Natural History of Paclitaxel-Associated Acute Pain Syndrome: Prospective Cohort Study NCCTG N08C1

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ABSTRACT

Purpose

The characteristics and natural history of the paclitaxel–acute pain syndrome (P-APS) and paclitaxel's more chronic neuropathy have not been well delineated.

Methods

Patients receiving weekly paclitaxel (70 to 90 mg/m²) completed daily questionnaires and weekly European Organisation for Research and Treatment of Cancer (EORTC) Chemotherapy-Induced Peripheral Neuropathy (CIPN) –20 instruments during the entire course of therapy.

Results

P-APS symptoms peaked 3 days after chemotherapy. Twenty percent of patients had pain scores of 5 to 10 of 10 with the first dose of paclitaxel. Sensory neuropathy symptoms were more prominent than were motor or autonomic neuropathy symptoms. Of the sensory neuropathy symptoms, numbness and tingling were more prominent than was shooting or burning pain. Patients with higher P-APS pain scores with the first dose of paclitaxel appeared to have more chronic neuropathy.

Conclusion

These data support that the P-APS is related to nerve pathology as opposed to being arthralgias and/or myalgias. Numbness and tingling are more prominent chronic neuropathic symptoms than is shooting or burning pain.

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INTRODUCTION

Paclitaxel is associated with a peculiar syndrome of subacute aches and pains, which has been referred to as paclitaxel-induced arthralgias and myalgias.^{1,2} This pain syndrome, described in up to 58% of patients, usually develops within 1 to 3 days of paclitaxel administration; symptoms largely resolve within a week.

The paclitaxel-associated acute pain syndrome (P-APS) may result from nociceptor sensitization on the basis of patient descriptors of pain; in addition, rats infused with paclitaxel develop nerve injury within 24 hours.³ The nature and temporal profile of the P-APS distinguishes it as a separate entity from chemotherapy-induced peripheral neuropathy; however, it is not known if those patients who develop the P-APS are more likely to develop peripheral neuropathy.

A randomized study comparing the efficacy of short versus extended infusion of paclitaxel in metastatic breast cancer demonstrated a 25% incidence

of acute pain problems in the 3-hour infusion group versus a 2% incidence in the 96-hour infusion group. This suggests perhaps that higher peak drug levels are responsible for P-APS.⁴

Nonopioid and opioid analgesics are often used for symptomatic management of P-APS. Few studies, mostly case series, have investigated the role of other medications for both prevention and treatment. Studies using Shakuyaku-Kanzo-To (a Japanese herb),⁵ antihistamines,⁶ corticosteroids,⁷ opioid analgesics,⁸ and amifostine⁹ have not yielded enough evidence to establish a standard practice. The lone published placebo-controlled, double-blinded, prevention study showed no superiority of glutamine versus placebo.¹⁰

This prospective study was designed to detail the natural history of the P-APS and also the natural history of paclitaxel-induced peripheral neuropathy, including a definition of a potential relationship that might exist between these two entities. It was hypothesized that a correlation between the degree of P-APS and subsequent neuropathy would support that P-APS was a form of neurotoxicity. Greater

understanding of the nature and etiology of P-APS might provide additional insight into ways to potentially alleviate this bothersome toxicity.

METHODS

Eligible patients needed to be scheduled to receive paclitaxel at a dose of at least 175 mg/m² at 2- to 4-week intervals versus 70 to 90 mg/m² weekly. Patient groups were also segregated by whether they were or were not receiving another concomitant neurotoxic drug (eg, platinum agents), which resulted in four cohorts of patients. The current study reports only on the cohort of patients who received weekly paclitaxel without the use of a concurrent neurotoxic agent, because this was the first cohort to complete its accrual goal.

Patients on this study were at least 18 years old, were able to provide written consent, and were able to complete study questionnaires. They had to have a life expectancy of greater than 6 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients were excluded if they had been diagnosed with peripheral neuropathy from any cause, had been diagnosed with fibromyalgia, had planned to receive concurrent neutrophil colony-stimulating factor therapy, or had previous exposure to paclitaxel or other neurotoxic chemotherapy drugs.

Institutional review board approval and individual signed patient consent were obtained for this study at each participating institution, per US federal guidelines. For pain that might develop related to paclitaxel, participants were instructed to initially use acetaminophen and/or nonsteroidal anti-inflammatory drug pain relievers, with escalation to opioid analgesics as needed.

