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Correspondence between neurophysiological and clinical measurements of chemotherapy-induced peripheral neuropathy: secondary analysis of data from the CI-PeriNoms study

Kathleen A. Griffith[1], **Susan G. Dorsey**[1], **Cynthia L. Renn**[1], **Shijun Zhu**[1], **Mary E. Johantgen**[1], **David R. Cornblath**[2], **Andreas A. Argyriou**[3], **Guido Cavaletti**[4], **Ingemar S. J. Merkies**[5], **Paola Alberti**[4], **Tjeerd J. Postma**[6], **Emanuela Rossi**[7], **Barbara Frigeni**[4], **Jordi Bruna**[8], **Roser Velasco**[8], **Haralabos P. Kalofonos**[3], **Dimitri Psimaras**[9], **Damien Ricard**[10], **Andrea Pace**[11], **Edvina Galie**[11], **Chiara Briani**[12], **Chiara Dalla Torre**[12], **Catharina G. Faber**[5], **Roy I. Lalisang**[13], **Willem Boogerd**[14], **Dieta Brandsma**[14], **Susanne Koeppen**[15], **Joerg Hense**[15], **Dawn J. Storey**[16], **Simon Kerrigan**[16], **Angelo Schenone**[17], **Sabrina Fabbri**[17], **Maria Grazia Valsecchi**[7], and **CI-PeriNomS Group**[**]

[1]University of Maryland, Baltimore, MD, USA [2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA [3]Division of Clinical Oncology-Department of Medicine, University Hospital of Patras, Patras, Greece [4]Department of Surgery and Translational Medicine, University of Milan-Bicocca and Department of Oncology, S. Gerardo Hospital, Monza, Italy [5]Department of Neurology, Maastricht University Medical Center, Maastricht and Spaarne Hospital, Hoofdorp, The Netherlands [6]Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands [7]Clinical Epidemiology and Biostatistic Research Center, Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Monza, Italy [8]Unit

Address correspondence to: Kathleen A. Griffith, University of Maryland, 655 W. Lombard Street #729B, Baltimore, MD 21201, USA. Tel: 410-706-1165; Fax: 410-706-3289; griffith@son.umaryland.edu..

[**]CI-PeriNomS Group Collaborators (Retrievable in Pubmed): MG Valsecchi, S Galimberti, Clinical Epidemiology and Biostatistic Research Center, Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Monza, Italy. C Briani, C Dalla Torre, M Lucchetta, M Campagnolo, Department of Neurosciences, University of Padova, Padova, Italy. CG Faber, EK Vanhoutte, M Bakkers, B Brouwer, M Boogerd, Department of Neurology, Maastricht University Medical Center, Maastricht and Spaarne Hospital, Hoofdorp, The Netherlands. RI Lalisang, Division of Medical Oncology, Department of Internal Medicine, GROW-School of Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands. W Boogerd, D Brandsma, Department of Neuro-oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands. S Koeppen, J Hense, Department of Neurology and West German Cancer Center, University of Essen, Essen, Germany. DJ Storey, S Kerrigan, R Grant, Edinburgh Centre for Neuro-Oncology and Edinburgh Cancer Research Centre, Western General Hospital, Edinburgh, UK. A Schenone, S Fabbri, L Reni, B Piras, Department of Neurosciences, Ophthalmology, Rehabilitation, Genetic and Maternal Infantile Sciences Center of Excellence for Biomedical Research, University of Genova, Genova, Italy. F Lanzani, L Mattavelli, ML Piatti, P Binda, P Bidoli, M Cazzaniga, D Cortinovis, Department of Surgery and Translational Medicine, University of Milan-Bicocca and Department of Oncology, S. Gerardo Hospital, Monza, Italy. A Pessino, Medical Oncology Division, University Hospital San Martino-IST, Genoa, Italy. L Padua, G Granata, Department of Neurosciences Cattolica University, Rome, Don C. Gnocchi Foundation, Italy. M Leandri, I Ghignotti, Interuniversity Centre for Pain Neurophysiology at the University of Genova, Italy. R Plasmati, F Pastorelli, I.R.C.C.S. of Neurological Sciences, Bellaria Hospital, Bologna, Italy. JJ Heimans, Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands. M Eurelings, RJ Meijer, Department of Neurology, Spaarne Hospital, Hoofddorp, The Netherlands. W Grisold, E Lindeck, Pozza Department of Neurology, Kaiser Franz Josef Hospital, Vienna, Austria. A Mazzeo, A Toscano, M Russo, Department of Neurosciences, Psychiatry and Anesthesiology, AOU “G. Martino”, Messina, Italy. C Tomasello, G Altavill, Department of Medical Oncology, University of Messina, Messina, Italy. M Penas Prado, C Dominguez Gonzalez, Servicio de Neurologia, Hospital Universitario Doce de Octubre, Madrid, Spain. J Brell, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

