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Measuring therapy-induced peripheral neuropathy: preliminary development and validation of the Treatment-induced Neuropathy Assessment Scale (TNAS)

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Abstract

Various sensory and motor effects are associated with cancer treatment-induced peripheral neuropathy. The current method for capturing the multifaceted nature of neuropathy includes a combination of objective tests, clinician evaluation, and subjective patient report—an approach that is often not logistically feasible, especially for multisite trials. We report the performance of a brief-yet-comprehensive, easily administered measure, the Treatment-induced Neuropathy Assessment Scale (TNAS), for assessing the severity and course of neuropathy across various cancer treatments. Data were derived from 4 longitudinal or cross-sectional patient cohorts (n=573). Patients with multiple myeloma treated primarily with bortezomib and patients with colorectal cancer receiving oxaliplatin evaluated candidate items. Cognitive debriefing showed that all items were easy to understand, and this preliminary TNAS demonstrated reliability,

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validity, and sensitivity. Numbness/tingling was the most-severe item, regardless of therapeutic agent. Although numbness and general pain were moderately correlated, patients perceived them as distinct. Most TNAS items were more severe at follow-up, demonstrating the instrument's sensitivity to accumulating dose. The TNAS will be refined with further patient input, with final psychometric evaluation conducted in a new patient sample receiving treatments known to be associated with peripheral neuropathy. The nonpainful component of neuropathy may be more disabling than the pain component.

Keywords

neuropathy; patient-reported outcomes; validation; multiple myeloma; colorectal cancer

INTRODUCTION

Patients treated with anticancer agents often experience sensory and motor effects associated with chemotherapy-induced peripheral neuropathy (CIPN).⁵ CIPN-related symptoms (e.g., pain, heightened sensitivity to temperature variations, numbness and tingling, impaired fine-motor skills, difficulty walking) are reported by 30%–90% of patients, depending on the treatment they receive.^{48,67} Patients endure compromised daily functioning and reduced quality of life^{6,20,39,59–61,67,74} because of these symptoms. When severe, CIPN can disrupt treatment plans, necessitate dose alterations, and possibly affect therapy outcomes. CIPN is often persistent⁴⁸ and, because agents that cause CIPN are standard therapy for multiple types of cancer, the number of patients experiencing residual treatment-related neuropathic effects is expected to increase. Despite the clinical importance of CIPN, there is little consensus about the best method to assess the severity of and changes in CIPN over time, primarily due to inconsistency in diagnosing and monitoring the condition^{2,18,80} and a lack of easily administered assessment measures.^{20,29,67,73,77,81}

The construct of CIPN has evolved since researchers and clinicians first began to study neuropathy. Many measures that were initially used to study CIPN focused largely on capturing its painful aspects. For example, the Brief Pain Inventory^{27,31} was the primary outcome measure in many trials of CIPN^{46,55,76} and of diabetic neuropathy,^{1,76,78} where pain is a predominant symptom. Other measures used extensively to assess neuropathy include the McGill Pain Questionnaire,⁵⁸ Neuropathic Pain Scale,⁴³ Assessment of Peripheral Neuropathy,¹⁹ Scale for Chemotherapy-Induced Long-Term Neurotoxicity,⁶⁴ Neuropathic Pain Symptom Inventory,¹⁷ Leeds Assessment of Neuropathic Symptoms and Signs,¹⁴ Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs,¹⁵ and the DN4 neuropathic pain diagnostic questionnaire.¹⁶ However, these measures also focus on pain and do not include motor-functioning aspects that can be debilitating even in the absence of pain. Indeed, our current understanding of neuropathy overwhelmingly indicates that pain is only one of its components, and often it is not the most distressing aspect of neuropathy to patients.^{4,7,49}

Methods for capturing the multifaceted nature of chemotherapy-induced peripheral neuropathy range from objective tests to clinician evaluation to subjective patient report.

Neurophysiological testing is an objective measurement method that employs nerve-conduction devices to test several aspects of nerve function. Neurophysiological testing is complicated and expensive, however^{20,36,37,44,56,80}; the devices are necessary but costly, and their proper use requires intensive training and expertise, making them difficult to employ in multicenter and multinational clinical research. Further, nerve-conduction study results correlate only moderately with patient report of symptoms.²² Similarly, clinician-rated peripheral neuropathy only modestly correlates with patient report.^{52,53}

Because the effects of symptoms are experienced subjectively, they are best described as patient-reported outcomes (PROs).^{32,33} PROs provide a unique patient perspective on treatment benefit and risk that goes beyond clinician-reported adverse events. PRO assessment tools that generate a more-complete picture of neuropathic symptoms are therefore warranted. Existing PRO tools that capture several aspects of neuropathy include the European Organisation for Treatment of Cancer (EORTC) Chemotherapy-Induced Peripheral Neuropathy Quality of Life Questionnaire (QLQ-CIPN-20, typically administered with the EORTC core Quality of Life Questionnaire, the QLQ-C30)⁷⁰; the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx)⁵⁰; and the Brief Pain Inventory, which also assesses pain's interference with functioning.^{26,27,31}