P-APS symptoms were measured by asking patients to keep a daily symptom log comprised of 10 items regarding pain symptoms and use of pain medications on days 2 through 7 after each paclitaxel dose. These questions were derived and adapted from Cleeland's Brief Pain Inventory, which has been widely used in cancer populations.¹¹ The modified items asked about aches as well as pain, anchored directly to the paclitaxel treatment. In addition, a 22-item summary questionnaire regarding symptom quality, location, alleviating/aggravating factors, and medication use was given the eighth day after each paclitaxel dose.

To measure chemotherapy-induced peripheral neuropathy (CIPN) symptoms, the EORTC (European Organization for Research and Treatment of Cancer) Quality of Life Questionnaire (QLQ)-CIPN-20 questionnaire was administered at baseline and weekly after each paclitaxel dose. The EORTC QLQ-CIPN-20 is a 20-item CIPN-specific questionnaire that includes three scales assessing sensory (nine items), motor (eight items), and autonomic (three items) symptoms and functioning, with each item measured on a scale of 1 to 4 (1, not at all; 4, very much). The EORTC QLQ-CIPN-20 has been tested in patients with cancer and has been shown to have internal consistency reliability on the basis of Cronbach α coefficients of 0.82, 0.73, and 0.76 for the three scales, respectively.¹²

In addition, NCCTG (North Central Cancer Treatment Group) simple, single-item measures of peripheral neuropathy, developed in response to issues raised with the measurement of oxaliplatin-related toxicity,^{13,14} were used. These simple, single-item measures have proved useful as screening tests for the appearance of CIPN relative to the Common Terminology Criteria of Adverse Events criteria,¹³ indicating that patients can identify clinically meaningful changes in CIPN 2 to 3 months before clinician-based Common Terminology Criteria of Adverse Events ratings.¹⁵ A score of 50 or worse on these 0-to-100 scale CIPN items are indicative of a clinically meaningful deficit.¹⁶

Patient-reported outcome (PRO) for acute pain was collected and evaluated on a 0 to 10 scale, in which 0 was the best possible score. All other PRO scores were converted into a 0- to 100-point scale, in which 100 was the best possible score.¹⁷⁻¹⁹

The primary goal for this trial was to describe the incidence and characteristics of, and change in, pain (ie, P-APS) related to paclitaxel infusions over several cycles. This analysis is descriptive and is intended to

detail the unique nature of the P-APS syndrome qualitatively. The frequency of the incidence and severity variables were plotted over the weeks of therapy with related CIs.

Depending on the variable of interest, mean (and standard deviation), median (and range), and frequency (as a percentage) were used to summarize data in a descriptive manner. Nonparametric Wilcoxon rank sum tests, two-sample *t* tests, and χ^2 tests (or Fisher's exact tests) were used to compare the difference in scores by pain groups defined in the first cycle.

To investigate the association between the P-APS symptoms and eventual chemotherapy-induced neuropathy, correlation coefficients were produced relating the worst pain scores for the first dose of therapy and the subsequent neuropathy scores at week 12. EORTC QLQ-CIPN-20 differences in sensory, autonomic, and motor neuropathy were evaluated by the actual change from baseline to week 12, percent change from baseline to week 12, and percent of baseline. Changes from baseline were tested between each pair of variables, and the differences in the area under the curve (AUC) were tested by using Kruskal-Wallis nonparametric procedures and mixed models. No adjustments were made for multiple comparisons.

RESULTS

A total of 94 patients were accrued on the above-defined patient cohort, from 23 NCCTG institutions between February and December 2009. All were women, with a mean age of 53 years. Seventy-eight percent were white; 12%, black; 10%, Asian; and 1%, unreported.

P-APS

First, the data will be presented regarding responses that patients provided when they were asked, daily for the first 6 days after the first dose of paclitaxel, "Please rate any aches/pains that are new since your last dose of paclitaxel and that you think might be related to your chemotherapy treatment by circling one number that best describes your aches/pains at its worst in the last 24 hours." Seventy-one percent of patients noted pain, ranging from 1 to 10 on a 0-to-10 scale. The pain peaked on day 4 after paclitaxel commencement (Fig 1A). With subsequent doses of paclitaxel, some level of pain was reported by 56% to 69% of respondents. To address whether P-APS pain intensity with the first cycle of therapy correlated with what was observed on subsequent cycles, worst individual pain scores for the 7 days after the first chemotherapy dose were then grouped according to commonly accepted pain severity classes.²⁰ Worst pain score severities, associated with the first cycle of paclitaxel, did not appear to predict pain difficulties with subsequent paclitaxel doses (Fig 1B). Figure 1B also provides the numbers of patients with different pain categories for each week of therapy. For the group as a whole, worse P-APS severities were quite stable over the 12 courses of weekly therapy (Fig 1B), as was analgesic use (Fig 2).

