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Chemotherapy-induced peripheral neuropathy as a predictor of neuropathic pain in breast cancer patients previously treated with paclitaxel

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Abstract

Neuropathic pain (NP) remains difficult to control for a significant number of patients with cancer. Chemotherapy-induced peripheral neuropathy (CIPN) has been postulated as an initial stage in the development of NP. To assess whether CIPN (defined as National Cancer Institute Common Toxicity Criteria grade 2 or higher) was associated with NP, we conducted a survey of breast cancer patients who had participated in clinical trials of paclitaxel. Of the 430 potential respondents, 240 responded to the survey. Results showed that 64% experienced CIPN during paclitaxel treatment. Follow-up survey data revealed that 27% of those with CIPN were subsequently diagnosed with NP. Logistic regression analyses showed that those who had experienced CIPN were 3 times more likely to develop NP (95% confidence interval=1.2-7.2; $p<0.001$), which persisted in the multivariate logistic model. In addition, NP patients reported twice as many visits to their health care provider ($p=0.02$) and had taken more prescription (50% versus 19%; $p=0.001$) and over-the-counter medications (62.5% versus 45%; $p=0.08$) for pain than those without NP. The results of this study confirm that CIPN is a predictor of NP, suggesting that survivors treated with paclitaxel should be regularly monitored for NP beyond treatment.

Introduction

Pain remains difficult to control for a significant proportion of patients with cancer. Neuropathic pain (NP), defined as “pain initiated or caused by primary lesion or dysfunction in the nervous system,” occurs in nearly 40% of patients with cancer pain.^{3,12} Studies suggest that patients with NP experience higher pain intensity and less effective control of their pain with conventional analgesia²¹. Specifically, NP patients rated their level of pain relief to be significantly lower than that of nociceptive pain (defined in the study as pain caused by activation of primary afferents in somatic or visceral tissues) patients in response to a single dose of an opioid,^{4,5} and a higher opioid dose is associated with NP.³⁰

Several mechanisms have been postulated to cause NP. In the context of cancer, NP may be a late effect of treatment with vinca alkaloids, taxanes, platinum-derived compounds,

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Perspective: The survival rates of breast cancer patients have steadily improved over recent years; thus, research into symptoms that persist after treatment is important. We found CIPN as a predictor of NP. Understanding the epidemiology of NP in breast cancer patients has high clinical and public health significance.

radiotherapy, or surgery. Among breast cancer patients, taxanes, platinum agents, and vinca alkaloids are most likely to cause NP. In fact, the dose-limiting toxicity of many of these chemotherapeutic agents is peripheral neuropathy^{16,22,23,33}. Chemotherapeutic agents may cause structural damage to peripheral nerves resulting in aberrant somatosensory processing of the peripheral and/or central nervous system. The symptoms of chemotherapy induced peripheral neuropathy (CIPN) vary depending on the type of chemotherapy and which nerve fibers are affected. Chemotherapies mainly affecting the sensory nerve fibers may result in unusual sensations (paresthesias), numbness, balance problems or pain. Whereas, weakness of the muscles in the feet and hands are experienced when the motor nerves are affected. While most breast cancer patients experience improvement of CIPN after chemotherapy, some develop persistent NP. However, to our knowledge, few studies have assessed the extent to which breast cancer survivors who experience chemotherapy-induced peripheral neuropathy (CIPN) during chemotherapy treatment develop NP. The purpose of this study was to determine the association between CIPN and neuropathic pain in breast cancer patients previously treated with paclitaxel. We also assessed the extent to which disease- and treatment-related variables (e.g., disease stage, tumor, chemotherapy and other cancer therapy, and chemotherapy dosage and duration), health status (e.g., comorbid conditions), and sociodemographic characteristics (e.g., age and race) influence the occurrence of NP. The survival rates of breast cancer patients have steadily improved over recent years; thus, research into symptoms that persist after treatment is important.¹⁹ Understanding the epidemiology of NP in breast cancer patients has high clinical and public health significance.

