

Co-occurrence and Metabolic Biomarkers of Sensory and Motor Subtypes of Peripheral Neuropathy from Paclitaxel

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Research Article

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Abstract

Purpose: Chemotherapy-induced peripheral neuropathy (CIPN) is the major treatment-limiting toxicity of paclitaxel, which predominantly presents as sensory symptoms, with motor symptoms in some patients. Differentiating CIPN into subtypes has been recommended to direct CIPN research. The objective of this study was to investigate whether sensory and motor CIPN are distinct subtypes with different predictive biomarkers in patients with breast cancer receiving paclitaxel.

Methods: European Organisation for Research and Treatment of Cancer Quality of Life questionnaire CIPN20 was used to evaluate CIPN. Clusters of the time course of sensory (CIPN_S), motor (CIPN_M), and the difference between sensory and motor (CIPN_S–CIPN_M) were identified using k-means clustering on principal component scores. Predictive metabolomic biomarkers of maximum CIPN_S and CIPN_M were investigated using linear regressions adjusted for baseline CIPN, systemic paclitaxel exposure, and body mass index.

Results: More sensory than motor CIPN was found (CIPN_S change: mean=10.8, ranged [-3.3, 52.1]; CIPN_M change: mean=3.5, range: [-7.5, 35.0]). Three groups were identified with No CIPN, Mixed CIPN, and Sensory-dominant CIPN (maximum CIPN_S: mean=12.7 vs. 40.9 vs. 74.3, $p<0.001$; maximum CIPN_M: mean=5.4 vs. 25.5 vs. 36.1, $p<0.001$; average CIPN_S–CIPN_M: mean=2.8 vs. 5.8 vs. 24.9, $p<0.001$). Biomarkers of motor CIPN were similar to previously identified biomarkers of sensory CIPN, including lower serum histidine ($p=0.029$).

Conclusion: Our findings suggest that sensory and motor CIPN co-occur and may not have differentiating metabolic biomarkers. These findings need to be validated in larger cohorts of patients treated with paclitaxel and other neurotoxic agents to determine the optimal approach to predict, prevent, and treat CIPN and improve patients' outcomes.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating side effect caused by several commonly used chemotherapy agents, including taxanes, platinum, and vinca alkaloids. CIPN causes sensory and motor symptoms in the upper and lower extremities that can progress to loss of function. CIPN symptoms can persist for years after chemotherapy [1–5] and severely diminish patient's quality of life [3, 6]. There are no effective agents to prevent or treat CIPN, so the only recommended management is to reduce or delay chemotherapy dosing or discontinue treatment, which reduces treatment efficacy and patient survival [7].

The clinical presentation of CIPN differs between and within drug classes [8, 9]. Paclitaxel-induced peripheral neuropathy presents with predominantly sensory symptoms including tingling, numbness, or burning pain [8, 9]. Some paclitaxel-treated patients also experience changes in motor functions caused

by muscle weakness [8–11], which is particularly concerning to older patients with cancer because they can lead to increased risk of falls [12, 13].

Expert panels have suggested differentiating CIPN into its sensory and motor subtypes in order to investigate pathophysiological mechanisms and develop preventive and treatment interventions [14, 15]. Additionally, if sensory and motor CIPN have distinct mechanisms, it would be reasonable to expect that they have distinct predictive biomarkers, which could help identify which patients should be prioritized for prevention trials or monitored more closely during treatment [14, 16, 17]. A previous analysis of patient-reported CIPN data prospectively collected from a cohort of patients receiving various neurotoxic chemotherapy agents identified four CIPN symptom subtype clusters: Sensory, Motor-dominant Mixed, Sensory-dominant Mixed, and a less clear autonomic cluster [18]. The prior study did not include a sufficient number of patients receiving individual neurotoxic agents to confirm this clustering pattern within each drug. Additionally, almost all biomarker studies have combined sensory and motor CIPN into a single endpoint or conducted analyses of sensory CIPN [19–28]; few studies have investigated predictive biomarkers of motor CIPN subtype [29].

The objective of this study was to investigate whether sensory and motor CIPN are distinct subtypes with different predictive metabolic biomarkers in patients with breast cancer receiving weekly paclitaxel treatment. We conducted an exploratory analysis of CIPN data collected weekly throughout treatment via a patient-reported outcome (PRO) questionnaire to evaluate the time course of sensory and motor CIPN, determine how sensory and motor CIPN co-occurred, and attempt to identify predictive metabolic biomarkers of the motor CIPN subtype.