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of Neuro-Oncology, Department of Neurology, University Hospital of Bellvitge, L'Hospitalet, Spain [9]Service de Neurologie Mazarin, Hôpital Pitié-Salpêtrière, Paris, France [10]Service de Neurologie, Hôpital du Val-de-Grâce, Paris, France [11]Neurology Unit, National Cancer Institute Regina Elena, Rome, Italy [12]Department of Neurosciences, University of Padova, Padova, Italy [13]Division of Medical Oncology, Department of Internal Medicine, GROW-School of Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands [14]Department of Neuro-oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands [15]Department of Neurology and West German Cancer Center, University of Essen, Essen, Germany [16]Edinburgh Centre for Neuro-Oncology and Edinburgh Cancer Research Centre, Western General Hospital, Edinburgh, UK [17]Department of Neurosciences, Ophthalmology, Rehabilitation, Genetic and Maternal Infantile Sciences Center of Excellence for Biomedical Research, University of Genova, Genova, Italy

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) lacks standardized clinical measurement. The objective of the current secondary analysis was to examine data from the CIPN Outcomes Standardization (CI-PeriNomS) study for associations between clinical examinations and neurophysiological abnormalities. Logistic regression estimated the strength of associations of vibration, pin, and monofilament examinations with lower limb sensory and motor amplitudes. Examinations were classified as normal (0), moderately abnormal (1), or severely abnormal (2). Among 218 participants, those with class 1 upper extremity (UE) and class 1 or 2 lower extremity (LE) monofilament abnormality were 2.79 (95%CI: 1.28-6.07), 3.49 (95%CI: 1.61-7.55) and 4.42 (95%CI: 1.35-14.46) times more likely to have abnormal sural nerve amplitudes, respectively, compared to individuals with normal examinations. Likewise, those with class 2 UE and class 1 or 2 LE vibration abnormality were 8.65 (95%CI: 1.81-41.42), 2.54 (95%CI: 1.19-5.41) and 7.47 (95%CI: 2.49-22.40) times more likely to have abnormal sural nerve amplitudes, respectively, compared to participants with normal examinations. Abnormalities in vibration and monofilament examinations are associated with abnormal sural nerve amplitudes and are useful in identifying CIPN.

Keywords

assessment; chemotherapy; neurophysiology; peripheral neuropathy

Introduction

Increased cancer survival is due in part to the development and expanded use of chemotherapeutic agents in the adjuvant setting. Chemotherapy-induced peripheral neuropathy (CIPN) ranks among the major dose-limiting toxicities of many of these agents resulting in significant dose adjustments (Mantyh, 2006; Argyriou et al., 2012; Speck et al., 2013). These dose adjustments result in the delivery of potentially sub-optimal chemotherapy in the setting where the goal is to optimize treatment for a potentially lethal disease. The benefit of continuing chemotherapy often outweighs the drawback of CIPN,

even in the setting of sub-optimal CIPN symptom relief. Treatment of CIPN with medications provides modest results at best *(Windebank and Grisold, 2008)*. Preventive treatment for CIPN is desirable but has not been established; scientific evidence is thus far insufficient to warrant recommendation of any medication for CIPN prevention *(Albers et al., 2011)*. Long-term consequences of CIPN include disability and reduced quality of life *(Quasthoff and Hartung, 2002; Mielke et al., 2006)*, which may be difficult to ameliorate.