Patients and Methods

We conducted a survey of breast cancer survivors between Sept. 2007-May, 2008. Eligibility criteria included patients who participated in clinical trials of paclitaxel between 1994 and 2001 at The University of Texas M. D. Anderson Cancer Center (Houston, TX).^{2,11} We searched the institutional database and identified 635 breast cancer patients, 430 of whom were alive and had current contact information on file as of July 2007. Two-hundred forty patients consented to participate in our study. Signed informed consent forms were obtained from all participants in accordance with procedures approved by the M. D. Anderson Cancer Center institutional review board.

Variable Definitions

Variables During Treatment—Demographic and clinical data (age, race, disease stage, and chemotherapy dosage and duration) obtained during the clinical trial were abstracted from a departmental clinical database.

Chemotherapy-Induced Peripheral Neuropathy (CIPN)—The National Cancer Institute Common Toxicity Criteria sensory neuropathy grade, obtained during treatment, was used to determine the presence of CIPN. A score of grade 2 or higher for sensory neuropathy was used to classify patients as having CIPN. The NCICTC sensory neuropathy grading were as follows: Grade 0=normal; Grade 1= loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function; Grade 2= objective sensory loss or paresthesia (including tingling), interfering with function but not with activities of daily living; and Grade 3= sensory loss or paresthesia interfering with activities of daily living; Grade 4= permanent sensory loss that interferes with function. Of note is that the severity of pain is not included in this measure.

Follow-up Survey—A questionnaire was mailed to those who consented to participate. Patients were initially contacted by telephone and were given detailed explanation of the study.

Upon obtaining verbal consent, questionnaires were sent to the patients' residence and stamped envelopes were provided.

Neuropathic Pain and Co-Morbid Conditions—A diagnosis of NP was based on the patient's response to the question “Have you ever been diagnosed by your physician or healthcare provider for neuropathic pain”? In addition, co-morbid conditions were assessed, including slipped discs and acute intervertebral disc herniation, hypertension, diabetes mellitus, cerebrovascular accident, rheumatoid arthritis, osteoarthritis, and fibromyalgia. Patients were also asked: “Did you have a recurrence (cancer came back) in the breast, lymph nodes or chest wall?” and “After your first diagnosis of breast cancer, has your cancer spread (metastasized) to other sites, such as lung, liver or bones?”

Pain Treatment and Management—Current treatment and management of pain was assessed by asking, “Are you being treated by or under the care of a health care professional for any problems with pain?” The number of visits to a health care professional was assessed by asking, “Approximately how many times have you visited a health care professional about your pain in the past year?” Pain treatment was assessed by asking, “Have you taken prescription medication for your pain during the past 3 months?” and “Have you ever taken over-the-counter medication for your pain during the past 3 months?”

Statistical Analyses

We assessed the association between study variables using Pearson's chi-square analysis and analyses of variance. The extent of the association between CIPN and NP was assessed using logistic regression, where the presence or absence of NP was coded as a dependent variable and CIPN and other risk factors (cumulative dose and duration of treatment, co-morbid conditions, and age) were included as predictor variables. In the multivariate logistic analysis, the first model included all variables considered significant ($p < 0.20$) in the univariate analysis. (A p value of 0.20 was used as the cut-off because a more traditional value [e.g., $p < 0.05$] often does not identify variables known to be important.) Further variable selection in the model was conducted using backward elimination. To result in the most parsimonious model, only variables with p values ≤ 0.05 were included in the final model.

Results

Of the 430 patients identified as alive and with current contact information on file, 240 responded to the survey. Follow-up survey data showed that the mean survival duration of respondents was 9.5 years (standard deviation=2.1). Eight percent of these patients had experienced local recurrence, and 8% had experienced progression to metastatic disease. The most common comorbid condition was hypertension (34%) followed by osteoarthritis (29%); diabetes (10%) and rheumatoid arthritis (6%).