Methods

Study Patients

This study is an exploratory analysis of a previously described cohort (NCT02338115) [19]. Adult female patients with stage I-III or oligometastatic breast cancer scheduled to receive paclitaxel 80mg/m² 1-hour infusion weekly for 12 doses were eligible to enroll in this observational study. Patients were excluded if they had prior or concurrent neurotoxic chemotherapy (taxane, vinca alkaloid, platinum, bortezomib, or thalidomide), concurrent duloxetine treatment or enrollment in a clinical study of any neuroprotective agent, existing severe peripheral neuropathy affecting activities of daily living, or known family history of hereditary peripheral neuropathy or Charcot-Marie-Tooth disease. Patients who withdrew from the study or discontinued paclitaxel treatment before receiving at least 3 doses were excluded from the analysis. Demographic and lifestyle information was collected from patients at baseline. All instances of treatment disruption including dose delay, dose decrease, and treatment discontinuation were determined from the electronic medical record. All patients signed written informed consent, and the study was approved by Institutional Review Boards of the University of Michigan Medical School (IRBMED) (HUM00086253). Baseline metabolomics [27] and nutrients [28] were measured in a subset of patients who consented to additional biomarker analyses.

Patient-reported CIPN

Patient-reported CIPN was evaluated at baseline and weekly throughout paclitaxel treatment using European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy (CIPN20). The 20 questions ask about 9 sensory, 8 motor, and 3 autonomic symptoms, which are graded on a scale from 1 to 4 (1=not at all, 2=a little, 3=quite a bit, and 4=very much). Sensory CIPN (CIPN_S) was defined as the sum score of the first 8 sensory items (excluding the ototoxicity item), which are the most common sensory symptoms, including tingling, numbness, or pain in the hands and feet, and having problems standing or walking due to difficulty feeling the ground, and having difficulty distinguishing between hot and cold water [19]. Motor CIPN (CIPN_M) was defined as the 8 motor items, including cramps in the hands and feet, and having problems holding a pen to write, having difficulty opening a jar or bottle due to weakness in the hands, having difficulty walking or climbing stairs due to weakness in the legs, and having difficulty manipulating small objects or using the pedals. All scores were converted to a scale of 0-100 with higher scores indicating more severe CIPN [30].

Statistical Analysis

CIPN Subtypes and Clustering Analysis

The time course of sensory (CIPN_S), motor (CIPN_M), the difference between sensory and motor CIPN (CIPN_S-CIPN_M), and CIPN_S vs. CIPN_M were plotted for all patients throughout paclitaxel treatment for visual inspection using R 3.6.3. Clusters of the time course of CIPN_S, CIPN_M, and CIPN_S-CIPN_M were identified using k-means clustering on principal component analysis (PCA) scores. CIPN scores at time points with $\geq 80\%$ valid data were included, and CIPN scores at missing time points were imputed using interpolation and extrapolation from individual patient's time course. CIPN_S and CIPN_M were scaled to 0-1, and CIPN_S-CIPN_M were scaled to (-1)-1. The number of clusters was determined by the elbow method of the within-cluster sum of squares. A thousand sets of random centers were tested, and the centers with lowest within-cluster sum of squares and highest between-cluster sum of squares were selected. To depict the characteristics of each cluster, CIPN scores, treatment administration information (paclitaxel systemic exposure and treatment disruptions), and demographics were compared between clusters using analysis of variance (ANOVA) for continuous variables and Chi-square tests for binary variables with $\alpha = 0.05$. If significant, post hoc analyses were performed using pairwise comparisons with Bonferroni correction.

Metabolic Biomarker Analysis

Baseline metabolomics [27] and nutrients [28] data were used in metabolic biomarker analyses. Missing data of metabolomics were imputed with half of the limit of detection. All measurements were \log_2 transformed and z-score normalized. Linear regression analyses were used to identify biomarkers associated with maximum CIPN_S and CIPN_M after adjusting for baseline CIPN_S and CIPN_M, paclitaxel

maximum concentration (C_{max}), and time above paclitaxel concentration threshold ($T_{C>0.05}$), and two-way interaction terms were included if significant [19]. Baseline clinical covariates such as prior or concurrent chemotherapy, age, race, body mass index, pretreatment neuropathy, diabetes, and use of pain medication were also included if significant.

