Brief Report

Oxaliplatin-Induced Peripheral Neuropathy and Identification of Unique Severity Groups in Colorectal Cancer

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Abstract

Context. Oxaliplatin-induced peripheral neuropathy (OIPN) is a dose-limiting toxicity of oxaliplatin and affects most colorectal cancer patients. OIPN is commonly evaluated by patient symptom report, using scales to reflect impairment. They do not discriminate between unique grouping of symptoms and signs, which impedes prompt identification of OIPN.

Objective. The objective of this study was to identify clusters of symptoms and signs that differentiated underlying clinical severity and segregated patients within our population into OIPN subgroups.

Methods. Chemotherapy-naive colorectal cancer patients ($N = 148$) receiving oxaliplatin were administered the Total Neuropathy Score clinical (TNSc©), which includes symptom report (sensory, motor, autonomic) and sensory examination (pin sense, vibration, reflexes). The TNSc was administered before chemotherapy initiation (T0) and after cumulative doses of oxaliplatin 510−520 mg/m^2 (T1) and 1020−1040 mg/m^2 of oxaliplatin (T2). Using mean T2 TNSc scores, latent class analysis grouped patients into OIPN severity cohorts.

Results. Latent class analysis categorized patients into four distinct OIPN groups: low symptoms and low signs ($n = 54$); low symptoms and intermediate signs ($n = 44$); low symptoms and high signs ($n = 21$); and high symptoms and high signs ($n = 29$). No differences were noted among OIPN groups on age, sex, chemotherapy regimen, or cumulative oxaliplatin dose.

Conclusion. We identified OIPN patient groups with distinct symptoms/signs, demonstrating variability of OIPN presentation regardless of cumulative oxaliplatin dose. Over half of the sample had positive findings on OIPN examination despite little or no symptoms. Sensory examination of all patients receiving oxaliplatin is indicated for timely identification of OIPN, which will allow earlier symptom management. J Pain Symptom Manage 2017;54:701−706. © *2017 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Chemotherapy-induced peripheral neuropathy, oxaliplatin, pain, chronic pain, latent class analysis, measurement

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Introduction

Oxaliplatin, a third-generation platinum-based agent, is the principal chemotherapeutic agent for the treatment of colorectal cancer (CRC) and is also used in patients with pancreatic, gastric, and other cancers.[1–3] Although oxaliplatin has improved overall survival rate,[4–6]oxaliplatin-induced peripheral neuropathy (OIPN) remains a treatment-limiting factor.[7,8] Some degree of OIPN occurs in nearly all patients,[6] and approximately two-thirds will have symptoms one-year post-treatment or beyond.[9,10] OIPN has been reported as dose dependent, with symptoms more likely to occur as the cumulative dose exceeds 780–850 mg/m^2. Unlike acute OIPN that is transient, chronic OIPN can persist for months or years[11,12] and includes pain, numbness, and dysesthesias that lead to reduced quality of life and function.[13] Little is known about how individual symptoms are related and whether they co-occur, which limits the management options and early identification of OIPN. Groupings of OIPN patients that better represent distinctions in underlying disease phenomena may facilitate better identification of those who require earlier or more targeted treatment.

Although predictors of OIPN have been identified, including chemotherapy treatment schedule, cumulative drug dose, and pre-existing peripheral neuropathy,[14,15] currently there is no effective strategy for preventing OIPN and pharmacologic management is limited.[16,17] In some cases, OIPN severity may require prolongation of oxaliplatin administration time, dose reduction, treatment delay, or drug discontinuation to avoid irreversible sensory nerve damage,[18–20] although evaluation of such management approaches in clinical trials has not resulted in reduced OIPN severity.[21]

The Total Neuropathy Score clinical (TNSc) version is a seven-item composite measure of impairment and has been well validated in chemotherapy-induced peripheral neuropathy (CIPN).[22] Composite scales incorporate results from self-report items and clinician examination to provide a complete profile of symptoms and signs and, thus, characterize the phenomenon. Latent class analysis (LCA) is an approach for identifying unmeasured group or cohort membership within a patient population and can be used with categorical data. The purpose of our analysis was to identify clusters of symptoms and signs that differentiated underlying clinical severity and segregated patients within our population into distinct subgroups of OIPN.

Methods

The details of the original study have been previously reported.[23] In brief, 200 CRC patients scheduled to receive oxaliplatin plus leucovorin and 5-fluorouracil (FOLFOX) or oxaliplatin plus capecitabine (XELOX), either in the adjuvant or metastatic setting, were enrolled in a multisite study. The study was conducted at four centers in three European countries after Institutional Review Board approval at all four centers.