Table 1 illustrates the nature of the P-APS as experienced by patients after their first infusions by listing indicated pain descriptors and location, which were provided in the questionnaire instrument. The most prominent pain was in the lower extremities, most often described as being aching. Symptoms were often quite diffuse. Severity was such that nonprescription medications were used by 30% to 41% of patients per week, whereas opioids were used by 12% to 20% (Fig 2).

CIPN

The EORTC QLQ-CIPN-20 instrument was utilized to record symptoms associated with evolution of peripheral neuropathy over

Fig 1. (A) Mean maximal daily pain scores and 95% CI during the first paclitaxel week from the patient-reported outcome questions related to the paclitaxel–acute pain syndrome (P-APS). (B) Worst mean maximum P-APS scores over the 12 weeks of paclitaxel, segregated by the worst mean maximum P-APS scores for the first week.

the series of paclitaxel infusions for each patient. Figure 3 illustrates the percent of baseline sensory, motor, and autonomic scores over time. Sensory nerve function was most impaired by paclitaxel, whereas symptoms associated with changes in autonomic or motor nerve function were quite limited. Mean sensory nerve function scores declined 23.4 points from baseline to 12 weeks ($P < .001$ for a sign test for determining if this change was significantly different than zero), whereas mean motor nerve function scores declined 11.5 points ($P < .001$), and autonomic nerve function scores declined 5.8 points ($P = .01$). Mixed-model statistics revealed that sensory changes were more marked than motor changes ($P = .001$) or autonomic changes ($P = .02$).

To test which of the three types of neuropathy had the biggest change from baseline, two analyses were done. First, the changes from baseline were tested between each pair of variables. Second, the differences in AUC were tested between each pair of variables. By both methods, the change in sensory nerve function was significantly greater than the change in autonomic nerve function ($P < .001$ for raw

Fig 2. Rates of analgesic agents used for the treatment of the paclitaxel–acute pain syndrome over time. OTC, over the counter.

change and $P = .05$ for AUC) and the change in motor nerve function ($P < .001$ for both methods). The differences in the changes between motor and autonomic nerve function were not as large ($P = .0203$ for raw difference and $P = .38$ for AUC).

Table 1. Description and Location of Pain From the PRO Questions Related to the P-APS

Pain Variable	%
Description	
Aching	45
Dull	19
Sharp	14
Throbbing	13
Shooting	12
Heavy	11
Cramping	11
Stinging	8
Gnawing	5
Hot	5
Pulsating	5
Stabbing	5
Splitting	1
Location	
Legs, lower	17
Legs, upper	16
Feet	15
Hips	13
Back, lower	11
Other	11
Neck	11
Shoulders	9
Head	7
Abdomen	8
Arms, upper	6
Arms, lower	6
Hands	6
Chest	6
Back, upper	6

Abbreviations: PRO, patient-reported outcome; P-APS, paclitaxel–acute pain syndrome.

Fig 3. Sensory, motor, and autonomic subscores from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy-20 instrument in terms of percent of baseline over time.

These sensory neuropathy changes were evaluated in more detail by examining data from the following three individual questions that this instrument contains: Do you have tingling fingers or hands? Do you have numbness in your fingers or hands? Do you have shooting or burning pain in your fingers or hands?

Figure 4 illustrates that, during the time of paclitaxel therapy, numbness and tingling are closely related to each other, whereas pain is less prominent. Three questions, similar to the ones stated in the previous paragraph, are also asked by the EORTC QLQ-CIPN-20, relating to toes and feet as opposed to hands and fingers. Data from the lower extremities basically replicate what is observed in the upper extremities, in terms of the relationship of pain, numbness, and tingling.

Fig 4. Mean numbness, tingling, and pain scores for hands and fingers (from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy [CIPN]-20 instrument).

The differences in the AUC were tested between upper versus lower extremities for tingling ($P = .46$), numbness ($P = .73$), and shooting or burning pain ($P = .82$), demonstrating that symptom severity was similar in the lower extremities and the upper extremities. This is also illustrated in Appendix Table A1 (online only).