Results

Patient-reported CIPN

A total of 60 patients were enrolled, but one patient who discontinued treatment after 2 doses due to non-neuropathy toxicity was excluded from the analysis. The average age of the 59 patients included in the analyses was 52 and >90% were Caucasian (Table 1). Most patients had no or limited sensory or motor CIPN at baseline (CIPN_S: mean=1.3 (range: [0, 12.5]), CIPN_M: mean=2.7 (range: [0, 25.0])). As expected, sensory and motor CIPN increased throughout paclitaxel treatment, and the increases were larger for sensory than motor CIPN (CIPN_S average change throughout treatment: mean=10.8 (range: [-3.3, 52.1]); CIPN_M average change throughout treatment: mean=3.5 (range: [-7.5, 35.0])) (Figure 1).

Table 1
Demographics of 59 patients that were included in the analysis.

Variable	Definition	N (%) or mean [range]
Age	Age at enrollment (years)	52.3 [28, 71]
Race	Caucasian	54 (91.5%)
Body mass index	kg/m ²	28.3 [19.2, 45.8]
Other cancer treatment	Prior AC	55 (93.2%)
	Concurrent H/P	29 (49.2%)
Paclitaxel treatment	Cumulative dose received (mg/m ²)	885 [432, 986]
	Number of doses received	11.2 [6, 12]
	Relative dose intensity	0.887 [0.379, 1]
	Treatment disruption ^a	35 (59.3%)
	Number of doses at first disruption	9 [2, 12]
Paclitaxel systemic exposure	C _{max} (ng/mL) (N=56)	2375 [907, 4340]
	T _{C>0.05} (hr) (N=58)	10.7 [7, 22]
Baseline neuropathy predictors	Diabetes or Hb _{A1c} ≥6.5% (N=52)	13 (25%)
	Use of alcohol (N=58)	27 (46.6%)
	Use of pain medication	7 (11.9%)
	Vitamin D insufficiency (≤20ng/mL) (N=36)	17 (47.2%)
Sensory CIPN (CIPN _S)	Baseline	1.3 [0, 12.5]
	Maximum during treatment	26.4 [0, 87.5]
Motor CIPN (CIPN _M)	Baseline	2.7 [0, 25]

^a All-cause (CIPN- and non-CIPN-related) treatment disruption includes any dose delay, dose decrease, or early treatment discontinuation.

AC: Adriamycin (doxorubicin) and cyclophosphamide. H/P: trastuzumab or pertuzumab

Variable	Definition	N (%) or mean [range]
	Maximum during treatment	13.8 [0, 58.3]
Difference between sensory and motor CIPN (CIPN _S -CIPN _M)	Baseline	-2 [-19.4, 12.5]
	Minimum during treatment	-3.4 [-29.2, 8.3]
	Maximum during treatment	17.7 [-5.6, 61.1]
^a All-cause (CIPN- and non-CIPN-related) treatment disruption includes any dose delay, dose decrease, or early treatment discontinuation.		
AC: Adriamycin (doxorubicin) and cyclophosphamide. H/P: trastuzumab or pertuzumab		

The time course of the difference between sensory and motor CIPN (CIPN_S-CIPN_M) indicates that most patients had greater sensory symptoms (CIPN_S-CIPN_M>0) or similar sensory and motor symptoms (CIPN_S-CIPN_M≈0); only one patient experienced meaningfully greater motor than sensory symptoms (Figure 2). Patients who had similar sensory and motor CIPN was comprised of two groups, those who experienced no or limited symptoms of either, and those who experienced both symptoms with approximately equal severity.

Clustering of CIPN Subtypes

The time course of sensory CIPN, motor CIPN, and the difference between the two (CIPN_S-CIPN_M) from baseline to week 11 were included in k-means clustering using PCA scores. Three distinctive clusters were identified, which were annotated as *No CIPN* (N=37, black), *Mixed CIPN* (N=16, red), and *Sensory-dominant CIPN* (N=6, green) based on the CIPN score profile (Figures 3 and S1). These annotations are further supported by the differences in CIPN symptom subtype severity (Table 2 and S1). *No CIPN* had minimal sensory or motor CIPN (maximum CIPN_S during treatment: mean=12.7, maximum CIPN_M during treatment: mean=5.4) compared to *Mixed CIPN* (CIPN_S=40.9, CIPN_M=25.5, both p<0.001). *Sensory-dominant CIPN* also had both sensory and motor CIPN, but only sensory CIPN was greater than the *Mixed CIPN* group (CIPN_S=74.3, p<0.001). *Sensory-dominant CIPN* had higher CIPN_S-CIPN_M than *Mixed CIPN*, further indicating that the primary distinction between these two groups is the dominance of sensory symptoms (average CIPN_S-CIPN_M during treatment: mean=24.9 vs. 5.8, p<0.001).