Sixty four percent had experienced CIPN during the trial. The mean cumulative dose of paclitaxel was significantly associated with CIPN (Table 1). To assess for potential bias, we compared the respondents ($N=240$) and non-respondents ($N=190$) with respect to the mean cumulative dose of paclitaxel received and reports of CIPN during clinical trial. We found no statistically significant differences between the respondents and non-respondents in these 2 measures: 64.4% of respondents and 64.5% of non-respondents had experienced CIPN ($p=0.54$), and the mean cumulative doses of paclitaxel had been 1035 mg/m^2 for respondents and 1018 mg/m^2 for non-respondents ($p=0.59$).

Eighteen percent of the total sample reported being diagnosed with NP. Of those with CIPN, 27% subsequently reported being diagnosed with NP. When we assessed the extent to which CIPN was associated with NP, univariate logistic regression analysis showed that those with

CIPN were 3 times more likely to report NP (odds ratio=3; 95% confidence interval=1.2-7.2; $p<0.001$) in the survey. Other variables found to be associated with NP in the univariate analyses included age, hypertension, diabetes, rheumatoid arthritis, and osteoarthritis.

Table 2 shows the variables that remained significant in the multivariate model. CIPN during treatment remained a significant risk factor for NP (OR=2.95; 95% confidence interval=1.00-8.85; $p=0.05$). We also found that comorbid conditions such as diabetes and osteoarthritis as significant predictors of NP in the multivariable model. Importantly, the cumulative dose of paclitaxel received during the trial remained as a significant predictor of NP.

We also found that many of the survivors had pain problems requiring medical care. As many as 25% of respondents reported being under the care of a health professional for pain problems; they had had a mean of 2 visits to their health care provider (standard deviation=5) in the past year. Twenty-seven percent reported taking prescription medication for pain, and 46.5% reported taking over-the-counter medication. We assessed the extent to which NP patients differed from non-NP patients with respect to the number of health care provider visits and pain treatment and found that NP patients reported twice as many visits to their health care provider ($p=0.028$) than did non-NP patients. In addition, 50% of NP patients reported taking prescription medication for pain versus 19% of non-NP patients ($p=0.0001$). The use of over-the-counter medication for pain was reported by 62.5% and 45% ($p=0.086$) of these patients, respectively.

Discussion

In this study, we found that patients who had experienced CIPN during paclitaxel treatment were 3 times more likely to receive a diagnosis of NP, and this persisted even after controlling for demographic and clinical factors. Thus, patients treated with paclitaxel should be regularly monitored for NP beyond treatment. As a chemotherapy agent, Paclitaxel promotes the formation of abnormal bundles of microtubules within the cytoplasm, leading to the disruption of normal cell function and proliferation.²⁷ While this mechanism results in the desired effect on the tumor, the same mechanism can render taxanes toxic to normal tissue. Microtubules are important for the development and maintenance of neurons by providing structural support and serve as major mediators of axonal transport. A generally accepted theory is that because paclitaxel disrupts microtubule assembly, a consequence of its administration is impairment in neuronal development and function. A recent animal study however, indicates that paclitaxel-induced pain is not associated with an abnormality of axonal microtubules, but that it induces an abnormality in axonal mitochondria⁹. Studies continue to explore the mechanisms underlying NP associated with paclitaxel therapy.

Published guidelines for the initial treatment of NP include the use of gabapentin, pregabalin, carbamazepine, tricyclic antidepressants, oxycodone, morphine, methadone, tramadol, duloxetine, and venlafaxine.^{1,17} Placebo-controlled trials have shown that medications such as gabapentin²⁵ and glutamine¹⁴ have no statistically significant effects on NP. To date, animal and human studies^{8,10,15,18,20,28,34} are being conducted to identify the best methods for treating and managing NP.

Consistent with other studies²², we found that the cumulative dose of paclitaxel was strongly associated with CIPN. In fact, the cumulative dose persisted as a significant factor in the multivariate analysis. At MD Anderson, patients on weekly paclitaxel therapy are monitored every 4 to 6 weeks for symptoms of worsening CIPN. If the intent of paclitaxel therapy is cure, the physician and patient should discuss the risks and benefits of continuing the current dose of paclitaxel in the setting of worsening neuropathy.