Data from the NCCTG peripheral neuropathy items demonstrated similar results to what was seen with the EORTC QLQ-CIPN-20 data. Additional detail from the NCCTG peripheral neuropathy items indicate that approximately half of the patients reported clinically significant numbness and tingling in hands and/or feet at some point in time over the 12-week period (scores of less than 50 on the 100 point scale), whereas, pain was considered to be clinically significant in only approximately a quarter of patients (Appendix Table A1).

To determine whether there was any relationship between the experience of P-APS and the later appearance of peripheral neuropathy, EORTC CIPN-20 scores were compared between those patients who had P-APS scores of 0 to 4 during the week after receiving their first dose of paclitaxel and those with higher scores. Figure 5 illustrates that patients with more prominent P-APS during the first cycle of therapy appear to have more eventual sensory neuropathy in the lower extremities after 12 weeks of therapy. This looked more pronounced for those experiencing a burning and shooting pain component of their sensory neuropathy. Similar data were observed in the upper extremities. Correlations between P-APS severity in the first study week and the various measures of eventual CIPN support a relationship, per mixed-model statistics (Appendix Table A2, online only).

DISCUSSION

This report provides a detailed prospective evaluation of P-APS in a cohort of patients treated with this drug alone for 12 weekly infusions at 70 to 90 mg/m²; it describes the relationship between the severity of this syndrome and the development of the other well-known complication of taxane therapy, namely, a predominant sensory neuropathy.²¹⁻²³ It substantiates the information that was provided in a retrospective study of 18 patients, in which it was proposed that P-APS was of neuropathic origin, possibly related to some form of preferential sensitization of mechanical nociceptive neurons, as opposed to being from musculoskeletal or joint pathology.³ The data from this study confirm the most common manifestation of this syndrome as a diffuse aching discomfort, most often in the legs, hips, and lower back, although it can be widespread; these manifestations are similar to observations reported from patients in a retrospective review.³ The data also confirm the time frame of evolution of symptoms associated with this syndrome, in which pain usually evolves over 24 to 96 hours and usually abates over the same time.

It was somewhat surprising that pain intensity noted in the first cycle did not correlate well with the amount of pain in subsequent cycles. Although pretreatment with analgesics before the development of severe pain in subsequent cycles could explain lower pain scores for those with initially more intense P-APS experiences, some of those with minimal acute pain with initial infusions reported more intense pain with subsequent infusions.

Although the initial intensity of pain experienced with the first paclitaxel infusion did not predict the experience of pain in subsequent cycles, it did appear to predict the later severity of symptoms

Fig 5. Total sensory neuropathy, numbness, tingling, and burning/shooting pain scores (from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy [CIPN]–20 instrument) segregated by lower paclitaxel–acute pain scores during the week after receiving the first dose of paclitaxel versus higher scores from the patient-reported outcome questions related to the paclitaxel–acute pain syndrome (P-APS).

associated with a sensory predominant peripheral neuropathy, which gradually evolved over the 12-week course of therapy. Interestingly, it looks like it predicts the severity of shooting/burning pain more than other symptoms. Therefore, this syndrome could serve as a sentinel for the need for aggressive prophylactic management, were an agent ever developed that could prevent the development of taxane-induced neuropathy or at least minimize a patient's experience of the symptoms associated with its development. Moreover, if P-APS could be averted, then, perhaps, so might the later neuropathy.

Presently, there is no established way of preventing P-APS, aside from paclitaxel dose reductions or the use of analgesics. There are reports that gabapentin may be helpful for alleviating P-APS.² Of interest, gabapentin, when given presurgically, has been shown to decrease postsurgical nociceptive pain.²⁴ Given these observations and the hypothesis that P-APS may be related to the occurrence of some form of preferential nociceptor sensitization, gabapentin deserves additional prospective, placebo-controlled evaluation for the prophylaxis of both P-APS and, subsequently, symptoms of taxane-induced neuropathy.

There is little precedent for the pattern of symptoms observed with P-APS.³ However, other conditions causing a sensory predominant polyradiculopathy or polyradiculoneuropathy produce a similar experience. A recent report of an autoimmune sensory predominant polyradiculoneuropathy in pork workers showed a prominent pattern

of diffuse aching axial and limb pain in the setting of a pronounced inflammation of nerve roots and dorsal root ganglia.²⁵ It is noteworthy, therefore, that, in rat models of taxane neuropathy, rapid infiltration of macrophages in trigeminal and nerve root ganglia were demonstrated after activation of expression of markers of nerve injury.^{26,27} This may suggest immune system activation as a component explanation for the appearance of P-APS.