Current practice employs a combination of measures to fully assess the range of CIPN-related symptoms, but this assessment approach is often not logistically feasible, especially in multisite trials. For example, Cavaletti et al. proposed using the clinician-rated Total Neuropathy Score,^{21,23,24,34,77} the patient-reported EORTC QLQ-CIPN20,⁷⁰ and a visual analog scale to assess CIPN. However, using several tools to measure the same phenomenon is inefficient and creates a time and logistic burden for both respondents and investigators.^{25,30,45,57,72} This so-called “respondent burden” could influence which PRO measures, if any, are incorporated into clinical trials. Data collection lasting no longer than 20 minutes at baseline and 10–15 minutes at subsequent time points is ideal when considering respondent burden.¹⁰ In addition, reliability and standardization are difficult to maintain in large multisite studies with a combination of several complicated methods of assessing CIPN.^{8,40,47} Terminology is often inconsistent from one instrument to another: for example, investigators sometimes refer to paresthesia (numbness) as “pain” or use both terms (“pain and numbness”),⁶⁵ and understandings of the concept of “pain” are not consistent from one patient to another and can vary with severity and type.^{26,27}

Another issue affecting the usefulness of a CIPN assessment tool is the way it was developed. Since the US Food and Drug Administration (FDA) issued its 2009 guidance on the development and use of PROs in labeling claims,⁷⁹ instrument developers are endeavoring to create PRO measures in parallel with guidance recommendations, which address issues related to conceptual framework, endpoint models, item development (with extensive input from patients), psychometric validity, and sensitivity to change.^{29,32,33,79} PRO-based CIPN assessment should be able to identify key patient symptoms, discriminate between agents associated with the development of neuropathy, and detect CIPN and change in its severity over time.^{51,75}

To address these issues, we are developing a new PRO measure, the Treatment-induced Neuropathy Assessment Scale (TNAS). Our focus has broadened from “chemotherapy-induced” to “treatment-induced,” because neuropathy can be caused by nonchemotherapy treatments (e.g., molecular therapies, radiation, surgery). The TNAS is being designed to capture multiple neuropathy-related symptoms across a range of cancer therapies, to be brief enough for repeated administrations,^{9,11,12,28,72} to be highly sensitive and reliable, and to demonstrate good content validity.^{10,68,79} In the first phase of instrument development, we evaluated the sensitivity and psychometric properties of candidate items generated by multidisciplinary expert panels and literature reviews of existing scales (TNAS v1.0), and we identified additional items from patient debriefing of this initial item set (yielding TINAS v2.0). We report the performance of these items in patients with either multiple myeloma (MM) or colorectal cancer (CRC) who were being treated with therapies known to cause peripheral neuropathy. In parallel, to elicit further symptom items (if any), we are conducting extensive one-on-one qualitative interviews in patients having treatments known to induce peripheral neuropathy. The ultimate aim is to develop a brief, easily administered scale with the fewest questions necessary to provide a comprehensive assessment of the severity and course of neuropathy across various cancer treatments.

METHODS

Tool Development

Proposed items for the TNAS v1.0 came from several sources. First, clinicians who manage patients being treated with neurotoxic agents developed a list of candidate symptoms. Second, we reviewed available PRO neuropathy scales (e.g., EORTC QLQ-CIPN20, FACT/GOG-Ntx, others) to derive additional candidate items. The resulting draft version consisted of 11 items. This 11-item TNAS v1.0 was administered to 20 patients with CIPN who were receiving induction therapy for MM. Patients were then cognitively debriefed and asked to suggest additional descriptors/symptoms. Two other items were added because more than 10% of the patients listed them as relevant, even though these symptoms could be specific to MM treatment. The resulting TNAS v2.0 thus contains 13 items.

We used a 0–10 numeric rating scale for the TNAS symptom severity items. The 0–10 numeric rating scale is easily adaptable to both clinical and research needs, having been found to be reliable and 10 easy to complete, even for less-educated patients,⁴¹ and to maximize the trade-off between a patient’s ease of responding and the marginal increase in reliability associated with a greater number of response choices.⁶³ National pain-treatment guidelines¹³ and consensus groups such as IMMPACT³⁸ increasingly recommend this scale, and most patients prefer it.^{42,66}

Participants

Four patient cohorts, 2 with MM and 2 with CRC at various stages of treatment, participated in either longitudinal or cross-sectional studies to evaluate the psychometric properties of the TNAS candidate items. Patients with MM were recruited in the Lymphoma & Myeloma Care Center at The University of Texas MD Anderson Cancer Center in Houston, Texas, from May 2008–October 2013; patients with CRC were recruited in the Gastrointestinal

Care Center at MD Anderson from July 2008–October 2013. The longitudinal cohorts completed the 11-item TNAS v1.0 at several time points, from the start of treatment (baseline assessment) up to a maximum of 6 cycles for the CRC cohort and 4 cycles for the MM cohort. The cross-sectional cohorts completed the 13-item TNAS v2.0 once during treatment. These studies were approved by the MD Anderson Institutional Review Board, and all participants provided written informed consent.

