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ORIGINAL ARTICLE

Evaluation of chemotherapy-induced peripheral neuropathy using current perception threshold and clinical evaluations

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Abstract
Purpose Chemotherapy-induced peripheral neuropathy (CIPN) is increasing with introduction of new and combination cancer pharmacotherapies. This study evaluated associations between clinical and self-report measurements and current perception threshold (CPT), a neuroselective measure of sensory nerve function that may detect asymptomatic CIPN damage.
Methods Data for this secondary analysis were from a prospective, observational study using CPT to evaluate CIPN. Bivariate mixed models, accounting for the intraclass correlation between repeated patient assessments, were used to assess the relationship between CPT at each frequency (5, 250, and 2,000 Hz) and each subjective measure (Neuropathic Pain Scale, FACT-GOGntx) and objective measurement (quantitative sensory testing, deep tendon reflexes, and grip strength).
Results A total of 29 chemotherapy-naïve subjects with various cancer types had a mean age of 56.7 (SD 10.4); nine subjects

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developed CIPN grade >1 using NCI CTC-AE criteria. Cold detection thresholds were inversely associated with CPT 5 [*b*(95 % CI)=−2.5(−4.5, −0.5)] and CPT 2,000 [−7.5(−11.8, −3.3)] frequencies. FACT GOG-ntx quality of life (QoL) scale and neurotoxicity and function subscales were inversely associated with CPT 2,000 [−1.8 (−3.5, −0.05), −2.2 (−4.2, −0.2), and −5.4 (−9.8, −0.9), respectively], indicating worsening QoL, impairment, and function as hypoesthesia increases.
Conclusions CPT 2,000 may identify impending worsening of patient-reported outcomes such as QoL.

Keywords Chemotherapy-induced peripheral neuropathy · CIPN · Chemotherapy · Quality of life · Pain · Cancer

Introduction

The number of patients affected with chemotherapy-induced peripheral neuropathy (CIPN) is anticipated to increase proportionately as clinical trials using new neurotoxic agents increase, dosing of existing agents intensifies, and long-term survival improves [1, 2]. Combination chemotherapy involving more than one neurotoxic agent coupled with higher cumulative doses of these drugs hastens CIPN development [3, 4]. CIPN may involve sensory, motor, and autonomic nerves, which results in neuropathic symptoms [5] as well as decline in physical function and quality of life. Initial symptoms of CIPN commonly include numbness, tingling, and burning pain in a stocking-and-glove distribution.

A number of chemotherapy agents have been implicated in the development of CIPN, including taxanes and platinum agents, two drug classes routinely given in commonly diagnosed malignancies [6]. The CIPN associated with these drugs is dose dependent, with an incidence of up to 100 % reported with some high dose regimens [7, 8]. Taxanes, which include paclitaxel and docetaxel, cause a length-dependent axonal polyneuropathy with a distal predominance. In animal experiments with paclitaxel, abnormal pain responses, including allodynia and hyperalgesia to thermal and mechanical stimuli, were sensitive to measures of neuropathic pain [9], suggesting impairment of function in Aβ and Aδ myelinated fibers [10]. Among platinum agents, which include cisplatin, carboplatin, and oxaliplatin, cisplatin has been shown to reduce fast axonal transport and to induce apoptosis in dorsal root ganglion cells, two mechanisms thought to be at least in part responsible for neuropathy symptoms [11]. Large, myelinated Aβ fibers are most commonly affected by this class of drugs. Patients treated with oxaliplatin develop a protracted and sometimes severe CIPN course, which includes acute symptoms that resolve within about week as well as chronic symptoms characterized by distal paresthesias with numbness [12].

Measures of CIPN used in oncology clinics typically encompass sensory, motor, and functional components, the latter of which is often referred to as quality of life (QoL). Commonly used measures of CIPN in clinical trials include National Cancer Institute Common Terminology Criteria (NCI-CTCAE) v3.0 [13], Eastern Cooperative Group [14], and World Health Organization [15] criteria. These scales range from 0 (asymptomatic) to 4 or 5 (paralysis or death), and as such, their ordinal construct limits the scale's ability to detect incremental changes in impairment [16]. As a consequence of inadequate CIPN measurement and lack of standardization, the progression and resolution of CIPN are not well characterized, and sensory nerve fiber damage can become irreversible by the time CIPN is identified clinically [17].