Paclitaxel-Induced Peripheral Neuropathy

Data from this large cohort treated only with paclitaxel confirm the sensory-predominant nature of the neuropathy that complicates the use of this agent. The clinical presentation is fairly uniform, and the incidence of symptoms of numbness and tingling are superimposable. Each is more prominent than the experience of shooting/burning pain, and both occur before these often more disquieting symptoms.²⁸ Data from this study support findings from Dougherty et al,²⁹ who evaluated 12 patients experiencing paclitaxel-induced neuropathy problems. Numbness was noted in 100% of patients, whereas tingling was noted in 80%. Burning pain was less frequent, observed in approximately 55% of patients. Patients in this study had decreased touch thresholds and required longer times to complete a grooved peg-board test compared to control participants. They did not have any significant differences in their ability to determine heat or coolness but did have less tolerance to colder temperatures and had resultant

cold-induced pain. These authors concluded that their data demonstrated a marked impairment of A-beta (large myelinated) fibers, with less apparent effects on A-δ (small myelinated) fibers. They also felt that their data suggested that unmyelinated small C fibers were not impaired with paclitaxel to any large degree.

These data are also consistent with data from individuals who entered a clinical trial for patients with established chemotherapy-induced neuropathy of greater than 4 of 10 severity.³⁰ Patients who entered this clinical trial had more complaints of numbness and tingling than complaints of burning/shooting pain, and numbness and tingling were far more closely correlated with each other than between either of these symptoms versus shooting/burning pain. Although it is well established pathologically that taxanes affect large myelinated, small myelinated, and unmyelinated sensory fibers,³¹ this pattern of symptoms suggest a greater vulnerability of large fiber function. The later appearance and persistence of bothersome painful shooting/burning pain suggest that smaller fiber involvement occurs after the myelinated fiber involvement is advanced. An evaluation to correlate patient reported outcome symptoms with quantitative neurologic testing, although not evaluated in this study, is planned in future studies.

Numerous agents have been studied as options to treat the bothersome symptoms of taxane-induced peripheral neuropathy. None, including gabapentin,³² despite some promise for preventing P-APS,

have been proven to be beneficial. Therefore, rather than focusing only on symptomatic therapy for established neuropathy, future studies should also focus on prophylaxis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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REFERENCES

- Rowinsky EK, Eisenhauer EA, Chaudhry V, et al: Clinical toxicities encountered with paclitaxel (Taxol). *Semin Oncol* 20:1-15, 1993 (suppl 3)
- Garrison JA, McCune JS, Livingston RB, et al: Myalgias and arthralgias associated with paclitaxel. *Oncology (Williston Park)* 17:271-277, 2003; discussion 281-282, 286-288
- Loprinzi CL, Maddocks-Christianson K, Wolf SL, et al: The paclitaxel acute pain syndrome: Sensitization of nociceptors as the putative mechanism. *Cancer J* 13:399-403, 2007
- Moulder SL, Holmes FA, Tolcher AW, et al: A randomized phase 2 trial comparing 3-hour versus 96-hour infusion schedules of paclitaxel for the treatment of metastatic breast cancer. *Cancer* 116:814-821, 2010
- Fujiwara H, Urabe T, Ueda K, et al: Prevention of arthralgia and myalgia from paclitaxel and carboplatin combination chemotherapy with Shakuyaku-kanzo-to [in Japanese]. *Gan To Kagaku Ryoho* 27:1061-1064, 2000
- Martoni A, Zamagni C, Ghika A, et al: Antihistamines in the treatment of taxol-induced paroxysmic pain syndrome. *J Natl Cancer Inst* 85:676, 1993
- Markman M, Kennedy A, Webster K, et al: Use of low-dose oral prednisone to prevent paclitaxel-induced arthralgias and myalgias. *Gynecol Oncol* 72:100-101, 1999
- Sarris AH, Younes A, McLaughlin P, et al: Cyclosporin A does not reverse clinical resistance to paclitaxel in patients with relapsed non-Hodgkin's lymphoma. *J Clin Oncol* 14:233-239, 1996
- Gelmon K, Eisenhauer E, Bryce C, et al: Randomized phase II study of high-dose paclitaxel with or without amifostine in patients with metastatic breast cancer. *J Clin Oncol* 17:3038-3047, 1999