Table 2
Patient-reported CIPN scores and treatment disruption between clusters.^a

Variable	Definition	No CIPN (N=37)	Mixed CIPN (N=16)	Sensory-dominant CIPN (N=6)	p-value ^b	Pairwise Tests ^c
CIPN _S	Maximum during treatment	12.7 (8.4)	40.9 (10.7)	74.3 (12.8)	<0.001	3>2>1
CIPN _M	Maximum during treatment	5.4 (5.1)	25.5 (14.2)	36.1 (20)	<0.001	3=2>1
CIPN _S -CIPN _M	Average during treatment	2.8 (4.7)	5.8 (8.4)	24.9 (6.7)	<0.001	3>2=1
Paclitaxel administration	Relative dose intensity	0.94 (0.10)	0.78 (0.18)	0.85 (0.12)	<0.001	1>2
	Early discontinuation	10.8%	62.5%	66.7%	<0.001	3=2>1
Paclitaxel systemic exposure	T _{C>0.05} (hr)	9.9 (1.7)	12 (4)	11.8 (1.7)	0.019	
^a Continuous variables are shown as mean (standard deviation), binary variables are shown as percentage.						
^b p-values that are smaller than 0.001 are shown as p<0.001.						
^c Post-hoc analyses were performed to identify pairwise differences between clusters, which are indicated by ">" ("=" indicates no significant difference between clusters).						

We then explored whether the differences between the clusters were associated with paclitaxel administration or paclitaxel systemic exposure. Patients in the *No CIPN* group had higher paclitaxel dose intensity than the *Mixed CIPN* (0.94 vs. 0.78, p=0.003), and fewer early treatment discontinuations than the *Mixed* or *Sensory-Dominant CIPN* groups (10.8% vs. 62.5% or 66.7%, p=0.007 or p<0.001, respectively). There were no differences in dose intensity or treatment disruption between the *Mixed* and *Sensory-Dominant CIPN* groups (p=0.261 and p=0.910). Interestingly, both *Mixed* and *Sensory-dominant CIPN* had nominally higher paclitaxel systemic exposure than *No CIPN* (T_{C>0.05}=12.0 and 11.8 vs 9.9 hours), but pairwise comparisons were not significant (Table 2 and S1).

Metabolic Biomarkers of CIPN Subtypes

Prior analyses in this dataset found that lower levels of histidine, phenylalanine, threonine, and vitamin D were associated with more severe sensory CIPN [27, 28] and remained significant after adjusting for relevant covariates including baseline CIPN severity, paclitaxel systemic exposure, and body mass index (Table 3). In the current analysis, lower histidine was also associated with more severe motor CIPN (Table

3 and Figure 4). The other biomarkers that had inverse associations with sensory CIPN had similar, though weaker and not statistically significant, associations with motor CIPN (Table 3 and Figure S2). None of the other tested metabolomic biomarkers were associated with sensory or motor CIPN (Table S2).

Table 3
Metabolomics and nutrient biomarkers of sensory and motor CIPN.

	Sensory CIPN		Motor CIPN	
	r	p-value ¹	r	p-value ^a
Histidine	-0.376	0.006	-0.254	0.029
Phenylalanine	-0.336	0.011	-0.124	0.110
Threonine	-0.283	0.014	-0.057	0.400
Vitamin D concentration	-0.352	0.043	-0.136	0.106
^a p-values from linear regression adjusted for baseline CIPN, paclitaxel systemic exposure, cumulative dose, relative dose intensity, and body mass index.				
r: Correlation coefficient				

Discussion

The major treatment-limiting toxicity of paclitaxel is CIPN [31–33], which predominantly presents as sensory symptoms [8, 9], with motor symptoms in some patients [8–11]. There are no known effective treatments that can prevent or ameliorate CIPN [7], which can be due to the unclear mechanism of CIPN [31]. Differentiation of CIPN into symptom subtypes has been recommended to improve the success of CIPN intervention and biomarker discovery trials [14, 16, 17]. This exploratory analysis used PRO CIPN data collected prospectively during weekly paclitaxel treatment to investigate whether sensory and motor CIPN are distinct subtypes. As expected, more sensory than motor CIPN was reported. Interestingly, patient groups were identified with no CIPN, mixed CIPN, and sensory-dominant CIPN, but not motor-dominant CIPN. The metabolomics and nutrient biomarker results for motor CIPN were similar to those previously reported for sensory CIPN, suggesting there may not be distinct predictive metabolic biomarkers for motor CIPN from paclitaxel treatment.