Current perception threshold (CPT) testing uses a painless electrical impulse to stimulate and measure sensory nerve functional integrity by determining the amount of current needed to stimulate a sensation that can be perceived by the subject [18–20]. The CPT test is neuroselective for each of the three major subpopulations of sensory nerve fibers [21], and a unique and distinct sensory response is evoked from each CPT frequency, corresponding to the particular sensory fiber subtype. The frequency required to depolarize and cause an action potential in a nerve is dependent on the diameter of the fiber [22]. The large myelinated Aβ fibers are stimulated at 2,000 Hz, the small myelinated Aδ fibers are stimulated at 250 Hz, and the small unmyelinated C fibers are stimulated at 5 Hz. Reduced CPT findings indicate a hyperesthetic condition (less current is needed to evoke a response) seen early in CIPN. Elevated CPT results indicate a loss of nerve function (more current is needed to evoke a response), reflecting a hypoesthesia, which is typical after repeated insults with neurotoxic chemotherapy.

Normative values for CPT have been established in healthy populations in both the USA (Neurotron.com) and abroad [23]. CPT testing has been validated and well-documented in peripheral neuropathy resulting from several different etiologies [24–27]. CPT values were found to decrease in diabetic patients at the 2,000-Hz frequency, and these values were moderately correlated with vibration testing [28]. However, studies utilizing CPT testing for evaluation of CIPN in cancer patients are limited. In patients with ovarian cancer treated with paclitaxel and carboplatin, CPT values peaked within days of chemotherapy administration, indicating hyposensitivity or sensory dullness. The CPT changes were seen at 2,000 Hz, indicating chemotherapy effect on large, Aβ myelinated nerve fibers, which are associated with touch, mild pressure, and vibration. Over time, CPT values decreased as patient complaints of CIPN rose, consistent with hyperesthesia [29].

When neurons become hyperexcitable, the amount of stimulation required to instigate depolarization and action potential is lowered. This in turn may result in a significant decrease in the CPT. If CPT is adequately sensitive and reliable in detecting sensory function changes at an early point during chemotherapy, the potential exists for improvement of clinical

care and CIPN management. The primary purpose of this pilot study was to evaluate feasibility of the CPT for use in an oncology population. In addition, we sought to investigate associations between CPT and clinical measures of CIPN, including quantitative sensory testing (QST), deep tendon reflexes, strength, and self-reported symptoms in patients receiving taxane and platinum chemotherapy in order to understand the potential role that CPT might play in CIPN identification and monitoring.

Methods

Data collection

Data from a prospective, observational pilot study, designed to evaluate the development of CIPN using CPT, were abstracted into a data file for this analysis using SAS version 9.0. The clinical study consisted of a convenience sample of 35 adult subjects at the University of Maryland Greenebaum Cancer Center.

Study eligibility included (a) age 21–85 years, (b) diagnosis with a solid tumor, (c) planned receipt of taxane and/or a platinum compound, (d) chemotherapy-naïve, and (e) able to speak English and provide written informed consent. Patients were excluded if they had a life expectancy of less than 3 months or neuropathy from pre-existing conditions. Chemotherapy was administered under direction of the treating physician at Greenebaum Cancer Center. All subjects who developed neuropathy were managed with standard supportive care.

Following approval by the University of Maryland Institutional Review Board, informed consent was obtained followed by collection of demographic and cancer treatment information. At baseline and with each drug cycle, which typically occurred every 7, 21, or 28 days, CIPN measurements were done. For participants who ended chemotherapy prematurely due to CIPN, a final set of study measurements was done at the last study visit. All other participants had ongoing assessments and underwent a final end of study assessment either at completion of the chemotherapy regimen or following 6 months of treatment whichever came first.

CIPN was graded using the NCI-CTCAE v3.0 for sensory neuropathy. The diagnosis of CIPN was based on the NCI-CTCAE v3.0 grade of ≥1 for sensory neuropathy, with at least a report of paresthesias of fingers or toes (grade 1). CIPN grading ranges from 1, which is a mild neuropathy not interfering with function, to 5, which is death. Participants without evidence of CIPN were classified as "no neuropathy."

