical symptoms has not been established. Patients have been observed to report symptoms earlier and as more or less severe than with these objective methods [10, 11]. Second, results reported in the medical literature demonstrate that these measurements cannot reliably diagnose, quantify, or monitor responsiveness to treatment for CIPN [12, 13]. Furthermore, neurophysiological measures such as NCV testing pose some major practical obstacles in a collaborative clinical trial because this testing has not been standardized and because of poor patient compliance as a result of the painful aspects of these invasive procedures. It is notable that insurers and the Centers for Medicare and Medicaid Services do not reimburse for these methods, largely because the diagnostic and therapeutic value have not been established.

Physician-based assessments that are widely used—including the National Cancer Institute Common Toxicity Criteria (NCI-CTC) neuropathy score, the World Health Organization guidelines, the Eastern Cooperative Oncology Group neuropathy scale, and Ajani scale—require patient cooperation and physician training. It is somewhat surprising that these are widely used and yet large interexaminer variations are reported in CIPN grading. One study, for example, found that two neurologists in the same institution examining the same patients could only agree on the assessment of seven of the 37 patients [14]. Careful examination of the individual items in these assessments highlights some of the imprecisions leading to varying conclusions. For example, it is unclear what is meant by “interfere with function but not interfere with activities in daily living (ADL)” when ADL is not even defined. Or, in the case of “decreased as compared to absent deep tendon reflexes, and which reflexes must be decreased or absent to be graded,” we cannot be certain whether the physician performed (or even knew to perform) reinforcement maneuvers to try to elicit such reflexes.

Although rating the severity and frequency of pain is critical, it is clear that additional information is required to completely assess clinical trials outcomes for neuropathy. In 2003, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) issued recommendations for evaluating neuropathic pain [15]. These include the severity of pain, physical and emotional functioning, ratings of improvement and satisfaction with treatment, symptoms and adverse effects, and the disposition of participants. To refine our endpoints, we also need better information about nonpain symptoms and functional impairment resulting from CIPN from prospective studies as well as completed trials. For example, pain intensity

scales do not usually capture hypersensitivity to cold, reduction in tactile sensation, loss of balance, or fine hand–eye coordination, which are clearly of great importance to patients. The current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Adult Cancer Pain (v.1.2009) [16] provide a more specific assessment quantifying intensity and characterizing the quality of pain. The NCCN guidelines also use patient-based pain intensity ratings (based on numerical and categorical scales) as well as a faces rating scale, and capture patient descriptions of pain characteristics (burning, itching, aching). The NCCN also recognizes that severe uncontrolled pain in a cancer patient is a medical emergency and should be evaluated promptly. In addition, the NCCN guidelines describe a comprehensive pain assessment regarding etiology, pathophysiology, and specific cancer pain syndromes, including neuropathic pain in cancer patients.

In order to develop a more reliable method for the assessment of CIPN in the clinic as well as for endpoint assessment of CIPN in clinical trials, several key factors must be addressed, in addition to the considerations described above: (a) key patient symptoms (numbness, paresthesias, dysesthesias, and pain) and severity of CIPN are subjective in nature, which is clinically analogous to the symptoms of depression, pain, or nausea (i.e., there is no laboratory or physical examination test that can grade their severity, other than history and observation); (b) a primary neuroprotection endpoint in a clinical study must be clinically meaningful and quantified by a reliable methodology; and (c) the diagnostic method employed must be sufficiently sensitive and specific and able to reliably detect the presence of CIPN as well as detect increased or decreased grades of CIPN. The use of diagnostic methods for CIPN assessment should be practical and convenient for patients and health care providers and should not require any invasive procedures or large amounts of time and resources to perform.