Compounding the lack of CIPN prevention and adequate treatment is the inconsistency with which CIPN is identified, characterized, and measured. A number of clinical measures are commonly used for documenting and grading CIPN (Oken et al., 1982; Ajani et al., 1990; Trotti et al., 2003), but reported reliability and construct validity estimates vary widely among the clinical measures *(Postma et al., 1998; Griffith et al., 2010)*. In addition, the responsiveness of these measures in the clinical trial setting is unknown. This leads to confusion for clinicians and researchers, who require well-validated clinical measures of CIPN. Furthermore, without validated outcome measures, therapeutic drug development is inhibited. Neurophysiological assessment of CIPN using nerve conduction studies (NCS) is considered the gold standard, as NCS are a reliable method to objectively quantify neuropathies including CIPN *(McHugh et al., 2012)*. The accuracy of clinical measures relative to that of NCS in CIPN is not yet known.

The Chemotherapy Induced Peripheral Neuropathy Outcomes Measures Standardization (CI-PeriNomS) study *(Cavaletti et al., 2013)* is a cross-sectional, multi-site, multi-national study of 281 participants with cancer, conducted between 2007-2009 and designed primarily to evaluate reproducibility and validity of existing CIPN measures, including impairment and quality of life. Initial findings from the CI-PeriNomS group included good inter- and intra-rater reliability estimates for a number of clinical CIPN examinations including vibration, light touch, and pin prick *(Cavaletti et al., 2013)*. This study established the reliability of clinical measurements of CIPN, providing evidence for their stability. NCS were also conducted in a subset of participants during the CI-PeriNomS study. The aim of the current analysis of data extracted from the prospective CI-PeriNoms study was to evaluate relationships between individual clinical measures and NCS among participants with CIPN. The evaluation of construct validity and ascertainment of clinical measures as equivalent substitutes for the reference standard of NCS in CIPN would indicate appropriateness of these measures for use in the oncology setting.

Materials and Methods

Sample

The details of the CI-PeriNomS study have already been reported *(Cavaletti et al., 2013)*. In brief, 281 participants with stable CIPN were recruited at 19 centers and evaluated twice by identically trained physician examiners. Importantly for the current study, individuals with co-morbid conditions that might confound clinical findings, (i.e., diabetes, alcohol abuse, select neurologic conditions such as paraneoplastic neuropathy) or peripheral nerve damage of another etiology were excluded *(Vorobeychik et al., 2011)*.

Participants were evaluated at two time-points, 2-3 weeks apart. During the first participant visit, two sets of CIPN clinical examinations were performed by two different trained physician examiners. If NCS were performed, they occurred during this first visit. NCS were performed at 13 of 19 participating study centers. During the second visit, clinical examinations were repeated by the same two examiners. In addition to inclusion criteria for the main CI-PeriNomS, this analysis also required NCS completion. A total of 218 participants met criteria for inclusion *(Cavaletti et al., 2013)*.

Measurement

Clinical variables from the CI-PeriNomS dataset chosen for comparison to NCS parameters were selected based on their potential content validity to detect CIPN and their ease of performance in clinical practice. These variables included vibration sense, light touch, and pin prick sensibility items from the modified Inflammatory Neuropathy Cause and Treatment Group Sensory Sumscore (mISS) *(Merkies et al., 2000a)* and vibration sense and pin prick sensibility items from the Total Neuropathy Score©, clinical version (TNS-c©) *(Cornblath et al., 1999)*. Strength and deep tendon reflexes (DTRs) were also assessed as part of the TNS-c© and were included in the analysis. All tests were performed bilaterally. For vibration sense, light touch, and pin prick sensibility scoring, the highest extension of dysfunction of the most affected arm and leg was recorded.

Vibration sense for both mISS and TNS-c© was assessed using the graduated Rydel-Seiffer tuning fork (U.S. Neurologicals, Poulsbo, WA), with printed directions on use and its normative data *(Martina et al., 1998)*. Initially, the tuning fork was placed on the dorsum of the right great toe between the nail and the distal interphalangeal joint. Readings from three separate examinations were averaged and recorded as the vibration value *(Merkies et al., 2000b)*.

Light touch for the mISS was assessed in all centers with standardized 10g monofilaments, contained within the Neuropen® (Owen Mumford, Woodstock, UK). 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 3 times and the subject was asked to report the ability to feel the fiber when it was applied. The reliability of mechanical detection threshold using Semmes-Weinstein monofilament fibers (SWMF) has been established in healthy participants and in patients with neuropathic injury (de Sonnaville et al., 1997; Felix and Widerstrom, 2009).