Measures

Sensory function assessments were made using CPT, QST, and mechanical sensation at the right great toe. Rationale for QST was to assist in determining sensory loss (hypoesthesia and hypoalgesia) or sensory gain (hyperesthesia, hyperalgesia, and allodynia) during the course of the patient's chemotherapy. In addition, motor function was evaluated by measuring grip strength of the dominant hand and deep tendon reflexes at the ankle of the right leg. Subjective questionnaires included the Neuropathic Pain Scale (NPS) and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group—Neurotoxicity (FACT&GOG-Ntx).

Patient-reported subjective assessments were obtained prior to objective testing to avoid potential influence of examinations on patient subjective responses and recall of symptoms. CPT measures were collected prior to other objective measures to avoid any influence of other clinical examinations on CPT measures. QST measures were sequenced consistent with the standardized QST protocol developed by Rolke et al. [30], which orders frequency testing from smaller Aδ and C fibers to larger Aβ sensory fiber function (Table 1).

Subjective measures

NCI-CTCAE This study utilized the neuropathy symptom profile of NCI-CTCAE v3.0, which includes sensory, motor, and pain symptoms [13]. Five categories of severity are graded from 1 (asymptomatic) to 5 (deceased). NCI-CTCAE v3.0 demonstrates moderate inter-rater reliability (ICC=0.71–0.75) for the sensory item [31]. Grade 1 or higher was used to classify subjects as having CIPN in this study, and only the sensory neuropathy item was used to classify patients.

NPS The NPS is a 10-item multidimensional tool that includes self-report visual analogue scales to quantify two global pain domains (pain intensity and unpleasantness), six neuropathic pain qualities (sharp, dull, hot, cold, sensitive, and itchy), two pain locations (surface and deep), and one semistructured question about temporal sequence [32]. The measure has been validated in patients with a number of diseases. The majority of the 10 items demonstrated correlations $r<0.50$ with one another, supporting item discriminant validity [32]. A higher score is associated with increased pain.

FACT&GOG-Ntx This 38-item chemotherapy treatment effect specific measurement tool used to evaluate the severity and impact of CIPN symptoms on functional status and health-related quality of life [33]. For the FACT&GOG-Ntx, higher scores indicate better quality of life. The FACT&GOG-Ntx has demonstrated reliability, with a Cronbach's alpha of 0.81 for the neurotoxicity subscale and an overall Cronbach's alpha of 0.84. Furthermore, the FACT&GOG-Ntx and the Ntx subscale have demonstrated sensitivity to clinical change over time [33]. The FACT&GOG-Ntx overall score with its neurotoxicity subscale (*ntx*) was able to differentiate between the chemotherapy naïve and those with CIPN ($p<0.01$),

Table 1 Description and sequence of measures administered at each visit

Test	Test score associations with CIPN	Afferent nerve fibers tested
NCI Common Toxicity Criteria	Increased	
Neuropathic Pain Scale	Increased	
FACT&GOG*ntx*	Decreased	
CPT	Increased early (hyperesthesia)	C (CPT 5 Hz)
	Decreased later (hypoesthesia)	Aδ (CPT 250 Hz)
		Aβ (CPT 2,000 Hz)
A. Thermal detection thresholds		
1. Cold detection threshold	Increased temperature	C
2. Warm detection threshold	Decreased temperature	C
B. Pinprick detection	Decreased frequency	Aδ
C. Mechanical detection threshold	Increased monofilament gauge	Aβ
D. Vibration detection	Decreased time to extinction	Aβ
E. Grip strength	Decreased strength	None
F. Deep Tendon Reflex	Decreased reflex response	Aβ

indicating discriminant validity. Others have reported the area under the curve for receiver operating curve FACT&GOG-Ntx as 0.81, indicating a good ability of the measure to discriminate between patients with and without an NCI-CTC-documented CIPN [34]. A functional subscale of the FACT&GOG-Ntx, the Trial Outcome Index (TOI), was also used in this analysis to evaluate aspects of physical function. The TOI is calculated by adding scores from physical well-being, functional well-being, and CIPN symptoms subscales.