Patients with breast cancer receiving taxane treatment experience both sensory and motor CIPN [34], but sensory CIPN is more common, especially with paclitaxel [6, 35–37]. Our findings are consistent with previous studies that sensory symptoms are more common, and we found that when motor symptoms occur, they usually co-occur with sensory symptoms. We did not find an appreciable group of patients with motor-only or motor-dominant CIPN; the only patient who experienced motor-dominant symptoms was also the only patient with appreciable motor CIPN symptoms at baseline (Figure 2, CIPN_M=25). A prior case report described a patient who developed objective evidence of motor-only CIPN based on

nerve function impairment, however, the motor symptoms were not detected by a PRO questionnaire [38]. Sensitive nerve conduction studies have found that distal motor symptoms can occur alone [39], but the evidence from patient-report and clinician-assessment indicates that this is rare and motor symptoms are more likely to be a progression from sensory symptoms [39, 40].

Our clustering analysis of paclitaxel-treated patients identified *No CIPN*, *Mixed CIPN*, and *Sensory-dominant CIPN* groups. A previous analysis in patients with any cancer receiving any neurotoxic chemotherapy identified four clusters: *Sensory*, *Motor-dominant Mixed*, *Sensory-dominant Mixed*, and a less clear *Autonomic* cluster; a subgroup analysis of patients receiving paclitaxel alone (N=33) or with the somewhat neurotoxic carboplatin (N=50) had similar clustering results [18]. While both studies agree that there is a lack of a motor-only subgroup from paclitaxel treatment, our study did not identify evidence of a Motor-dominant group. One of the core symptoms in their Motor-dominant Mixed cluster was difficulty manipulating small objects [18], which can be indicative of either motor or sensory impairment [40, 41]. We explored alternative definitions of the motor subtype that removed the two potentially confounded items, manipulating small objects and using pedals [41, 42], and still did not identify any motor-only or motor-dominant clusters (data not shown). The other difference between the studies is that we did not identify an autonomic cluster. We did not analyze the autonomic subscale of the CIPN20 because this subscale has been shown to be unstable and an unreliable indicator of CIPN [41–44], and autonomic CIPN symptoms are uncommon from paclitaxel treatment [3, 45].

Our analysis found that predictive metabolic biomarkers for motor CIPN were generally similar to those we previously reported for sensory CIPN [27, 28]; we did not find any evidence of distinct motor CIPN biomarkers. The majority of paclitaxel CIPN biomarker research has not differentiated between CIPN subtypes or has focused exclusively on the sensory subtype [19–28]. We are aware of only one study, also conducted in patients with breast cancer receiving paclitaxel, that found higher baseline levels of sphingolipids were associated with higher incidence of motor, but not sensory, CIPN [29]. These hypothesis-generating results require validation in independent patient cohorts to determine whether baseline lipid levels may be predictive biomarkers of motor CIPN in patients treated with paclitaxel and perhaps other neurotoxic chemotherapy agents.

Overall, our results cast some doubt on recent recommendations for differentiating between motor and sensory CIPN in clinical trials and biomarker research, at least for paclitaxel [14, 16, 17]. The lack of a motor-only or motor-dominant subtype, and previous evidence that motor symptoms may be a progression from sensory symptoms, instead favors focusing prevention and treatment efforts on earlier sensory symptoms to avoid onset of the clinically troubling motor effects [12, 13]. In terms of CIPN monitoring, PRO questionnaires have several advantages over clinician-assessment [30, 46–49], one of which may be the ability to more clearly differentiate sensory and motor symptoms. This would be particularly helpful if someday there were treatments that were specifically effective in one or the other subtype. Finally, although it was only a single patient, our results indicate that patients with baseline motor neuropathy symptoms may have elevated risk of treatment-induced motor CIPN. This suggests that more sensitive baseline screening may help identify patients who should be considered for non-

neurotoxic alternatives or enhanced CIPN monitoring, perhaps using novel wearable or app-based monitoring strategies [50].