Pin prick sensibility for the mISS and TNS-c© was assessed using the disposable Neurotip (Owen Mumford, Woodstock, UK). Three sharp and three dull stimuli (total of 6) were applied in a random order to the plantar surface of the great toe with sufficient force to cause a slight indentation but no 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.

Strength for the TNS-c© was evaluated using the Medical Research Council (MRC) criteria *(Medical Research Council, 1976)*. The following were evaluated bilaterally: toe extension and flexion; ankle dorsiflexion; ankle plantar flexion; hip flexion; finger spread; thumb

abduction; wrist extension and flexion; and arm abduction. DTRs were assessed using the National Institute of Neurological Disorders and Stroke Myotatic Reflex Scale *(Hallett, 1993)*. DTRs were assessed at the ankle, knee, supinator, triceps, and biceps bilaterally.

Scores for individual clinical examinations comprising the mISS and TNS-c© measures originally ranged from 0-4, with definitions provided in Table 1. Anatomical extension of abnormalities were recorded differently between the two measures, with each mISS score corresponding to an identified abnormality at a particular upper *or* lower anatomical point, and each TNS-c© score associated with an abnormality up to an anatomical point for lower and upper extremities combined *(Cornblath et al., 1999; Merkies et al., 2000a)*. Because we anticipated relatively few clinical findings at levels 3 and 4 for both the mISS and TNS-c©, sensory item scores were combined in the following way: 0= normal findings; 1= CIPN with abnormal findings to the wrist/ankle; 2= CIPN with abnormal findings to the shoulder/groin. Strength and DTR scoring was similarly contracted.

NCS of the sural and fibular nerves on the non-dominant limb were recorded with standard surface recording techniques. The amplitude of the sural nerve sensory action potential (SAP) was measured form the first positive peak to the highest negative peak (peak-to-peak). The compound muscle action potential (CMAP) amplitude (baseline-to-peak) of the common fibular nerve was also recorded and analyzed. The distal skin temperature was maintained between 32° and 34°C. Values for each variable were compared with normal values by age from each center.

Statistical analysis

Data from CI-PeriNomS were abstracted into a data file for analysis. Descriptive statistics, including means, standard deviations for continuous variables as well as frequencies and percentages for categorical variables, were computed to profile the population. Due to the multi-center study design, the intra-class correlation among testing centers was done to assess clustering of participants within the same center. Lack of independence was accounted for in the regression analyses. Generalized linear mixed models with random intercept of centers, controlling for age, gender, and chemotherapy class, were used to evaluate the relationship between NCS and each of the 4 clinical measures changes. All analyses were performed using STATA 12.0 and SAS 9.3.

Results

Left and right measurements of the sural nerve SAP were strongly correlated ($r=0.75$, $p<0.001$). The characteristics of the study participants are summarized in Table 2. The mean age of the 218 participants was 62.7 (SD=9.8) years, and nearly half (46.8%) were 65 years and older. The majority was male (53.2%). Over two-thirds had received either platinum compounds (57.9%) or platinum-taxane combinations (14.4%).

Demographic characteristics and clinical test findings did not differ between those with normal or abnormal amplitudes of the sural and common fibular nerves, with the exception of chemotherapy type and cancer diagnosis among common fibular nerve abnormalities (Table 3). Multivariate mixed model results demonstrated monotonic, or changing in the

same direction, relationships between measures of vibration and light touch and sural SAP amplitude, when controlling for testing center, age, gender, and chemotherapy type (Tables 4 and 5). For vibrationusing the mISS, those with grade 2 upper extremity examination were nearly nine times (aOR=8.65; 95%CI: 1.81, 41.42) more likely to have an abnormal sural SAP amplitude compared to those with a grade 0 (normal) examination (Table 4). Participants with grade 1 and grade 2 lower extremity vibration examinations were more than two times (aOR=2.54; 95%CI: 1.19, 5.41) and seven times (aOR=7.47; 95%CI: 2.49, 22.40) more likely to have an abnormal sural SAP amplitude, respectively, compared to those with a normal examination. For the TNS-c©, which combines into a single score results from upper and lower extremity examinations, participants with a grade 2 vibration examination were four times (aOR=4.04; 95%CI: 1.57, 10.42) more likely to have an abnormal sural SAP amplitude.