- Jacobson SD, Loprinzi CL, Sloan JA, et al: Glutamine does not prevent paclitaxel-associated myalgias and arthralgias. *J Support Oncol* 1:274-278, 2003
- Cleeland C: How to assess cancer pain, in Tuck DC, Medzak R (eds): *Handbook of Pain Assessment*. New York, NY, The Guilford Press, 1992, pp 360-387
- Postma TJ, Aaronson NK, Heimans JJ, et al: The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: The QLQ-CIPN20. *Eur J Cancer* 41:1135-1139, 2005
- Morton TF, Sloan JA, Grothey A, et al: A comparison of simple single-item measures and the common toxicity criteria in detecting the onset of oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer. *J Clin Oncol* 23:750s, 2005 (suppl; abstr 8087)
- Liu H, Tan AD, Grothey A, et al: Comparing and validating simple measures of patient-reported peripheral neuropathy for NCTG clinical trials: A pooled analysis of 2,440 patients. *J Clin Oncol* 26:510s, 2008 (suppl; abstr 9534)
- Sloan JA, Berk L, Roscoe J, et al: Integrating patient-reported outcomes into cancer symptom management clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. *J Clin Oncol* 25:5070-5077, 2007
- Huschka MM, Mandrekar SJ, Schaefer PL, et al: A pooled analysis of quality of life measures and adverse events data in north central cancer treatment group lung cancer clinical trials. *Cancer* 109:787-795, 2007
- Sloan J, O'Fallon J, Suman V, et al: Incorporating quality of life measurement into oncology clinical trials. *Proc Am Stat Assoc* 1998:282-287, 1998
- Sloan J, Symonds T, Vargas-Chanes D, et al: Practical guidelines for assessing the clinical significance of health-related quality of life changes within clinical trials. *Drug Information J* 37:23-31, 2003
- Sloan JA, Dueck A: Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. *J Biopharm Stat* 14:73-96, 2004
- Serlin RC, Mendoza TR, Nakamura Y, et al: When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain* 61:277-284, 1995
- Sahenk Z, Barohn R, New P, et al: Taxol neuropathy: Electrodiagnostic and sural nerve biopsy findings. *Arch Neurol* 51:726-729, 1994
- Scripture CD, Figg WD, Sparreboom A: Peripheral neuropathy induced by paclitaxel: Recent insights and future perspectives. *Curr Neuropharmacol* 4:165-172, 2006
- Windebank AJ, Grisold W: Chemotherapy-induced neuropathy. *J Peripher Nerv Syst* 13:27-46, 2008
- Ho KY, Gan TJ, Habib AS: Gabapentin and postoperative pain: A systematic review of randomized controlled trials. *Pain* 126:91-101, 2006
- Lachance DH, Lennon VA, Pittock SJ, et al: An outbreak of neurological autoimmunity with polyradiculoneuropathy in workers exposed to aerosolized porcine neural tissue: A descriptive study. *Lancet Neurol* 9:55-66, 2010
- Jimenez-Andrade JM, Peters CM, Mejia NA, et al: Sensory neurons and their supporting cells located in the trigeminal, thoracic and lumbar ganglia differentially express markers of injury following intravenous administration of paclitaxel in the rat. *Neurosci Lett* 405:62-67, 2006
- Peters CM, Jimenez-Andrade JM, Jonas BM, et al: Intravenous paclitaxel administration in the rat induces a peripheral sensory neuropathy characterized by macrophage infiltration and injury to sensory neurons and their supporting cells. *Exp Neurol* 203:42-54, 2007
- Reyes-Gibby CC, Morrow PK, Buzdar A, et al: Chemotherapy-induced peripheral neuropathy as a predictor of neuropathic pain in breast cancer patients previously treated with paclitaxel. *J Pain* 10:1146-1150, 2009

29. Dougherty PM, Cata JP, Cordella JV, et al: Taxol-induced sensory disturbance is characterized by preferential impairment of myelinated fiber function in cancer patients. *Pain* 109:132-142, 2004

30. Wolf SL, Qin R, Barton DL, et al: Relationship of sensory symptoms and motor function in

patients with chemotherapy-induced peripheral neuropathy (CIPN) utilizing the EORTC QLQ CIPN20: NCCTG study N06CA. *J Clin Oncol* 27: 504s, 2009

31. Argyriou AA, Koltzenburg M, Polychronopoulos P, et al: Peripheral nerve damage associated with administration of taxanes in patients with cancer. *Crit*

Rev Oncol Hematol 66:218-228, 2008

32. Rao RD, Michalak JC, Sloan JA, et al: Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: A phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer* 110: 2110-2118, 2007

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