This analysis used sensitive PRO data collected weekly throughout treatment in a relatively homogeneous cohort of patients with breast cancer receiving paclitaxel and investigated metabolic and nutrient biomarkers of motor CIPN. Despite these strengths, this study has several limitations. First, the modest sample size limits our confidence in concluding there is no motor-dominant patient group or motor-specific biomarkers. Second, although PRO are more sensitive and reliable than CTCAE [49], there is evidence that the CIPN20 subscale structure may have suboptimal structural validity [41, 43, 44], and the subscales may not optimally characterize the symptom subtypes [42]. Third, we only examined a subset of metabolites and nutrients including vitamin D, vitamin B₁₂, folate, homocysteine, and metabolite data generated by nuclear magnetic resonance spectroscopy; this metabolomics approach is less sensitive and results in fewer named metabolites than liquid chromatography-mass spectroscopy. Our ongoing lipidomics and proteomics analyses will attempt to validate previously reported biomarker candidates of sensory and/or motor CIPN [26, 29]. Finally, our findings are likely confined to only paclitaxel, and further research is needed to determine whether they should be generalized to docetaxel and perhaps other classes of neurotoxic chemotherapy. We plan to investigate symptom subtype clusters and predictive biomarkers in SWOG 1714 (NCT03939481), a recently completed observational clinical trial investigating clinical and physiologic predictors of CIPN in patients receiving paclitaxel or docetaxel treatment.

In conclusion, our findings suggest that in paclitaxel-treated patients, introduce the possibility that sensory and motor are not independent CIPN subtypes. Rather, motor symptoms co-occur with sensory symptoms. Prediction, prevention, and treatment of CIPN from paclitaxel should focus primarily on the more common sensory subtype. These findings need to be validated in larger cohorts of patients treated with paclitaxel and then tested in cohorts receiving docetaxel and other neurotoxic agents to determine the optimal approach to evaluate interventions for CIPN prevention and treatment, which could improve clinical outcomes in patients with cancer.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Data analyses were performed by Ciao-Sin Chen. The first draft of the manuscript was written by Ciao-Sin Chen and Dan L Hertz, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets analyzed during the current study are not publicly available due to patient privacy requirements but are available from the corresponding author on reasonable request.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Institutional Review Boards of the University of Michigan Medical School (IRBMED) (HUM00086259).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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Figures