We also found that diabetes and osteoarthritis were significantly associated with NP. While the exact mechanism of enhanced vulnerability to toxic neuropathy in patients with diabetes is not known, studies have shown that NP is prevalent in this population.^{29,31,32} In this study, we found that patients with diabetes had the highest risk for NP, both in the univariate and multivariate analyses. We also found that patients with osteoarthritis had a 3-fold risk for NP. Osteoarthritis is characterized by joint pain and muscle pain, and the observed relationship between osteoarthritis and NP in this study may be biased by the fact that these patients are more likely to be diagnosed with NP. However, it is also important to note that pre-clinical studies have demonstrated the presence of a neuropathic mechanism in the pathology of osteoarthritis¹³ and furthermore, there is continuing discussion as to whether components of osteoarthritic pain are also neuropathic.^{7,26}

Numerous guidelines on acute pain have been published, but the treatment and management of NP pose considerable challenges. In this study, NP patients reported twice as many visits to their health care provider as did non-NP patients; in addition, 50% and 62.5% of NP patients reported taking prescription medications and over-the-counter medications for pain, respectively. These findings highlight the major health and economic effects of NP.

This study has limitations. Since information on the diagnosis of NP was based on self-report and the question asked was that of “Have you ever been diagnosed by your physician or healthcare provider for neuropathic pain?”, misclassification of patients as having NP is a distinct possibility and may therefore lead to a bias in the findings. We also lacked information on specific cancer treatments (such as subsequent chemotherapy) and the extent to which these factors may have influenced the development of NP was not assessed in this study. We also did not assess prior injury which may have led to a bias in our findings since prior injury has been shown to affect neuropathic pain development^{6,24,35}. In addition, although this study is among the first studies to assess the relationship between CIPN and NP in a relatively large number of breast cancer survivors, 44% of patients did not respond to the survey, which may influence the generalizability of our findings. Additional studies are needed to address these issues.

In conclusion, our study provides empirical evidence of the importance CIPN as a risk factor for NP in breast cancer patients. We also demonstrated the influence of several factors (co-morbid conditions and demographic and clinical variables) in the epidemiology of NP. Prospective studies with larger cohorts are needed to validate our findings.

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Table 1

Association between mean cumulative dose of paclitaxel and CIPN during paclitaxel trial*

NCI CTC neurotoxicity grade**	Number of patients (n=197)	Mean cumulative paclitaxel dose	Standard deviation
0	11	890.45	124.06
1	61	968.85	156.47
2	92	1050.85	276.81
3	33	1151.07	381.98
Mean		1033.29	269.43

NCI CTC, National Cancer Institute Common Toxicity Criteria.

* Analysis of variance $p=0.004$.

** Grade 0: normal; grade 1: loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function; grade 2: objective sensory loss or paresthesia (including tingling), interfering with function but not with activities of daily living; grade 3: sensory loss or paresthesia interfering with activities of daily living; grade 4: permanent sensory loss that interferes with function.

Table 2

Risk factors for NP: unadjusted and adjusted analyses

Variable	Unadjusted		Adjusted	
	p value	Odds ratio	p value	Odds ratio
Age	0.043	1.04 (1.00-1.01)	NS	
Cumulative paclitaxel dose	0.006	1.00 (1.00-1.00)	0.005	1.00 (1.00-1.00)
Hypertension	0.020	2.53 (1.2-5.50)	NS	
Diabetes	0.003	5.04 (1.7-14.70)	0.003	6.67 (1.87-23.63)
Rheumatoid arthritis	0.093	3.14 (0.09-11.80)	NS	
Osteoarthritis	0.003	3.43 (1.50-7.70)	0.003	3.97 (1.57-10.03)
CIPN	0.019	2.92 (1.20-7.20)	0.05	2.95 (1.00-8.85)

NP-Have you ever been diagnosed by the physician or healthcare provider for neuropathic pain?

NS, not significant.