Although no single measure will be applicable to all studies, the development of a short, reliable, and valid questionnaire for CIPN that might be used in all studies would markedly improve comparability across studies, as has been suggested by IMMPACT for other measures. One such measure is the Patient Neurotoxicity Questionnaire (PNQ) developed to reliably measure the response to a treatment intervention over time [9] in patients who are at risk for neurotoxic complications. To be most useful, the PNQ needed to be meaningful and define a level of severity and functional impairment that is recognized by the patient, interpreted by the physician, and with sufficient validity to be useful for regulatory agencies. The PNQ was developed and validated over a 10-year period by Hausheer and colleagues in collaboration with the FDA, to reliably diagnose and quantify the incidence

of CIPN and to provide a clear and reliable endpoint definition for the assessment of CIPN [9]. The PNQ has been used to assess CIPN in controlled clinical trials and is recognized by the FDA as well as other major regulatory agencies (the European Medicines Agency and the Pharmaceuticals and Medical Devices Agency in Japan) as a suitable primary endpoint assessment for CIPN.

The PNQ was designed to obtain clinically relevant and quantifiable information directly from the patient regarding the subjective symptoms (e.g., tingling, pain and numbness) and activities of daily living (e.g., walking, eating). The PNQ is comprised of two clinically defined symptom areas relevant to CIPN, namely, sensory (numbness, tingling, and pain) and motor (weakness), with a clear demarcation between interference and noninterference in daily activities. The PNQ is not a complete solution to the assessment and management of CIPN, but it appears to represent substantial progress toward the goal of developing a simple, convenient, and effective means of CIPN evaluation for clinical management as well as a useful common clinical trial endpoint definition suitable for CIPN research.

Its usefulness was demonstrated in a 300-patient, randomized, prospective study comparing the physician-reported diagnosis, severity, and frequency of CIPN using a standardized neurological examination with NCI-CTC grading with the patient-reported CIPN severity and frequency using the PNQ. That study demonstrated an enormous under-reporting of neurosensory (86%) and neuromotor (96%) grades by physicians, compared with patients [17]. The compliance in reporting by patients and physicians in the study was exceptional, exceeding 90% throughout the study. Additionally, when asked about the diagnostic and clinical utility of the PNQ, 84% of the physicians reported that the PNQ was helpful in the diagnosis and assessment of patients at risk for CIPN [18].

In developing patient-reported outcome measures, several requirements must be met, and these have been described extensively elsewhere [9]. The endpoint definition must be clearly linked to a beneficial patient outcome that is clearly interpretable in terms of benefit and risk to the physician, the nurse, and the patient. For example, one might develop a treatment that reduces the duration of, reduces the severity of, or

actually prevents CIPN associated with a specific chemotherapeutic agent or combination in a defined patient population. Furthermore, there must be a clear clinically important definition for determining the primary endpoint in a clinical trial so that there is no ambiguity as to the presence or absence of benefit from an intervention. The continued validation and refinement of the PNQ is an area of active, ongoing research and development with the primary objective of extending its utility into all the major areas of CIPN based on drug classification and the diagnostically relevant constellation of patient-reported symptoms and activities of daily living.

CONCLUSIONS

Important progress has been made in the treatment of cancer; however, it is clear that much more research and development in the diagnosis and management of neuropathic pain in cancer patients is needed. One of the most important areas for future research and development for this area is the development of convenient, noninvasive, and easily administered diagnostic and assessment tools that clinicians as well as health care providers can use. Also, the development of reliable endpoint definitions and assessment methods for clinical trials involving the treatment, prevention, and mitigation of neuropathic pain as primary efficacy outcomes is of considerable importance. We do not yet have a set of clearly defined patient symptom grades and outcome measures that we can use across different key neuropathies to conclude whether or not a particular treatment offers benefits. When better assessment methods are used and can be directly compared with physician-based assessments as well as used in conjunction with physician history and examination, this will be a major advance. Specifically, the large-scale deployment of such methods would allow a more accurate means to evaluate the actual prevalence, time of onset, severity, duration, and functional impact on activities of daily living of cancer-associated neuropathy, and would be a major advance.

AUTHOR CONTRIBUTIONS

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