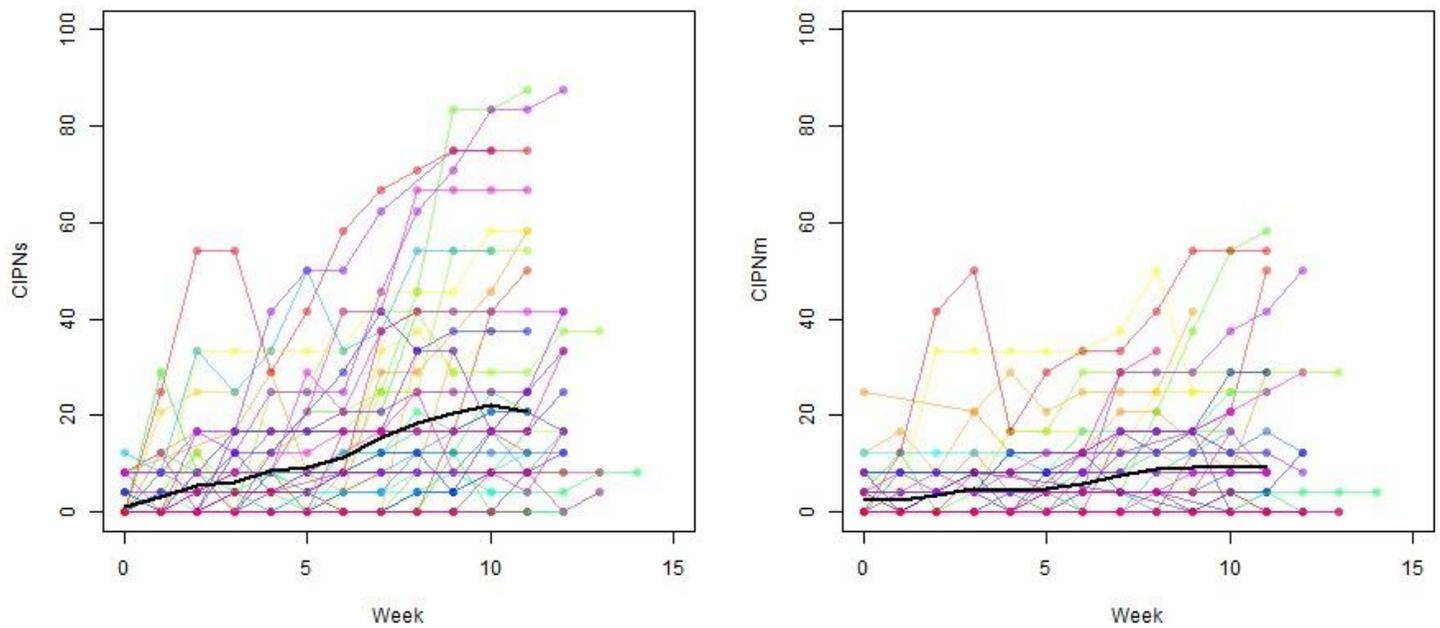


Figure 1

The time course of CIPN_S (left) and CIPN_M (right). Each color represents an individual patient that is represented by the same color in both plots. Dots represent CIPN scores at individual time points and are connected by lines linking consecutive weeks. Black solid line indicates the average score at each week. Score values after week 11 were missing in over 80% of the patients.

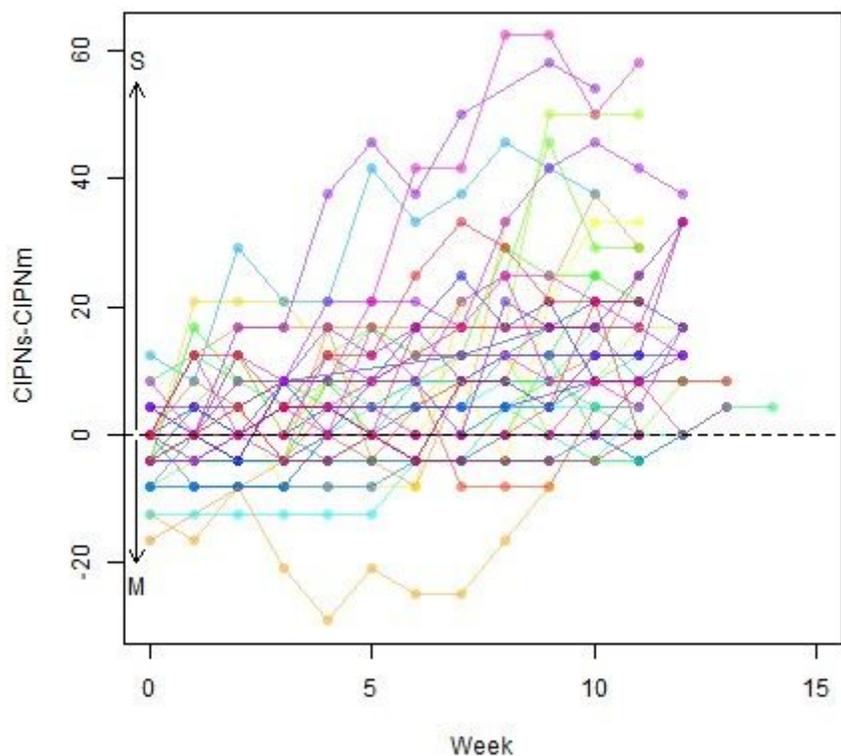


Figure 2

The time course of the difference between sensory and motor CIPN ($CIPN_S - CIPN_M$). Individual patients were labeled with the same colors as in Figure 1. Dots represent CIPN scores at individual time points and are connected by lines linking consecutive weeks. Values greater than zero indicate sensory-dominant symptoms, and values less than zero indicate motor-dominant symptoms. Most patients had sensory-dominant or mixed CIPN symptoms; few patients had motor-dominant symptoms.