Eligibility criteria included: 1) preparation to receive oxaliplatin-based chemotherapy for CRC, 2) no evidence of other systemic disease or peripheral neuropathy, 3) life expectancy of more than nine months; 4) Karnofsky performance score ≥70, and 5) ability to understand study information delivered by investigators. Additional exclusion criteria included history or evidence of pre-existing peripheral neuropathy at baseline screening, co-morbidities, such as diabetes, alcohol abuse (>5 IU/d), and any other condition or medication that could interfere or complicate the clinical assessments.

Participants were followed prospectively and monitored for OIPN development and severity at three time points during chemotherapy with the TNSc composite instrument. The TNSc was administered before chemotherapy initiation (T0), following 510–520 mg/m^2 of oxaliplatin (T1), and following 1020–1040 mg/m^2 of oxaliplatin (T2). The TNSc is a seven-item scale (sensory, motor and autonomic symptoms, pinprick, vibration, light touch, deep tendon reflex [DTR], strength), each scored 0–4, with higher scores indicating greater impairment.[24–26]

This study used de-identified participant data from the original study and was designated by the University of Maryland IRB as nonhuman subjects' research. The number of participants with data sufficient for LCA approach was $N = 148$.

Analysis

Data from the primary study were abstracted into a data file for analysis. LCA was used to stratify OIPN phenotypes derived from the TNSc scoring instrument. The strength item was removed from the LCA procedure because all participants scored 0. The final number of TNSc items for LCA was 6, therefore, with a potential score range of 0–24. LCA (Mplus 7.0)[27] produced mutually exclusive participant classes based on OIPN patient-reported symptoms and clinical examination signs. To determine the number of classes in the mixture modeling, we chose the Lo, Mendell, and Rubin likelihood ratio test,[28] which statistically compares the fit of a given model with the fit of a model with one fewer class. Once the class membership was determined, chi-square tests for categorical variables and ANOVA for continuous variables were used to compare the differences with regard the patients' demographic and clinic characteristics across the classes.

Results

Participants had an average age of 63 years, were primarily men, and had nonmetastatic disease (67%).

Table 1
Participant Characteristics and TNSc Values Overall and Within Each OIPN Severity Group ($N = 148$)

Characteristics	Total, *n* (%)	Class 1: Low/Low, $n = 54$, *n* (%)	Class 2: Low/Inter, $n = 44$, *n* (%)	Class 3: Low/High, $n = 21$, *n* (%)	Class 4: High/High $n = 29$, *n* (%)	*P*-Value
Age, mean (SD)	63.3 (9.1)	63.7 (8.4)	64.0 (9.4)	64.5 (7.3)	60.7 (10.8)	0.363
Gender						0.058
Male	92 (62.2)	32 (59.3)	26 (59.1)	10 (47.6)	24 (82.8)	
BSA, m^2, mean (SD)	1.74 (.22)	**1.68 (.26)**	1.73 (.21)	1.76 (.14)	**1.83 (.20)**	**0.032**
Cumulative oxaliplatin at T2, dose/m2 mean (SD)	963.4 (145.4)	962.9 (142.4)	951.1 (163.6)	962.0 (154.3)	984.0 (117.8)	0.829
TNSc (T1), mean (SD)	2.4 (3.5)	**0.06 (.3)**[a]	**1.0 (1.5)**[b]	**3.9 (2.1)**[ab]	**7.9 (3.5)**[ab]	**<0.001**
TNSc (T2), mean (SD)	5.9 (5.5)	**0.2 (.6)**	**5.5 (1.2)**	**9.7 (.9)**	**14.6 (.6)**	**<0.001**

OIPN = oxaliplatin-induced peripheral neuropathy; TNSc = Total Neuropathy Score clinical.
P-values calculated from either chi-square or ANOVA tests. Values in bold indicates groups that were significantly different in the post hoc pairwise comparisons. Differences between groups at TNSc T1 are identified further with matching superscript alphabets.

Participant characteristics can be found in Table 1. The LCA results, based on T2 final TNSc scores in this longitudinal study, demonstrated a statistically significant, best-fitting model of four latent classes (Supplemental Table 1). The LCA stratified the CRC participants into four phenotype groups: Class 1: low symptoms and low signs ($n = 54$), indicating that both patient report and provider examination revealed little or no OIPN; Class 2: low symptoms and intermediate signs ($n = 44$), meaning that patients complained of little to no symptoms but examination findings showed some OIPN; Class 3: low symptoms and high signs ($n = 21$), with patients complaining of little to no symptoms but examination findings showed clear OIPN; and Class 4: high symptoms and signs ($n = 29$), which indicated high levels of patient-reported symptoms with correspondingly high examination findings (Fig. 1).