Objective measures

CPT The Neurometer® (Neurotron, Baltimore MD) uses a painless electrical stimulus, which generates constant alternating current via sinusoid waveform with a stimulus output intensity range of 0.01 to 9.99 milliamperes (mA). The skin of the stimulus site was cleaned with a mildly abrasive cream to remove any excess oil or dead skin that could impede the transmission of the electrical stimulus. The introduction of electrical stimulation was done through two gold electrodes (12 mm diameter) placed on the surface of the skin resulting in distal afferent sensory nerve fiber depolarization, which was transmitted and perceived by the individual being tested. As previously described, lower CPT values indicate hyperesthesia, with higher values consistent with hypoesthesia, which is indicative of established CIPN.

QST QST measurements were assessed at the right great toe, targeting the peroneal nerve using the following order described in Table 1. Thermal sensation was assessed by measuring warm and cold detection threshold (WDT and CDT), the number of paradoxical heat sensations with alternating cold and warm stimuli or thermal sensory, and cold and heat pain threshold. Mechanical sensation was measured by determining mechanical detection threshold, pinprick detection, and vibration perception threshold. In addition to the QST measures, two tests of sensorimotor function (grip strength and deep tendon reflexes) were included to assess the effects of the neurotoxic drugs on the sensorimotor system.

Thermal detection thresholds Thermal testing was measured using the Pathway Model ATS (Medoc, Israel) peltier device. This device is computer operated, and study subjects were provided with a button to terminate the stimulus at any time during the testing procedure. A thermode with a 16×16 mm surface area was applied to the plantar surface of the right great toe, and a baseline thermode temperature was set to 32 °C. During application of the thermal stimuli, the temperature increased or decreased from 32 °C with a 1 °C/s ramp, and the stimuli were terminated when the subject first perceived the hot or cold sensation and pressed the stop button. Mean detection threshold temperatures were calculated from three consecutive cold and three consecutive warm measurements. During threshold detection testing, the subjects were asked to report any paradoxical heat sensations, which were recorded by the investigator. C fibers are tested using this instrument. For warm detection threshold, reduced heat tolerance is associated with CIPN. Similarly, with cold detection threshold, reduced cold tolerance is associated with CIPN.

Mechanical detection thresholds MDT was obtained using Semmes-Weinstein monofilaments (Touch Test Sensory Kit, myNeurolab.com) beginning with the 2.83 fiber (0.07 g). During testing, the fiber was applied perpendicular to the plantar surface of the great toe until the fiber began to bend and was held in place for 1 second and removed. This was repeated three times, and the subject was asked to report if the fiber could be felt when it was applied. If the subject was able

to detect the application of this fiber during at least one out of three applications, the testing stopped and this fiber was recorded as the mechanical detection threshold [35]. If the application was not detected, the subject was tested with the next larger fiber in the series. The reliability of mechanical detection threshold using Semmes-Weinstein monofilament fibers has been established in healthy participants and in patients with neuropathic injury [36, 37]. Aβ fibers are tested using this method. Greater gram force is required for a positive test in patients with CIPN.

Vibration perception threshold Vibration detection was measured using a graduated tuning fork (Rydel-Seiffer, US Neurologicals, Poulsbo, WA) placed on the dorsum of the right great toe between the nail and the distal interphalangeal joint. The two arms of the 128-Hz tuning fork are fitted with calibrated weights at the ends, and as the amplitude decreases, the intersection of the triangles moves upward on the weight (toward the 8 mark). This test was performed three times, and a mean of the scores was calculated. The reliability and validity of the Rydel-Seiffer graduated tuning fork has been reported in several reports in healthy subjects and in those with various peripheral neuropathic pathologies [38–40]. Aβ fibers are tested using this method. Vibration sensation is lost sooner in CIPN, which means that lower scores are associated with increased CIPN.