Cohort 1 (cross-sectional) comprised MM patients treated with combination therapy that included bortezomib (n=223). Data collected were used to evaluate content validity and item clustering, calculate internal consistency, and describe the prevalence and severity of neuropathic symptoms.

Cohort 2 (cross-sectional) comprised CRC patients treated with combination therapy that included oxaliplatin (n=186). Data collected were used to demonstrate item clustering, calculate internal consistency, describe the severity of neuropathic symptoms, and establish criterion validity in comparison with the EORTC QLQ-CIPN20.

Cohort 3 (longitudinal) comprised MM patients undergoing induction therapy that included bortezomib (n=93). We used data from this cohort to examine the sensitivity of the TNAS to accumulating treatment dose.

Cohort 4 (longitudinal) comprised CRC patients receiving chemotherapy that included oxaliplatin (n=71). We used data from this cohort to examine the sensitivity of the TNAS to accumulating chemotherapy dose.

The use of both cross-sectional and longitudinal cohorts enhances the psychometric evaluation of the tool being developed. First, patients in the cross-sectional cohorts were recruited anywhere along the continuum of their treatment trajectory, and thus the reliability and validity of the TNAS are generalizable to treatment-related neuropathic symptoms at any point during treatment. Second, patients in the longitudinal cohorts were recruited at the beginning of their treatment and contributed data for several cycles of treatment, thus providing an optimal method for evaluating the sensitivity of the TNAS to accumulating treatment dose.

Data Collection

Methods—At enrollment, research staff asked participants to complete self-administered questionnaires and assisted with completion of survey forms as needed. For the longitudinal cohorts, follow-up data was collected during treatment, and the initial (pretreatment) TNAS and 1 follow-up TNAS (the last TNAS completed by a given patient) were used in the analysis. Primary diagnosis, concomitant disease, and other disease-related and treatment-related data were collected from the patients' medical records by research staff. Sociodemographic information, including birth date, sex, ethnicity, education level, place of residence, marital status, and employment status, were also collected.

To ensure that we were demonstrating the reliability and validity of the TNAS in a condition that was present, for the cross-sectional cohorts we excluded patients who responded 0 (not

present) to the TNAS item “numbness or tingling in your hands or feet at its worst.” However, we did not apply the same exclusion criterion to the longitudinal cohorts because the intent was to demonstrate sensitivity to neurotoxic therapy, and we were specifically interested in patients who developed neuropathic symptoms during treatment.

Measures

TNAS: The TNAS asks patients to rate the severity of their neuropathy-related symptoms in the last 24 hours. The 11-item (v1.0) and 13-item (v2.0) TNAS instruments are scored on a 0–10 scale, with 0=the symptom is not present and 10=the symptom is as bad as you can imagine. On average, the TNAS takes <2 minutes to complete.

MD Anderson Symptom Inventory (MDASI): The MDASI asks patients to rate the severity of 13 common cancer-related and treatment-related symptoms and the degree to which these symptoms interfered with daily functioning during the past 24 hours.³⁰ Items are rated on the same 0–10 severity scale and with the same anchors as the TNAS. The MDASI was administered at the same time as the TNAS. We included the MDASI pain item in our analysis so that we could examine the utility of a general pain item and determine how general pain relates to the TNAS items.

EORTC QLQ-CIPN20: The EORTC QLQ-CIPN20 is a 20-item questionnaire that assesses CIPN-associated symptoms and functional limitations. The EORTC QLQ-CIPN20 is administered in combination with the QLQ-C30. The items are rated on a 0–4 scale and are divided into sensory, motor, and autonomic subscales. This questionnaire was selected because it is used frequently in the cancer population.^{54,71,84}

Statistical Analysis

Analyses were conducted using Statistical Package of the Social Sciences (SPSS) software v21. Means, standard deviations (SDs), and percentages of missing data were computed for all TNAS items. We used paired t-tests to determine the statistical significance of change scores from baseline to follow-up as tests of sensitivity. The corresponding effect sizes associated with the change scores were calculated. Statistical significance was set using a 2-tailed alpha level of 0.05.