There was no significant difference in age, gender, or OIPN regimen among the four severity groups (Table 1). As expected, the low OIPN group had statistically significant lower overall TNSc scores than the high OIPN group at time of chemotherapy completion ($P < 0.001$). Body surface area was higher in the Class 4 group, where symptom report and clinical examination findings were most severe.

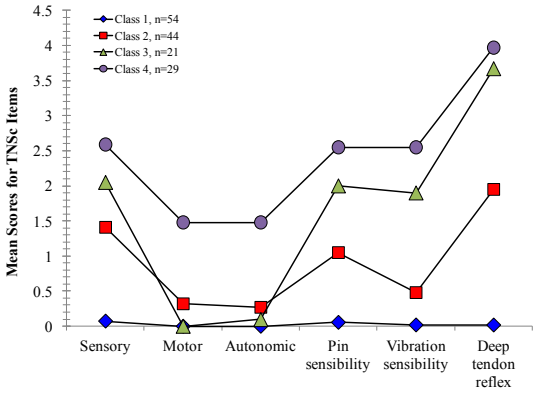

Fig. 1. Mean TNSc scores for each item within OIPN severity group. OIPN = oxaliplatin-induced peripheral neuropathy; TNSc = Total Neuropathy Score clinical.

Discussion

Our rigorously phenotyped sample of OIPN in a chemotherapy-naive, homogeneous population of CRC participants from a prospective trial allowed analysis of data without the influence of other diseases or pre-existing neuropathy. Previous investigators have used traditional methods of phenotyping based on the total scores of ordinal-based measures and simple classification of OIPN with scales such as the National Cancer Center Common Toxicity Criteria of Adverse Events. Our LCA approach used a least-squares model to categorize OIPN features by assessing how individual items within the TNSc form discrete groups or classes. Using a composite measure of patient symptom report and clinical examination, the LCA method provided a robust definition of OIPN severity and distinguished distinct clinical groups. Routine evaluation of both patient symptoms and clinical signs of OIPN may be more accurate for defining OIPN.

The TNSc has been validated in a number of studies and has demonstrated very good reproducibility indices. The American Society of Clinical Oncology recommends using TNSc for ongoing assessment of CIPN in survivor populations, given the combination of subjective and objective measurements thought to strengthen its surveillance value.[16] Additional credence of the TNSc has been demonstrated with a Rasch transformation of ordinal-based TNSc to an interval-based one, indicating that the TNSc properties are suitable for parametric testing and supporting its continued use in the longitudinal setting.[29] In sum, performing an LCA clustering of OIPN phenotypes using the TNSc clinical assessment scores is robust and facilitates the effective clinical classification of OIPN patients.

The recognition of four phenotypic groups may be clinically meaningful, in that it will help identify

distinct OIPN states. The literature confirms that some patients do not experience any OIPN symptoms over the course of chemotherapy,[30] and we identified a similar low symptoms/signs group, which comprised 36% of the sample. Group 2, representing 30% of the sample, had mild sensory symptoms accompanied by positive findings on physical examination (reduced pin sense, vibration sense, and reflexes). It is possible that Group 2 may be at highest risk of having OIPN overlooked if only a report of symptoms is relied on. Based on our findings, a sensory examination is recommended in all patients receiving oxaliplatin, even if no symptoms are present. In our view, to detect even subclinical changes is essential to eventually be able to accurately follow up the course of OIPN. Groups 3 and 4 were analytically distinct; these groups include patients most likely to be diagnosed with OIPN in the clinic because they exhibited both OIPN symptoms and signs. Still, these groups may represent patients with different functional profiles and exploration of their experiences during treatment may help clarify their treatment needs.

As described in Figure 1, DTRs followed by pin sense were the most impaired examinations in our analysis. DTRs are a measure of the sensorimotor system, and reduced response is an indication of sensory neuropathy in the setting of OIPN. Reduced DTRs have been shown to occur in association with hypoesthesia using current perception threshold in the setting of CIPN.[31] We have also reported reduced vibration perception in combination with reduced DTRs using TNSc, where DTRs were the most sensitive component of the neurologic examination in CIPN.[32] With toxic neuropathies, there is a predominant spectrum, such as sensory impairment in the case oxaliplatin, but not all the sensory neurons demonstrate the same susceptibility to damage. For example, the unmyelinated c fibers are generally preserved in OIPN with differential impairment of Aα fibers, which are responsible for innervating the muscle spindle. For this reason, we observed a worse impairment in DTRs compared with other sensory tests.