Pinprick sensibility Pinprick detection was assessed using a sterile 18 g needle (sharp stimulus) and a sterile paper clip with one end bent at 90° away from the clip body to form a probe (dull stimulus). Three sharp and three dull stimuli (total of six) were applied in a random order to the plantar surface of the right great toe with sufficient force to cause a slight indentation without puncture of the skin. With each application, the subject was asked to identify whether the sensation was sharp or dull. The investigator recorded the stimulus type and subject response.

The reproducibility of pinprick sensation between examiners is fair in patients with diabetes (Cohen's $\kappa = 0.36$) [41]. When compared to healthy controls, subjects with CIPN demonstrate significant reductions in pin prick sensibility ($p < 0.001$) [10]. Aδ fibers are evaluated using this test. Lower scores are associated with CIPN.

Deep tendon reflexes Deep tendon reflexes were tested at the ankle of the right leg. With the foot supported, a reflex hammer was used to strike the Achilles tendon. This test was performed three times, and a mean of the scores was calculated. Reflexes were graded on a 0–4+ plus scale using the National Institute of Neurological Disorders and Stroke guidelines [42]. When combined with vibration perception and position sensibility, these measures identify peripheral neuropathy in older diabetics with a sensitivity of 94 % and specificity of 84 % [43]. Lower scores indicate reduced DTRs, which are seen in CIPN.

Grip strength Grip strength of the dominant hand was measured using a Jamar Dynamometer (US Neurologicals, Poulsbo, WA). The subject was asked to quickly exert a maximal grip force and then relax the grip. The investigator recorded the maximal force and reset the dynamometer needle to zero. This test was performed three times, with a rest period of 30 seconds between trials, and a mean of the scores was calculated. Lower scores are associated with decreased motor strength, which may occur in CIPN.

Statistical analysis

Descriptive analyses were conducted with means and standard deviations for continuous variables and proportions for categorical variables. T-tests assessed continuous variable (age and number of chemotherapy cycle) differences between the CIPN group and non-CIPN group; either chi-square or Fisher's exact test, whichever was appropriate, was used to test the difference for categorical variables (race, gender, and patient characteristics) among the two groups. Bivariate mixed models, accounting for the intraclass correlation between repeated assessments in patients, were used to assess the relationship between CPT at each frequency (5, 250, and 2,000 Hz) and each of the subjective and objective measurements described in Table 1.

Results

Following Institutional Review Board approval of the study, 35 patients provided written consent to participate and were enrolled. Of the 35 participants, six were not included in the final analysis due to death prior to the second treatment ($n = 1$), concurrent enrollment in another treatment study which precluded continued participation ($n = 1$), failure to disclose a pre-existing neuropathy ($n = 1$), and transfer of medical care to another facility ($n = 3$). For the final data analysis, therefore, 29 subjects were evaluable. In the present analysis, the sample eligible for analysis included the same 29 subjects from the primary study based on identical eligibility criteria.

Overall, the mean age of participants was 57 years, and the average number of chemotherapy visits was seven. Participant characteristics are provided in Table 2. An independent sample t-test showed no statistically significant difference between the mean age of those developing CIPN compared to those who did not develop CIPN ($p = 0.368$). Similarly, there were no significant differences between subjects with and without CIPN in regard to gender ($p = 0.245$) or race ($p = 0.106$). There were, however, differences between groups in the number of chemotherapy cycles, with those developing CIPN having received more chemotherapy treatment ($p =$

0.014). According to the NCI-CTCAE v 3.0 definition of CIPN used in this study (grade ≥1), nine participants developed sensory symptoms consistent with CIPN, three of whom progressed in severity sufficient to require chemotherapy cessation. Among the final clinical tests, which were conducted in subjects following the highest cumulative chemotherapy dose, warm detection thresholds differed between individuals with and without NCI-CTCAE determined CIPN ($p=0.01$). For self-report measures, the FACT total score ($p=0.006$) as well as the FACT ntx neurotoxicity subscale ($p<0.001$) and NPS ($p=0.014$) were significantly different between those with and without NCI-CTCAE defined CIPN (Table 3). There was no significant relationship between CIPN and CPT at each frequency (2,000 Hz, $p=0.80$; 250 Hz, $p=0.76$; 5 Hz, $p=0.15$, Table 4).