Participants with a grade 1 upper extremity light touch examination with the mISS were nearly three times more likely to have an abnormal sural nerve SAP amplitude compared to those with a normal examination. Those with a grade 1 or 2 abnormal lower extremity light touch examination were more than three times and four times more likely to have an abnormal sural nerve SAP amplitude, respectively. Light touch is not a component of the TNS-c© and as such was not evaluated.

Pin sense was found to be predictive of abnormal neurophysiology only by TNS-c©, with participants with moderately abnormal findings more than two times likely to demonstrate abnormal sural nerve SAP amplitude (Table 5). There were no confirmatory associations observed with the mISS.

Because of significant findings between sural nerve SAP amplitude and grade 1 clinical examinations, additional analyses were done to explore further how CIPN limited to fingers and toes (Table 1) was associated with sural nerve SAP amplitude. For light touch, compared to those with a normal examination, those with abnormality in the fingers or toes were 3 (aOR=3.03; 95%CI: 1.23-7.47) and 2.5 (aOR=2.56; 95%CI: 1.03, 6.30) times more likely to have an abnormal sural nerve SAP amplitude, respectively (data not shown). Similar associations were not noted for vibration or pin sense findings limited to the fingers and toes.

Using the same control variables, no significant associations were noted between clinical variables and common fibular CMAP amplitude, with the exception of upper extremity pin prick sensibility test. Participants with grade 1 and 2 pin prick examinations on upper extremity were less likely (aOR=0.37; 95%CI: 0.15, 0.92, and aOR=0.09; 95%CI: 0.01, 0.68 for abnormal examinations to wrist and to shoulder, respectively) to have an abnormal common fibular CMAP amplitude as compared to controls. These findings on CMAP amplitude were not monotonic.

Discussion

The main purpose of the current secondary analysis of data extracted from the prospective, multicenter CI-PeriNoms study was to test correspondence between NCS and clinical

examinations in order to further ascertain the value of clinical examination in documenting CIPN. Moreover, this study aimed to demonstrate the ability of easily implemented clinical examinations of peripheral nerve impairment to predict abnormal sensory nerve amplitudes in participants with CIPN. Our findings indicate that as impairment progresses, the association strength between both vibration and light touch and NCS increases, indicating the potential value of these examinations in tracking CIPN progression over time, necessary for CIPN identification and management in the oncology setting. In particular, lower extremity examinations using both vibration assessed with the Rydel-Seiffer tuning fork and light touch assessed with the Neuropen® are the most closely associated with abnormal sural nerve amplitudes. Because CIPN tends to present initially in the lower extremities, stronger associations of lower compared to upper extremity examinations with abnormal sural SAP amplitude are understandable, and preferential use of lower extremity examinations is recommended when both cannot be evaluated.

Pin prick examination findings also assessed with the Neuropen® were more weakly associated with sural nerve amplitudes and were not consistent between mISS and TNS-c©. Only a single association was found between moderately abnormal TNS-c© and sural nerve SAP amplitude. Compared to vibration and light touch, examinations which had multiple associations with sural nerve amplitudes, pin prick does not offer equivalent strength of evidence for its clinical use. In addition, unlike vibration and light touch, which in conjunction with sural nerve SAP amplitude evaluate large nerve fiber function, pin prick measures impairment of small, thinly myelinated Aδ fibers. Because Aδ impairment likely happens in conjunction with Aβ fiber damage with CIPN, we predicted that an association may exist between a clinical measure of Aδ fiber impairment and the referent standard of Aβ function. Lack of an association allows us to conclude that sural nerve SAP amplitude is useful only for evaluation of clinical measures of large, myelinated Aβ fibers and not of other types of nerve fibers, which may be damaged concurrently by chemotherapy. Small fiber neuropathy in the context of CIPN can also occur as a result of Aδ and C fibers dysfunction which can be assessed with techniques such as intra-epidermal nerve fiber density or quantitative sensory testing *(Joint Task Force of the EFNS and the PNS, 2010)*. Clinical findings were also not predictive of abnormal common fibular nerve CMAP amplitudes. Although the upper extremity pinprick examination was less likely to predict abnormal common fibular nerve CMAP amplitudes compared to those with a normal pin prick test as CIPN severity increased, this association was not clinically relevant. Lack of association between clinical examinations and common fibular nerve CMAP amplitude indicates discriminant validity of the clinical measures, as the clinical examinations chosen to evaluate are designed to identify sensory nerve changes as opposed to those of the motor nerve. CIPN-associated motor impairment is also of concern, and motor symptoms generally occur following initial sensory dysfunction. Establishment of a reliable and easily applicable sensory clinical examination regimen is recommended, allowing fast and early identification of patients at risk to develop CIPN, hence avoiding late complications like motor deficits. The differences reported in Table 3 between groups with normal and abnormal CMAP amplitudes on chemotherapy type are likely due to the fact that oxaliplatin is much more likely to cause motor nerve changes acutely compared to other agents *(Hill et al., 2010; Burakgazi et al., 2011)*. This difference is not evident with SAP amplitudes, where sensory