Item Clustering—To describe how the items of the TNAS are interrelated, we performed hierarchical cluster analysis of the 13 symptom items³ for each cross-sectional cohort. The resulting dendrograms allowed us to determine how the items cluster together. Bivariate correlations were calculated to examine the relationship of the general MDASI pain item with TNAS items. We used paired t-tests to determine whether there were significant differences in severity between the MDASI pain item and the TNAS numbness/tingling item. The cross-sectional cohorts (Cohorts 1 and 2) were used for this analysis.

Reliability of the TNAS—Reliability refers to the extent to which a measure is able to yield consistent, reproducible results. Cronbach coefficient alphas were computed to estimate the internal consistency reliability of all TNAS items and the 2 TNAS subscales

(sensory and motor). The criterion for good internal consistency (reliability) is a Cronbach alpha 0.70. We used the cross-sectional cohorts (Cohorts 1 and 2) for this analysis.

Validity of the TNAS—Content validity assesses whether questionnaire items adequately represent the construct of interest (here, neuropathic symptoms). Cognitive debriefing provides evidence to support the content validity of a measure.⁶⁹ In the current study, cognitive debriefing was used to elicit patient feedback about the 14 relevance of the neuropathic symptom items for the patient's disease and treatment conditions and whether the items were understandable and clear. Participants first completed a paper TNAS questionnaire in full and then participated in the cognitive debriefing interview.⁸³ Participants were asked about the ease of completion, comprehensibility, acceptability, and redundancy of the TNAS items and about the ease of use, ease of understanding, and their level of comfort in using the 0–10 numeric rating scale. They were asked for suggestions as to whether any items needed to be clarified to make them easier to understand. Finally, participants were asked to recommend additional items that were not asked but that they thought should be included, if any. The first 20 patients of Cohort 1 participated in this analysis.

Criterion validity refers to the extent to which an instrument correlates with another instrument that measures a similar concept. To examine criterion validity, we correlated TNAS overall and subscale scores with corresponding subscale scores from the EORTC QLQ-CIPN20. The CRC cross-sectional cohort (Cohort 2) was used for this analysis. The protocol under which the MM cross-sectional cohort (Cohort 1) were accrued did not include this questionnaire.

Sensitivity of the TNAS—Sensitivity is the ability of an instrument to detect change in outcome when such change is expected. We used paired t-tests to assess TNAS sensitivity to the effect of increasing doses of neurotoxic cancer therapies. We expected patients with ongoing treatment to report worsening neuropathic symptoms. Effect sizes were calculated to estimate the magnitude of differences in subscale scores and items. Norman et al.⁶² have suggested that effect sizes of 0.5 SD and higher can be considered clinically meaningful. The longitudinal cohorts (Cohorts 3 and 4) were used for these analyses.

RESULTS

Patient Characteristics

Demographic and clinical characteristics of the 4 patient cohorts are summarized in Table 1. The median age ranged from 54–64 years. There were more men than women, and the sample was predominantly non-Hispanic white. Most patients had good Eastern Cooperative Oncology Group performance status (0–1).

For the cross-sectional cohorts, we excluded 209 of 395 CRC patients and 125 of 348 MM patients who responded 0 (not present) to the TNAS item “numbness or tingling in your hands or feet at its worst.” Thus, our effective sample sizes were $n = 186$ for the CRC cohort and $n = 223$ for the MM cohort.

Symptom Severity

Symptom Hierarchy by Cancer Diagnosis—Table 2 shows the TNAS severity ratings for the 2 cross-sectional cohorts. Numbness/tingling was the most severe symptom for both cohorts. Coldness in the hands/feet was also among the 5 most-severe symptoms for both cohorts. Otherwise, the 2 cohorts were dissimilar: for the MM cohort, numbness was followed by cramps in the hands/feet, sensations of pins/needles in the arms/legs, and trouble walking, whereas for the CRC cohort, numbness/tingling was followed by hot/burning sensations in the hands/feet and trouble grasping small objects.

Differences in Symptom Severity by Cancer Treatment—MM patients, who received bortezomib-based therapy, reported significantly higher levels of neuropathic symptoms compared with CRC patients, who were treated with oxaliplatin-based regimens, as follows: numbness/tingling (MM: 4.57 ± 2.49 vs. CRC: 4.06 ± 2.73 , $P < .05$), cramps in the hands/feet (MM: 2.38 ± 3.26 vs. CRC: 1.36 ± 2.29 , $P < .05$), sensations of pins/needles in the arms/legs (MM: 2.36 ± 2.86 vs. CRC: 1.23 ± 2.34 , $P < .05$), and trouble walking (MM: 2.35 ± 3.05 vs. CRC: 1.17 ± 2.35 , $P < .05$). See Table 2.

Item Clustering—Figures 1A and 1B demonstrate how a general pain item and the TNAS items are related to one another for the cross-sectional cohorts. Items that joined together earlier (from left to right) were perceived similarly. As expected, motor subscale items, such as trouble walking and difficulty with balance due to loss of feeling in legs/feet, joined early for both cohorts. The third motor item, trouble grasping small objects (e.g., buttoning buttons, handling coins, holding a pen) joined with these 2 items rather than with other items.