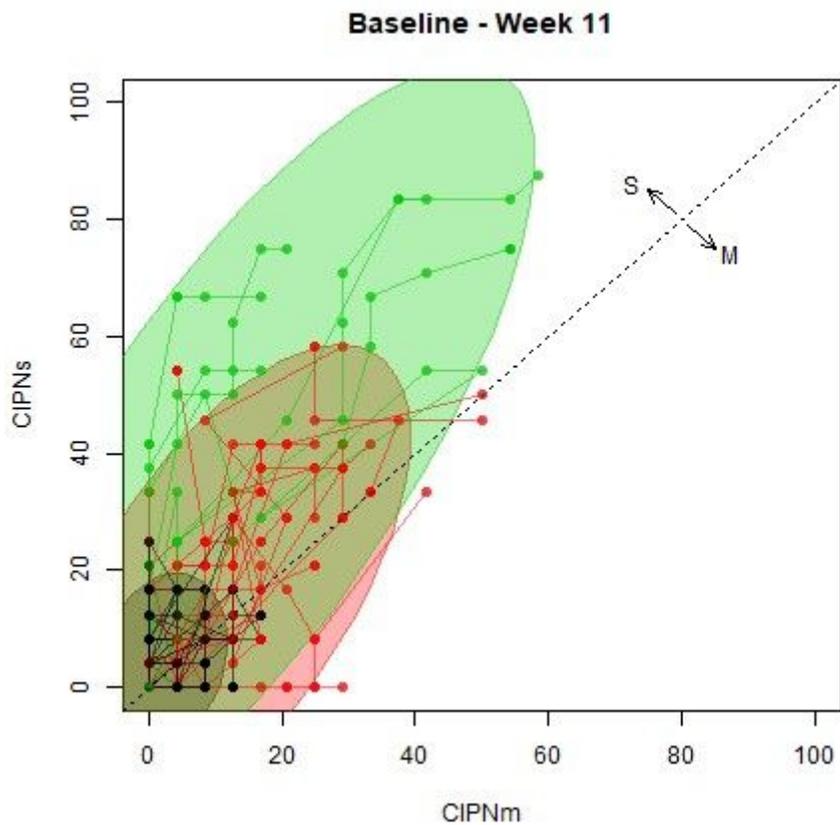


Figure 3

The scatter plot of $CIPN_S$ (sensory CIPN) vs $CIPN_M$ (motor CIPN) from baseline to week 11. Values shifting above the diagonal line indicate sensory-dominant symptoms, and values shifting below the diagonal line indicate motor-dominant symptoms. Clusters No CIPN (black), Mixed CIPN (red), and Sensory-dominant Mixed CIPN (green) were identified by k-means clustering. Each line represents a patient. The ellipses indicate 95% confidence intervals of the CIPN score distributions in each cluster from baseline to week 11.

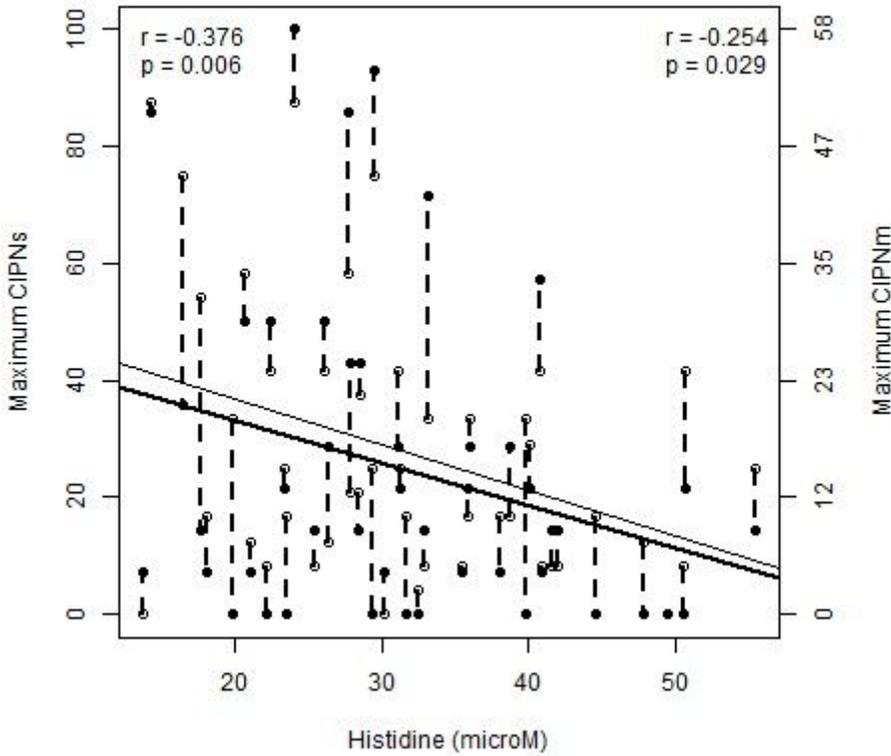


Figure 4

Correlation between histidine levels and maximum CIPN_S or CIPN_M. The scale, correlation coefficient, and p-values of CIPN_S are on the left, and the ones of CIPN_M are on the right. White dots and thin regression line are CIPN_S. Black dots and bold regression line are CIPN_M. Each patient's CIPN_S and CIPN_M are connected by a dashed line. In general, the CIPN_S and CIPN_M scores are similar for most patients, resulting in a similar association for histidine with each CIPN subtype.

Supplementary Files

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