effects occur more consistently, regardless of agent. The correlation between malignancy type and drug choice for treatment is likely responsible for the significant finding on this variable, which represents the same oxaliplatin phenomenon.

The current study had several limitations. Our ability to analyze the data, as with all secondary data sources, was limited by the variables available. Ideally, other variables that would have been useful to control for in the analyses include disease stage and cumulative dose of neurotoxic drug. Such variables would have allowed more possibilities to evaluate clinical test association with NCS in subgroups of participants with low, medium, and high cumulative doses of drug, for example. Evoked pain responses were not assessed in the primary study and as such were not evaluated in the present analysis. Because it is a potential confounding variable, including evoked pain as part of the clinical examination battery in future studies should be done.

The most important point resulting from study findings is that in this population of subjects with CIPN peripheral neuropathy can be measured with simple tools and that the results of those simple tool tests correlate with the gold standard test of neuropathy, nerve conduction studies. In addition, the tools are easy to use, and we believe they could become standard for objective assessment of CIPN in settings where more sophisticated tools are not available or necessary. Our analysis demonstrated correspondence between clinical tests of light touch and vibration with NCS, which does support diagnostic value of light touch and vibration. Future work by our group will evaluate patient reported outcomes as well as responsiveness of the clinical tests in tracking CIPN change over time. The first CI-PeriNomS study report demonstrated excellent inter-rater and intra-rater reliability of examinations evaluated in this study including vibration, light touch, and pin prick assessments *(Cavaletti et al., 2013)*. That work completed an essential first step in assuring that measures of interest perform consistently if they are administered sequentially by the same trained clinician and at the same point in time by more than one trained clinician. Our analysis adds to clinical test validity by demonstrating that vibration and light touch are associated with sural nerve amplitude abnormalities, which are commonly affected in CIPN. Our study, therefore, provides evidence for usefulness of these two clinical examinations, which can be introduced easily into the oncology clinic for initial and ongoing evaluation of CIPN. With relatively simple training, vibration and light touch testing can be completed within two minutes. Furthermore, the finding of increasingly abnormal clinical examinations as more predictive of abnormal sensory NCS, suggests potential for light touch and vibration responsiveness, the ability of a non-invasive measure to reflect changes in the patient's clinical condition over time. Vibration and light touch are therefore reliable indicators of CIPN impairment, acceptable for immediate use in oncology settings, and worthy of further evaluation for responsiveness.

Previous evidence indicates that a precise clinical evaluation combined with detailed electrophysiological testing could predict the final neurological outcome of CIPN *(Cavaletti et al., 2004; Argyriou et al., 2005)*. In particular, abnormalities in sural nerve amplitudes (reduction by >50% of the baseline value prior the initiation of chemotherapy) have been suggested to be independently predictive of worse neurological outcome *(Argyriou et al., 2005)*. A longitudinal study will be required in order to evaluate responsiveness of vibration

and light touch in this population. In particular, documentation of CIPN development and its trajectory through prospective study of chemotherapy naïve patients will build greater understanding of the CIPN clinical course in a consistent way, which is essential to move forward, towards a practical resolution of this serious side effect of cancer treatment.

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Table 1

CI-PeriNomS clinical tests, original and adapted scoring for current analysis.