Interestingly, numbness/tingling, which is a predominant neuropathic symptom, joined together with the general pain item from the MDASI before joining any other TNAS items. This was true for both cohorts but was more pronounced in the CRC cohort. The correlations of pain with numbness were 0.30 (CRC) and 0.40 (MM). For the CRC cohort, the severity of the numbness/tingling was significantly worse than the general pain item from the MDASI (4.1 ± 2.7 vs 2.2 ± 2.9 , respectively; $P < .001$). A similar observation was made for the MM cohort, for whom numbness/tingling was more severe than pain (4.6 ± 2.5 vs 3.6 ± 3.0 , respectively; $P < .001$).

Validation of the TNAS Candidate Items

In exploratory analysis, a global TNAS (v2.0) score was calculated by taking the average of all 13 item scores. Two subscale scores were calculated to evaluate symptoms related to sensory or motor functioning dimensions. The sensory subscale score was the mean of 10 sensory items: numbness/tingling in hands/feet, cramps in hands/feet, sensations of pins/needles in arms/legs, feelings of coldness in hands/feet/fingers, hot/burning sensations in hands/feet, swelling in hands/feet, sensations of electric shock, discomfort when touching things, discomfort when skin comes into contact with something (e.g., blanket, clothing), and pain when touching cold things. The motor subscale score was the mean of 3 motor items: trouble walking due to loss of feeling in legs/feet, difficulty with balance due to loss of feeling in legs/feet, and trouble grasping small objects.

Reliability—On the basis of data from the cross-sectional cohorts, the TNAS subscales showed good internal consistency reliability (Table 3). Overall Cronbach coefficient alpha values were 0.86 (MM cohort) and 0.87 (CRC cohort); the sensory subscale ranged from 0.80–0.82, while the motor subscale was 0.85 for both cohorts.

Validity—Content validity was ensured by the methods used to construct the item list for the TNAS, including patient cognitive debriefing, clinician input, and literature review to identify the initial items, and further patient testing to identify any missing items. See Tool Development above. Cognitive debriefing of 20 patients from the cross-sectional MM cohort indicated that all items were easy to understand. Two additional items, feeling of coldness in hands/feet/fingers and swelling in hands/feet, were added to the TNAS as result of the cognitive debriefing. Table 2 lists all 13 TNAS v2.0 items.

Our analysis of criterion validity using data from the cross-sectional CRC cohort (n=186) showed that the global score and subscales of the TNAS were correlated with the EORTC QLQ-CIPN20 subscales ($P < .05$ for all comparisons), as expected (Table 4). The motor subscale of the TNAS was more strongly correlated with the EORTC QLQ-CIPN20 motor subscale than with EORTC QLQ-CIPN20 sensory or autonomic subscales (0.71 vs. 0.57 or 0.39). However, the sensory subscale of the TNAS was slightly more correlated with the EORTC QLQ-CIPN20 motor score than with the EORTC QLQ-CIPN20 sensory score.

Sensitivity to Accumulating Neurotoxic Therapy Dose—Using data from the longitudinal cohorts, we assessed whether the TNAS could detect changes in neuropathic symptoms during the course of therapy. Generally, the CRC cohort reported greater increase in neuropathic symptoms than did the MM cohort (Table 5). For the CRC cohort, the severities of 10 of 11 TNAS items were significantly worse at follow-up than at baseline. With an average follow-up at 4.6 chemotherapy cycles, only 1 item, discomfort when skin comes into contact with something, did not differ significantly between time points.

For the MM cohort, the severities of 4 of 11 TNAS items worsened significantly over time, with an average follow-up duration of 3.7 therapy cycles. These items included sensations of electric shock, numbness/tingling in hands/feet, hot/burning sensations in hands/feet, and sensations of pins/needles in arms/legs.

In addition to conducting paired t-tests for each TNAS item, we calculated effect sizes for each item from baseline to the follow-up assessment. Most of these effect sizes were 0.5 SD and higher (Table 5) and as such can be considered clinically meaningful.

DISCUSSION

In the pain literature, there is often confusion between neuropathic pain and neuropathy. Nonpainful neuropathy may be more disabling than that which has a pain component. The data from the current study demonstrate that neuropathic symptoms are associated with neurotoxic cancer therapies (such as bortezomib, a targeted therapy, and oxaliplatin, a cytotoxic chemotherapy) and are rated as more severe than pain. In particular, patients in

both the MM and CRC cohorts rated the severity of their numbness or tingling to be significantly higher than the severity of their pain.