Associations between CPT and clinical measures

Cold detection thresholds were inversely associated with CPT 5 [$b=-2.5$, 95 % CI, (−4.5, −0.5)] and 2,000 frequencies [$b=-7.5$, 95 % CI, (−11.8, −3.3)], indicating reduced ability to tolerate cold temperatures as hyperesthesia increased (Table 5). Deep tendon reflexes were also inversely associated with CPT 2000 [$b=-52.8$, 95 % CI, (−94.6, −10.9)], indicating diminished reflexes in the presence of hypoesthesia. No other associations were found between any CPT frequency and remaining clinical tests. Among subjective measures, the FACT&GOG total score [$b=-1.8$, 95 % CI, (−3.5, −0.05)] as well as *ntx* neurotoxicity [$b=-5.4$, 95 % CI, (−9.8, −0.9)] and *toi* function subscales [$b=-2.2$, 95 % CI, (−4.2, −0.2)] were inversely associated with CPT 2000, indicating reduced QoL, increased CIPN symptoms, and reduced function as hypoesthesia increases. The NCI-CTCAE V3.0 sensory neuropathy item was positively associated with CPT 2000 [$b=37.5$, 95 % CI, (1.4, 73.6)], demonstrating more CIPN symptoms as hypoesthesia increased.

Table 2 Patient Characteristics

Characteristic	Overall $N=29$	CIPN $N=9$	No CIPN $N=20$
	Mean (SD)		
Age	56.7 (10.4)	54.0 (10.3)	57.9 (10.5)
Number of chemotherapy cycles	7.0 (3.2)	9.1 (3.3)	6.0 (2.8)
	Frequencies (%)		
Gender			
Male	15 (51.7)	3 (33.3)	12 (60.0)
Female	14 (48.3)	6 (66.7)	8 (40.0)
Race			
Caucasian	17 (58.6)	3 (33.3)	14 (70.0)
African-American	10 (34.5)	5 (55.6)	5 (25.0)
Hispanic	1 (3.4)	0	1 (5.0)
Asian	1 (3.4)	1 (11.1)	0
Cancer site			
Breast	8(27.5)	4 (44.4)	4 (20.0)
Head/neck	8 (27.5)	2 (22.2)	6 (30.0)
Lung	4 (13.8)	1 (11.1)	3 (15.0)
Gastrointestinal	3 (15.0)	1 (11.1)	3(15.0)
Genitourinary	4 (13.8)	1 (11.1)	3 (15.0)
Skin	1 (3.4)	0	1 (5.0)
Stage of disease			
I	2 (6.9)	1 (5.0)	1 (11.1)
II	6 (20.7)	5 (25.0)	1 (11.1)
III	11 (37.9)	6 (30.0)	5 (55.6)
IV	10 (34.5)	8 (40.0)	2 (22.2)
Chemotherapy regimen			
Cisplatin	9 (31.0)	2 (22.2)	7 (35.0)
Paclitaxel	5 (17.2)	4 (44.4)	1 (5.0)
Paclitaxel/cisplatin	2 (6.8)	0	2 (10.0)
Oxaliplatin	2 (6.8)	1 (11.1)	1 (5.0)
Docetaxel	2 (6.8)	0	2 (10.0)
Carboplatin	1 (3.4)	0	1 (5.0)
Paclitaxel/carboplatin	5 (17.2)	2 (22.2)	3 (15.0)
Docetaxel/carboplatin	3 (10.3)	0	3 (15.0)
Chemotherapy cycle interval			
Weekly	7 (24.1)	3 (33.3)	4 (5.0)
Every 2 weeks	3 (10.3)	1 (11.1)	2 (10.0)
Every 3 weeks	19 (65.5)	5 (55.6)	14 (70.0)

Discussion

This exploratory pilot study, which included subjects with a variety of malignancies and chemotherapy regimens, was designed as a proof-of-concept investigation to evaluate the feasibility of using CPT in CIPN patients. Participant enrollment and retention in this longitudinal study demonstrated feasibility of using CPT in patients undergoing chemotherapy. CPT 2,000 was the frequency most often associated with physical examinations and subjective measures of CIPN. This finding suggests a potential role for CPT 2,000 in evaluating patients prior to and along the neurotoxic treatment trajectory. However, the presumed specificity of CPT 2,000 for large, myelinated Aβ fibers is challenged by its correlation with cold detection thresholds, which reflects changes in small, unmyelinated nerve fiber conduction and functional thresholds. As expected, in view of the frequent decrease or disappearance of deep tendon reflexes in CIPN patients, an inverse association with CPT 2,000 was identified, indicating increased hyporeflexia as hypoesthesia progresses [44].