Clinical test	Original Score	*Recoded* Clinical Test	Updated Score
mISS Upper/Lower Extremity (for vibration, light touch, pin prick)			
Normal at index finger/hallux	0	Normal	0
Abnormal at index finger/hallux	1	Abnormal to wrist/ankle	1
Abnormal at wrist/ankle	2		
Abnormal at elbow/knee	3	Abnormal to shoulder/groin	2
Abnormal at shoulder/groin	4		
TNSc Both Extremities (for vibration, light touch, pin prick)			
Normal	0	Normal	0
Reduced in fingers/toes	1	Reduced up to wrist/ankle	1
Reduced up to wrist/ankle	2		
Reduced up to the elbow/knee	3	Reduced to and/or above elbow/knee	2
Reduced above the elbow/knee	4		
TNSc Strength			
Normal- MRC 5	0	Normal	0
Mild weakness – MRC 4	1	Moderately abnormal strength	1
Moderate weakness- MRC 3	2		
Severe Weakness – MRC 2	3	Severely abnormal strength	2
Paralysis – MRC 0-1	4		
TNSc Deep Tendon Reflexes			
Normal ankle reflex	0	Normal	0
Ankle reflex reduced	1	Moderately abnormal reflexes	1
Ankle reflex absent	2		
Ankle reflex absent, others reduced	3	Severely abnormal reflexes	2
All reflexes absent	4		

Table 2

Sample characteristics, N=218

Characteristic	N (%)
Age	
Mean age (SD) 62.7(9.8)	
Under age 50	27(12.4)
50-64	89(40.8)
65 and older	102(46.8)
Cancer diagnosis	
Colorectal	96(44.5)
Breast	34(15.7)
Lung	19 (8.8)
Multiple myeloma	18 (8.3)
Ovary	18 (8.3)
Other	31(14.4)
Chemotherapy Agent	
Platinum compounds	125(57.9)
Platinum-Taxane combinations	31(14.4)
Taxanes	29(13.3)
Other	31(14.4)

Table 3

Differences within subject characteristic on normal and abnormal amplitudes.

Characteristic	Sural Nerve Amplitude			Common Fibular Nerve Amplitude		
	Normal (n=72) N(%)	Abnormal (n=146) N(%)	p-value	Normal (n=155) N(%)	Abnormal (n=63) N(%)	p-value
Age			0.151			0.197
Under age 50	11(40.7)	16(59.3)		19(70.4)	8(29.6)	
50-64	34(38.2)	55(61.8)		69(77.5)	20(22.5)	
65 and older	27(26.5)	75(73.5)		67(65.7)	35(34.3)	
Sex			0.069			0.176
Women	40(39.2)	62(60.8)		68(66.7)	34(33.3)	
Men	32(27.6)	84(72.4)		87(75.0)	29(25.0)	
Cancer diagnosis			0.784			**<0.001**
Colorectal	27(28.1)	69(71.9)		81(84.4)	15(15.6)	
Breast	14(41.2)	20(58.8)		20(58.8)	14(41.2)	
Lung	6(31.6)	13(68.4)		15(79.0)	4(21.1)	
Multiple myeloma	6(33.3)	12(66.7)		8(44.4)	10(55.6)	
Ovary	7(38.9)	11(61.1)		10(55.6)	8(44.4)	
Other	11(35.5)	20(64.5)		20(64.5)	11(35.5)	
Chemotherapy Agent			0.064			**<0.001**
Platinum compounds	37(29.6)	88(70.4)		104(83.2)	21(16.8)	
Plat-Tax combination	7(22.6)	24(77.4)		17(54.8)	14(45.2)	
Taxanes	14(48.3)	15(51.7)		18(62.1)	11(37.9)	
Other	14(45.2)	17(54.8)		15(48.4)	16(51.6)	

Table 4

Odds ratios estimates of abnormal sural nerve SAP and common fibular nerve CMAP by individual clinical measures (N=218). Modified Inflammatory Neuropathy Cause and Treatment Group Sensory Sumscore (mISS) examinations.