We have described the development and initial validation of a new PRO questionnaire for assessing treatment-related peripheral neuropathy. We present data for both preliminary versions (v1.0 and v2.0) of the TNAS. We have found the items in these versions to be sensitive to expected change and internally consistent, and we expect that the TNAS will be a concise method of assessing treatment-related peripheral neuropathy using patient report.

A strength of this study is that 2 cancer groups (MM and CRC) undergoing different neurotoxic therapies were included. This enabled the comparison of TNAS responses in patients with different primary diagnoses and exposure to different therapeutic agents (primarily bortezomib or oxaliplatin). Although we refer to the phenomenon under study as CIPN, bortezomib is a targeted as opposed to a cytotoxic agent,³⁵ and other nonchemotherapy cancer treatments (e.g., certain targeted therapies, surgery, radiation) have also been associated with peripheral neuropathy-related toxicities.

A second strength of the study was longitudinal assessment to evaluate sensitivity to cumulative dose of neurotoxic therapy. For both patient cohorts, numbness/tingling, cramps in hands/feet, sensations of pins/needles, and trouble walking were among the most-severe symptoms (Table 2). The mean severities of the items “discomfort when your skin comes into contact with something (e.g., blanket, clothing) at its worst” for the CRC cohort and “pain when touching cold things at its worst” for the MM cohort were some of the lowest, indicating that patients find them to be less severe. These items are potential candidates for removal, such that the final TNAS may have fewer items.

We also asked patients about their general pain on a 0–10 scale, separately from the TNAS items. Figure 1 shows that pain and numbness were closely related for both cancer groups but that patients perceived this relationship to be not as similar as the relationships among the 3 TNAS motor-related items. This cluster analysis, along with clinical knowledge, suggest that a pain-severity item should be part of the final TNAS.

As mentioned previously, because of the FDA’s 2009 guidance on the development and use of PROs in labeling claims,⁷⁹ many instrument developers are incorporating guidance recommendations so that their tools can be used to make claims in drug development.^{29,32,33,79} The FDA’s 2009 guidance on PRO tool development recommends establishing the tool’s psychometric properties,⁷⁹ including reliability and validity. Generally, the Cronbach coefficient alpha test is the preferred method for estimating reliability, with alpha values 0.70 indicating good reliability. The candidate items comprising the TNAS subscales showed good internal consistency, with Cronbach coefficient alpha values of 0.80 indicating acceptable reliability. Cognitive debriefing refined the item list, resulting in v2.0 of the TNAS, and the TNAS compared as expected with a similar tool, the EORTC QLQ-CIPN20. These results are indicative of the TNAS’s validity.

The FDA also recommends that PRO tools have a documented ability to detect change (sensitivity).⁷⁹ This is particularly important in treatment-induced disorders such as CIPN,

because symptom severity changes with accumulating dose. The TNAS was shown to be sensitive to changes when such changes were expected (i.e., increasing scores with accumulating dose).

This study had limitations. First, we did not include cancer patients who have neuropathy based on nonsystemic therapies, such as surgery or radiation, or patients with neuropathy based on disease alone. Second, we need to conduct qualitative interviews with patients who have neuropathy to ensure that there are not additional symptoms that should be included in the TNAS. To that end, in-depth qualitative interviewing of patients receiving various neurotoxic cancer therapy agents is underway. These qualitative interviews allow patients to relate what is most important to them about the symptoms they are experiencing as a result of the treatment they are receiving. The information gathered from the qualitative interviews will be used to verify existing TNAS items and generate additional ones, if needed, to further refine the TNAS.⁸²

CONCLUSION

We have data to suggest that neuropathy is a complex phenomenon. Patients receiving treatment for cancer reported a variety of pain descriptors, such as electric shocks and painful cold; abnormal sensations such as hot or burning and pins and needles; and motor impairment such as trouble walking and trouble grasping small objects. For patients receiving cancer treatment, pain was rated lower in severity compared to numbness or tingling, suggesting that pain is not always the most distressing symptoms of neuropathy.

We developed a preliminary TNAS v2.0 and have demonstrated the sensitivity, responsiveness, reliability, and validity of its candidate items. This suggests that the TNAS is an informative, useful PRO assessment tool that incurs little patient burden and is of use in clinical trials conducted at multiple sites. The TNAS will be further refined with the input of patients with cancer experiencing CIPN, and psychometric evaluation of the final measure will be conducted in a new sample of patients receiving treatments known to be associated with peripheral neuropathy. 22

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Abbreviations

CRC	colorectal cancer
MDASI	MD Anderson Symptom Inventory
MM	multiple myeloma
TNAS	Treatment-induced Neuropathy Assessment Scale

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PERSPECTIVE

Our data suggest that the nonpainful components of neuropathy may be more disabling than the pain component during cancer treatment. Here we report data on sensory and motor symptoms reported by patients receiving neurotoxic cancer therapy, and we develop a neuropathy assessment scale that follows regulatory guidance for patient-reported outcomes.