CPT 2,000 was also associated with a well-validated measure of neuropathy-related QoL, the FACT&GOG overall

Table 3 Differences of final clinical test scores between those with and without CIPN by *t* test

Characteristic	Overall ($n=29$)	CIPN status		
	Mean (SD)	CIPN ($n=9$) Mean (SD)	No CIPN ($n=20$) Mean (SD)	p value
Cold detection threshold	19.1(5.0)	19.8(3.9)	18.7(5.4)	0.576
Warm detection threshold	48.8(3.0)	46.7(4.3)	49.7(1.6)	*0.010*
Pinprick sensibility	0.78(0.17)	0.78(0.19)	0.78(0.16)	0.961
Vibration detection threshold	5.0(2.4)	4.2(2.9)	5.3(2.2)	0.273
Mechanical detection threshold	1.7(2.2)	2.4(3.4)	1.4(1.5)	0.273
Grip strength	32.4(9.4)	30.1(11.4)	33.5(8.5)	0.385
Ankle deep tendon reflexes	1.1(0.7)	1.0(0.7)	1.2(0.7)	0.482
Neuropathic pain scale	13.3(18.1)	25.2(25.3)	7.9(10.8)	*0.014*
Fact/GOG-Ntx total score	96.5(19.0)	82.8(14.3)	102.7(17.7)	*0.006*
FACTntx subscale	9.5(9.6)	21.3(7.9)	4.2(3.7)	*<0.001*

Italics indicate significant findings/associations

score, as well as its neurotoxicity and functional subscales. This association suggests an important clinical opportunity because increased CPT readings may indicate impending reduction in QoL and serve as a red flag for clinicians as they plan treatment that may further reduce performance of daily activities. The NCI-CTCAE v3.0 sensory score was associated with CPT 2,000 Hz, indicating CIPN impairment occurs alongside worsening hypoesthesia and providing evidence of convergent validity of CPT 2000 for sensory neuropathy identification. The lack of significant differences on CPT frequencies between groups with and without CIPN is not surprising, given the small sample of individuals with CIPN and wide range of drug type and cumulative dose for the overall sample. Future research in a larger, homogeneous patient population will provide a more accurate evaluation of how well CPT differentiates between patients with and without CIPN.

Limitations The small sample size restricted some analyses, allowing mainly for descriptive statistics and bivariate associations. Furthermore, subject heterogeneity may have precluded additional significant findings. Although patients with a variety of malignancies and chemotherapy regimens provided important early information about recruitment feasibility as well as the value of CPT in assessing CIPN impairment across treatments, future study involving subjects receiving the same chemotherapy regimen will reduce potential confounding influences during CPT evaluation. Another benefit of conducting CPT examinations in subjects with identical chemotherapy includes more sophisticated statistical analyses, such as mixed modeling, where intercorrelations between treatments may be controlled for each patient. Measurement consistency may have been affected by multiple examiners. Inter-rater reliability was not examined during the study, and in future studies, evaluating the similarity with which raters are implementing clinical tests will assure that clinical examinations are being conducted consistently. However, these preliminary results indicate that CPT, a noninvasive, objective tool to measure the integrity of selected nerve fibers, deserves to be tested in a large, prospective study with a homogeneous patient population receiving neurotoxic chemotherapy. The use of CTCv3.0 criteria for classifying participants with CIPN is not a sensitive or specific measure of the phenomenon. In future studies, it is prudent to employ a more robust clinical measure of CIPN, such as Total Neuropathy Score©-clinical version, in order to make more confident classification of presence and degree of CIPN. This will allow for improved interpretation of CPT findings in the setting of CIPN.