Autonomic symptom scores were low except in those with the most severe signs and symptoms. A longitudinal study of oxaliplatin using self-report measurement of autonomic symptoms demonstrates minor change overall in autonomic vs. sensory symptoms over the course of treatment.[33] Our findings echo these data except that we found pronounced autonomic symptoms in the high symptoms and signs group. This exception underscores the strength of the LCA use to unmask unique groupings of OIPN presentation.

We found that as body surface area increased so did OIPN severity, with differences noted between classes 1 and 4, although cumulative doses of oxaliplatin were not different between groups. This has been documented elsewhere[34] and warrants further examination. However, based on our findings, body surface area alone places patients at increased risk for OIPN because those with obesity-related comorbidities, such as diabetes, were excluded from the study. Although the relationship among obesity, CIPN, and pain has been documented across chemotherapy regimens and primary disease sites,[35] a pathogenic mechanism has not been proposed. Nonetheless, the increased risk of OIPN in overweight and obese patients warrants careful monitoring during chemotherapy.

The OIPN groups identified in this analysis may explain why some pharmacologic treatments, such as serotonin norepinephrine reuptake inhibitors (SNRIs), are more effective in some patients than in others. Our analysis will provide important information to those studying SNRI management in chemotherapy-induced neuropathic pain. It is possible that earlier initiation of SNRIs at the point of examination abnormality and before positive sensory symptoms onset may attenuate painful symptom development, although such determinations will be made by those conducting research into the mechanisms of SNRI action in the setting of OIPN. Identifying who may benefit from duloxetine or venlafaxine is especially important given the dearth of effective interventions for OIPN. Furthermore, it is possible that earlier symptom intervention produces better responses. For some patients, there is a role for medications, such as anticonvulsants and SNRIs, and more prompt initiation may produce better responses by reducing the positive sensory symptom burden. In particular, anticonvulsants acting through the voltage-gated sodium channel blockade, such as carbamazepine, oxcarbazepine, or even lacosamide, deserve to be further tested. They may have potential as a symptomatic and maybe preventive intervention in OIPN, based on their ability to target central and peripheral sensitization mechanisms.[36,37] Improving the accuracy of OIPN identification, especially in individuals with limited symptom profiles, may allow closer surveillance and more immediate intervention when indicated. An ideal pharmacologic approach for OIPN management is currently lacking as both SNRIs and anticonvulsants only alleviate the component of neuropathic pain in OIPN and are generally not useful to reduced negative sensory symptoms, such as numbness. As such, nonpharmacologic treatment strategies for OIPN management should be also considered, including the "Stop-and-Go" concept, which uses the predictability and reversibility of neurologic symptoms, to aim at delivering higher cumulative OXL doses as long as the therapy is still effective.[21] Other promising interventions might include exercise[38] and possibly neuromodulation via spinal cord electrical stimulation or neurocutaneous stimulation.[39]

Although our study has many strengths, including large sample size of homogeneous patients and excellent measurement of OIPN, the use of secondary data precludes measurement of variables that are not available in the existing data set. For example, depression, which has more recently been shown to commonly co-occur in chemotherapy-induced neuropathy[40] may have provided further post hoc elucidation of how groups are formed. We used only final TNSc scores to conduct our LCA, and in future describing patients at mid-treatment and observing how OIPN severity group membership may change over time could be helpful for additional insights about the OIPN phenotype.

From a clinical standpoint, the identification of four groups of OIPN symptom and sign combinations demonstrates that there is significant variability in OIPN manifestation, severity, and presentation. All patients should be examined for signs of OIPN, even if they do not complain of symptoms. Our results will help clinicians to treat patients earlier and more accurately.

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Supplemental Table 1
Latent Class Analysis Results

	H0	H1				Sample Size		LMR LRT Test[a]		Bootstrap	
Number of Classes	LL	LL	Number of Free Parameters	AIC	BIC	Adj. BIC	Entropy	Test Value	*P*-Value	LRT *P*-Value[a]	Number of Patients in Each Class
2	−1231.88	−873.677	19	1785.354	1842.301	1782.173	0.997	716.411	<0.001	<0.001	95/52
3	−873.677	−641.128	26	1334.255	1412.183	1329.903	0.990	465.098	0.049	<0.001	54/44/50
4	−641.128	−502.197	33	1070.940	1169.302	1064.869	0.999	277.862	0.032	<0.001	54/44/21/29
5	−502.197	−408.515	40	897.031	1016.919	890.334	1.000	187.363	0.642	<0.001	54/41/26/11/16

adj. = adjusted; LL = log-likelihood; LMR = Lo-Mendell-Rubin; LRT = likelihood ratio test; AIC = Akaike information criterion; BIC = Bayesian information criterion.
[a] $n - 1$ classes (H0) vs. n classes.