HIGHLIGHTS

1. Nonpainful component of neuropathy may be more disabling than the pain component
2. Assessment with objective tests may be problematic in multicenter trials
3. We report the development of a treatment-induced peripheral neuropathy measure

Figure 1.

TNAS item clustering, (A) MM cohort (n=223) and (B) CRC cohort (n=186). We used hierarchical cluster analysis to identify TNAS symptom items that form groups or clusters. Clusters were formed using Ward's method, whereas the distances between symptoms were calculated using squared Euclidian distances. The figure shows the distance between items/clusters rescaled from 0–25. The minimum and maximum distances between symptoms from various stages of clustering correspond to 1 and 25, respectively. Symptoms are separate items on the left of the dendrogram, but begin to cluster as they progress until they merge completely on the right, indicated by the joining of lines across the figure from left to right. Items within clusters were perceived by patients to be more similar than items from other clusters.

Abbreviations: CRC, colorectal cancer; MDASI, MD Anderson Symptom Inventory; MM, multiple myeloma; TNAS, Treatment-induced Neuropathy Assessment Scale.

Table 1

Patient Demographic and Disease Characteristics

	Cross-Sectional Cohort		Longitudinal Cohort	
	MM	CRC	MM	CRC
Sample size	223	186	93	71
Age, years				
Median	64	54	62	57
Range	38–96	25–84	40–79	19–82
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Sex				
Women	96 (43)	74 (40)	36 (40)	27 (38)
Men	127 (57)	112 (60)	54 (60)	44 (62)
Race				
Asian or Pacific Islander	6 (3)	4 (2)	1 (1)	5 (7)
Black non-Hispanic	46 (21)	25 (13)	16 (17)	11 (15)
Hispanic	24 (11)	22 (12)	8 (9)	10 (14)
Native American or Alaskan Native	0 (0)	0 (0)	1 (1)	0 (0)
White non-Hispanic	146 (65)	133 (72)	65 (71)	44 (62)
Other	1 (0)	2 (1)	1 (1)	1 (1)
ECOG performance status				
0	51 (23)	100 (61)	18 (23)	51 (72)
1	165 (74)	57 (35)	54 (68)	17 (24)
2	7 (3)	5 (3)	7 (9)	3 (4)
3	0 (0)	2 (1)	0 (0)	0 (0)
Disease stage*				
I	112 (50)	45 (30)	43 (47)	0 (0)
II	58 (26)	27 (18)	23 (25)	6 (9)
III	52 (23)	76 (51)	26 (28)	28 (40)
IV	0 (0)	0 (0)	0 (0)	36 (51)

Abbreviations: MM, multiple myeloma; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group.

* Stage of disease is not comparable across disease type.

Table 2
Severity and Missing-Data Rate for Individual TNAS Items and Subscales (Cross-Sectional Cohorts)

TNAS Item	MM (n = 223)			CRC (n = 186)		
	Mean	SD	% Missing	Mean	SD	% Missing
Numbness/tingling in hands/feet at its worst [*]	4.57	2.49	0.0	4.06	2.73	0.0
Cramps in hands/feet at their worst [*]	2.38	3.26	0.4	1.36	2.29	0.5
Sensations of pins/needles in arms/legs at their worst [*]	2.36	2.86	0.4	1.23	2.34	0.5
Trouble walking due to loss of feeling in legs/feet at its worst [†]	2.35	3.05	0.4	1.17	2.35	0.5
Feelings of coldness in hands/feet/fingers at its worst [*]	2.29	3.21	0.9	1.41	2.40	1.1
Difficulty with balance due to loss of feeling in legs/feet at its worst [†]	2.26	2.99	0.4	1.13	2.25	0.5
Trouble grasping small objects (e.g., buttoning buttons, handling coins, holding a pen) at its worst [†]	1.91	2.96	0.4	1.48	2.48	0.5
Hot/burning sensations in hands/feet at their worst [*]	1.88	2.90	0.0	1.50	2.53	0.0
Swelling in hands/feet at its worst [*]	1.70	2.66	0.9	0.88	2.00	1.1
Sensations of electric shock at their worst [*]	1.33	2.65	0.0	0.99	2.11	0.0
Discomfort when touching things at its worst [*]	1.17	2.43	0.0	0.81	1.78	0.0
Discomfort when skin comes into contact with something (e.g., blanket, clothing) at its worst [*]	1.12	2.30	0.4	0.67	1.84	0.5
Pain when touching cold things at its worst [*]	0.65	1.98	0.0	1.06	2.15	0.0
Subscales						
Total	2.00	1.46	0.0	1.36	0.92	0.0
Sensory	1.67	2.71	0.4	1.11	2.19	0.4
Motor	3.11	2.87	0.3	2.22	2.45	0.4

Abbreviations: TNAS, Treatment-induced Neuropathy Assessment Scale; MM, multiple myeloma; CRC, colorectal cancer; SD, standard deviation.