Clinical Examination			Abnormal Sural Nerve Amplitude	Abnormal Common Fibular Nerve Amplitude
		N(%)	aOR(95% CI) †	aOR(95% CI) †
mISS Pinprick Arms				
Normal index finger	(normal)	96(44.0)	1.00 (Ref.)	1.00 (Ref.)
Abnormal to wrist	(moderately abnormal)	108(49.5)	1.43(0.68, 2.99)	**0.37(0.15, 0.92)** *
Abnormal to shoulder	(severely abnormal)	14(6.5)	2.11(0.49, 9.13)	**0.09(0.01, 0.68)** *
mISS Pinprick Legs				
Normal at hallux	(normal)	45(20.6)	1.00 (Ref.)	1.00 (Ref.)
Abnormal to ankle	(moderately abnormal)	154(70.7)	2.04(0.94, 4.44)	0.92(0.39, 2.18)
Abnormal to groin	(severely abnormal)	19(8.7)	2.60(0.70, 9.62)	0.20(0.03, 1.22)
mISS Vibration Arms				
Normal index finger	(normal)	131(60.1)	1.00 (Ref.)	1.00 (Ref.)
Abnormal to wrist	(moderately abnormal)	58(26.6)	1.21(0.51, 2.91)	1.65(0.63, 4.33)
Abnormal to shoulder	(severely abnormal)	29(13.3)	**8.65(1.81, 41.42)** **	0.26(0.07, 1.03)
mISS Vibration Legs				
Normal at hallux	(normal)	66(30.3)	1.00 (Ref.)	1.00 (Ref.)
Abnormal to ankle	(moderately abnormal)	105(48.1)	**2.54(1.19, 5.41)** *	1.72(0.73, 4.06)
Abnormal to groin	(severely abnormal)	47(21.6)	**7.47(2.49, 22.40)** ***	0.81(0.27, 2.39)
mISS Light Touch Arms				
Normal index finger	(normal)	91(41.7)	1.00 (Ref.)	1.00 (Ref.)
Abnormal to wrist	(moderately abnormal)	111(50.9)	**2.79(1.28, 6.07)** *	0.87(0.36, 2.10)
Abnormal to shoulder	(severely abnormal)	16(7.4)	3.12(0.72, 13.51)	0.30(0.05, 1.70)
mISS Light Touch Legs				
Normal at hallux	(normal)	46(21.1)	1.00 (Ref.)	1.00 (Ref.)
Abnormal to ankle	(moderately abnormal)	146(67.0)	3.49(1.61, 7.55)**	1.21(0.49, 2.98)
Abnormal to groin	(severely abnormal)	26(11.9)	4.42(1.35, 14.46)*	0.67(0.16, 2.78)

†: aOR: Adjusted Odds Ratio for each of the clinical examinations, adjusted for age, gender, chemotherapy type and clustering in centers;

‡:the aOR was not estimated due to small sample size;

*: p<0.05;

**: p<0.01;

***: p<0.001.

Table 5

Odds ratios estimates of abnormal sural nerve SAP and common fibular nerve CMAP by individual clinical measures (N=218): Total Neuropathy Score-clinical® version examinations.

Clinical Examination			Abnormal Sural Nerve Amplitude	Abnormal Common Fibular Nerve Amplitude
		N(%)	aOR(95% CI) †	aOR(95% CI) †
TNSc Pin Sensibility				
Normal	(normal)	50(22.9)	1.00 (Ref.)	1.00 (Ref.)
Reduced up to wrist/ankle	(moderately abnormal)	140(64.2)	**2.68(1.18, 6.10)** *	1.19(0.49, 2.92)
Reduced to above elbow/knee	(severely abnormal)	28(12.8)	1.35(0.45, 4.02)	0.30(0.07, 1.31)
TNSc Vibration Sensibility				
Normal	(normal)	60(27.5)	1.00 (Ref.)	1.00 (Ref.)
Reduced up to wrist/ankle	(moderately abnormal)	98(45.0)	1.99(0.89, 4.44)	1.83(0.74, 4.52)
Reduced to above elbow/knee	(severely abnormal)	60(27.5)	**4.04(1.57, 10.42)** **	0.73(0.26, 2.05)
TNSc Deep tendon reflexes				
Normal		6(2.8)	--‡	--‡
Moderately abnormal		109(50.7)	1.00 (Ref.)	1.00 (Ref.)
Severe abnormal		100(46.5)	1.69(0.86, 3.32)	0.93(0.43, 1.98)
TNSc Strength				
Normal		145(66.5)	1.00 (Ref.)	1.00 (Ref.)
Moderately abnormal		69(31.7)	0.72(0.31, 1.68)	0.68(0.27, 1.75)
Severe abnormal		4(1.8)	--‡	--‡

†: aOR: Adjusted Odds Ratio for each of the clinical examinations, adjusted for age, gender, chemotherapy type and clustering in centers;

‡: the aOR was not estimated due to small sample size;

*: p<0.05;

**: p<0.01;

***: p<0.001.