CPT 2,000 measurement may allow anticipation of impending worsening of patient-reported outcomes, such as QoL, and could be useful for earlier intervention with chemotherapy dose modification, pharmacologic treatment, or other preventive measures as they are developed. In addition, CPT 5 may be a potentially useful evaluation of earlier onset CIPN affecting C fiber activity, especially if it is used in conjunction with CPT 2,000. However, longitudinal study

Table 4 Differences in normalized means of final CPT measures between patients with and without CIPN

CIPN			
CPT frequency	No ($N=20$)	Yes ($N=9$)	t (p value)
CPT2000	626.3 (289.5)	597.4 (277.0)	0.25 (0.80)
CPT250	186.4 (117.1)	172.8 (88.0)	0.31 (0.76)
CPT5	129.2 (124.5)	63.0 (66.9)	1.49 (0.15)

Table 5 Bivariate association between CPT and clinical measures in linear mixed models using patients as random intercept

Measures	CPT 5		CPT 250		CPT 2000	
	b(95 % CI)	*p* value	*b*(95 % CI)	*p* value	*b*(95 % CI)	*p* value
Clinical examination						
Measure of C fiber activity						
Cold detection threshold	*−2.5(−4.5, −0.5)*	*0.015*	−2.6(−5.7, 0.4)	0.091	*−7.5(−11.8, −3.3)*	*<0.001*
Warm detection threshold	2.2(−1.5, 5.9)	0.248	5.2(−0.3, 10.7)	0.066	6.5(−1.1, 14.2)	0.093
Measure of Aδ fiber activity						
Pinprick sensibility	12.5(−45.4, 70.3)	0.672	−32.8(−119.5, 53.9)	0.457	−50.5(−170.7, 69.7)	0.408
Measure of Aβ fiber activity						
Vibration detection threshold	1.3(−4.8, 7.5)	0.675	1.7(−7.6, 10.9)	0.721	−2.8(−16.2, 10.6)	0.684
Mechanical detection threshold	0.9(−5.5, 7.3)	0.778	−2.2(−11.7, 7.4)	0.655	2.0(−11.4, 15.4)	0.771
Measures of motor system						
Grip strength	2.1(−0.1, 4.2)	0.063	1.2(−4.0, 6.4)	0.652	1.2(−4.0, 6.4)	0.652
Ankle deep tendon reflexes	−16.6(−36.4, 3.2)	0.100	−12.6(−42.5, 17.3)	0.407	*−52.8(−94.6, −10.9)*	*0.014*
Subjective measures						
Neuropathic Pain Scale	0.4(−0.4, 1.2)	0.301	0.4(−0.7, 1.6)	0.475	0.6(−1.1, 2.3)	0.498
Fact-GOG-Ntx Total Score	−0.02(−0.05, 0.02)	0.346	−0.6(−1.7, 0.6)	0.321	*−1.8(-3.5, −0.05)*	*0.044*
FACT_toi Subscale	−0.4(−1.3, 0.6)	0.454	−0.3(−1.7, 1.1)	0.671	*−2.2(−4.2, −0.2)*	*0.035*
FACT-ntx Subscale	0.2(−1.8, 2.3)	0.822	0.1(−3.0, 3.2)	0.936	*−5.4(−9.8, −0.9)*	*0.019*
NCI-CTCAE v3.0 neuropathy						
Motor item	2.4(−19.9, 24.6)	0.834	−12.9(−46.2, 20.3)	0.443	43.1(−1.8, 87.9)	0.060
Sensory item	11.8(−5.9, 29.4)	0.191	14.0(−12.6, 40.6)	0.300	*37.5(1.4, 73.6)*	*0.042*
Pain item	2.1(−28.0, 32.3)	0.889	−6.4(−51.6, 38.9)	0.782	1.9(−60.3, 64.0)	0.953

Italics indicate significant findings/associations

in subjects with homogeneous chemotherapy regimens is required in order to provide definitive data about the predictive value of CPT. If predictive validity is established in future, identification of changes in sensory fiber function following chemotherapy initiation and prior to symptom onset may lead to earlier CIPN detection when testing novel chemotherapeutic agents. Such strides will improve the likelihood that patients achieve chemotherapy completion while avoiding permanent nerve damage and declines in function as well as QoL.

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