^{*} Sensory subscale item.

[†] Motor subscale item.

Table 3

Internal Consistency Reliability of the TNAS (Cross-Sectional Cohorts)

TNAS Subscale	No. of Items	Cronbach Coefficient Alpha	
		MM	CRC
All items	13	0.86	0.87
Sensory [*]	10	0.80	0.82
Motor [†]	3	0.85	0.85

Abbreviations: TNAS, Treatment-induced Neuropathy Assessment Scale; MM, multiple myeloma; CRC, colorectal cancer.

^{*} The 10 sensory subscale items include numbness/tingling in hands/feet, cramps in hands/feet, sensations of pins/needles in arms/legs, feelings of coldness in hands/feet/fingers, hot/burning sensations in hands/feet, swelling in hands/feet, sensations of electric shock, discomfort when touching things, discomfort when skin comes into contact with something (e.g., blanket, clothing), and pain when touching cold things.

[†] The 3 motor subscale items include trouble walking due to loss of feeling in legs/feet, difficulty with balance due to loss of feeling in legs/feet, and trouble grasping small objects (e.g., buttoning buttons, handling coins, holding a pen).

Table 4

Criterion Validity of the TNAS: Correlations with the EORTC QLQ-CIPN20 (Cross-Sectional CRC Cohort, n = 186)

TNAS Scale	EORTC Sensory	EORTC Motor	EORTC Autonomic
Total	0.640	0.709	0.461
Sensory [*]	0.593	0.611	0.441
Motor [†]	0.570	0.714	0.385

Abbreviations: TNAS, Treatment-induced Neuropathy Assessment Scale; EORTC, European Organisation for Treatment of Cancer; EORTC QLQ-CIPN20, Chemotherapy-Induced Peripheral Neuropathy Quality of Life Questionnaire; CRC, colorectal cancer.

^{*} The 10 sensory subscale items include numbness/tingling in hands/feet, cramps in hands/feet, sensations of pins/needles in arms/legs, feelings of coldness in hands/feet/fingers, hot/burning sensations in hands/feet, swelling in hands/feet, sensations of electric shock, discomfort when touching things, discomfort when skin comes into contact with something (e.g., blanket, clothing), and pain when touching cold things.

[†] The 3 motor subscale items include trouble walking due to loss of feeling in legs/feet, difficulty with balance due to loss of feeling in legs/feet, and trouble grasping small objects (e.g., buttoning buttons, handling coins, holding a pen).

Table 5
Sensitivity of the TNAS: Change in TNAS Items from Start of Treatment to Last Follow-Up (Longitudinal Cohorts)

TNAS Item	CRC Cohort (n = 71)				MM Cohort (n = 93)				Effect Size*
	Baseline Mean	SD	Follow-Up Mean	SD	Baseline Mean	SD	Follow-Up Mean	SD	
Hot/burning sensations in hands/feet [†]	0.14	0.87	0.66	1.88	0.24	1.07	0.86	2.11	0.58
Pain when touching cold things	0.65	1.53	1.20	2.33	0.09	0.83	0.17	1.00	0.10
Cramps in hands/feet	0.30	1.09	0.66	1.69	0.28	1.31	0.76	2.01	0.37
Discomfort in contact with fabric [‡]	0.07	0.39	0.27	1.01	0.24	1.33	0.27	1.29	0.02
Trouble grasping small objects	0.46	1.29	1.49	2.58	0.36	1.18	0.57	1.46	0.18
Pins/needles in arms/legs [†]	0.28	0.97	0.68	1.61	0.20	0.76	1.07	2.08	1.15
Difficulty with balance	0.29	1.13	1.04	2.18	0.34	1.28	0.66	1.81	0.25
Numbness/tingling in hands/feet [†]	0.70	1.63	2.24	2.89	0.85	1.68	1.88	2.32	0.61
Difficulty walking	0.42	1.37	1.25	2.41	0.33	1.42	0.67	1.85	0.24
Sensations of electric shock [†]	0.23	0.91	0.72	1.77	0.01	0.10	0.23	0.95	2.12
Discomfort when touching things	0.18	0.68	0.85	2.02	0.10	0.94	0.14	0.97	0.04

Abbreviations: TNAS, Treatment-induced Neuropathy Assessment Scale; CRC, colorectal cancer; MM, multiple myeloma; SD, standard deviation.

* Calculated as mean difference/baseline SD. Effect sizes larger than 0.5 SD are considered clinically significant.

[†] For the MM cohort, differences between baseline and follow-up for these items were statistically significant at $P < .01$.

[‡] For the CRC cohort, only this item was not statistically different between baseline and follow-up. Differences for the remaining items were statistically significant at $P < .01$.