Clinical Assessment of Chemotherapy-Induced Peripheral Neuropathy: The Road Less Traveled

CONSTANCE VISOVSKY, PHD, RN, APRN-BC

From the University of Nebraska Medical Center College of Nursing, Omaha, NE.

The author has no conflicts of interest to disclose.

Correspondence to: Constance Visovsky, PhD, RN, APRN-BC, University of Nebraska Medical Center College of Nursing, 985330 Nebraska Medical Center, Omaha, NE 68198-5330. E-mail: cvisovsky@unmc.edu.

Abstract

The cornerstone of treatment for many cancers includes chemotherapy agents known to induce peripheral neuropathy . Chemotherapy-induced peripheral neuropathy (CIPN) is a potential side effect of treatment for which few patients are prepared. CIPN continues to pose challenges to heatlh care providers for a variety of reasons, including a lack of gold-standard clinical- or laboratory-based assessments and variable clinical presentation. Advanced oncology practitioners are in an ideal position to provide baseline and ongoing clinical assessments. These assessments can be used as a supplement to toxicity-grading scales to provide comprehensive documentation about the functioning of the peripheral nervous system and the effects of cancer therapies on activities of daily living and quality of life. Patient-reported symptoms and clinical examinations such as testing for deep tendon reflexes, touch, vibration, and proprioception can assist in determining the tolerability and safety of cancer treatment for at-risk patients.

J Adv Pract Oncol 2010;1:31–38

Recent advances in cancer treatment modalities, including novel agents and dose-intensive treatment schedules, have resulted in increased survival for many patients. However, these advances often include neurotoxic chemotherapeutic agents that can cause significant side effects. Chemotherapy-induced peripheral neuropathy (CIPN) has emerged as a common dose-limiting toxicity of many cancer chemotherapy regimens (Hauscheer, Schilsky, Bain, Berghorn, & Lieberman, 2006; Quastoff & Hartung, 2002). Plant alkaloids, taxanes, platinum-based compounds, thalidomide (Thalomid), lenalidomide (Revlimid), and bortezomib (Velcade) are all associated with the development of CIPN (Verstappen, Heimans, Hoekman, & Postma, 2003; Windebank & Grisold, 2008; Table 1).

The mechanisms associated with the development of CIPN are not fully understood and can vary according to chemotherapy class and agent. The symptoms associated with CIPN also depend on the type of nerve fiber affected. Sensory nerve damage can induce numbness, tingling, painful dysesthesias, sensitivity to cold, diminished or absent touch or deep tendon reflexes, and decreases in vibration and proprioception. Damage to motor neurons can cause muscle weakness and gait disturbances. When

Table 1. Chemotherapy agents associated with chemotherapy-induced peripheral neuropathy

Class/drug	Incidence of PN	Sensory symptoms	Motor symptoms	Autonomic symptoms
Taxanes[a,b,c]				
Paclitaxel	57%–83%	Numbness, tingling, pain of hands and feet. Decreased vibration, proprioception, reduced or absent Achilles tendon reflex, occasional gait disturbances	Weakness of distal muscles with high doses	Rare but transient paralytic ileus[d]; cardiac disturbances[e]; and bladder dysfunction[f]
Docetaxel	11%–64%			
Paclitaxel (albumin)	73%			
Vinca alkaloids[g,h,i]				
Vincristine, vinblastine, and vinorelbine	30%–47%	Numbness, tingling, burning/stabbing pain of hands and feet, reduced or absent Achilles tendon reflex	Weakness of distal muscle groups, decreased deep tendon reflexes, foot drop	Constipation, urinary retention
Platinums[j]				
Cisplatin	28%–100%	Numbness and tingling of hands and feet, painful paresthesia, reduced or absent Achilles tendon reflex, cold-induced dysesthsia (oxaliplatin)	Motor neuron hyperexcitability (with spasms, myotonia, and fasciculations of the limb and jaw muscles occurring during and for hours after drug infusion[k]	Rare but atonic bladder[l]
Carboplatin	6%–42%			
Oxaliplatin	85%–95% (acute) 10%–18% (chronic)			
Immunomodulatory agents[m,n]				
Thalidomide	25%–83%	Numbness and tingling, pain	Occasional gait disturbance, weakness	Occasional constipation
Lenalidomide	10%–23%			
Proteasome inhibitors[o]				
Bortezomib	31%–55%	Burning pain, painful paresthesia	Occasional gait disturbance, weakness	Hypotension

Note: PN = peripheral neuropathy. From [a]Lee & Swain, 2006; [b]Burstein et al., 2000; [c]Gradishar et al., 2005; [d]Wiernik et al., 1987; [e]Rowinsky et al., 1991; [f]Shah-Khan & Shah, 2008; [g]Windebank & Grisold, 2008; [h]Pace et al., 1996; [i]Verstappen et al., 2005; [j]Hauscheer et al., 2006; [k]Wilson et al., 2002; [l]Taieb et al., 2002; [m]Plasmati et al., 2007; [n]Richardson et al., 2006; and [o]Jagannath et al., 2004.

autonomic nerves are affected, orthostatic blood pressure and heart rate alterations, constipation, urinary retention, and sexual dysfunction can result (Stubblefield et al., 2009). These symptoms interfere with quality of life and activities of daily living (Dunlap & Paice, 2006).

The onset of CIPN is generally seen between the first and third cycles of therapy and peaks at 3 months (Dougherty, Cata, Cordella, Burton, & Weng, 2004). This side effect commonly presents as a distal "stocking and glove" distribution, with symptoms beginning in the fingertips and toes and then spreading proximally (Wolf, Barton, Grothey, & Loprinzi, 2008). The development of CIPN is typically dose-related and cumulative (Windebank & Grisold, 2008). With the use of some agents, notably the platinum analogues and taxanes, CIPN symptoms can progress for weeks or months beyond completion of treatment, also known as a "coasting effect" (Quastoff & Hartung, 2002). Reportedly, oxaliplatin has two types of CIPN observed with its use: an acute, cold-induced neuropathy and a more chronic, cumulative neuropathy, which is dose-limiting (Antonacopoulou et al., 2010).

Diagnosis and Treatment of CIPN

Currently, there is no gold-standard clinical- or laboratory-based assessment from which the diagnosis of CIPN can be made, though several grading scales are available (Table 2). Clinical trials that report neurotoxicity as an adverse event often use

Table 2. Grading scales for chemotherapy-induced peripheral neuropathy

Name of tool	Grade 0	1	2	3	4	5
National Cancer Institute, Common Terminology Criteria for Adverse Events[a]						
Peripheral motor neuropathy	None	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	None	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Severe symptoms; limiting self-care ADL	Death
Total Neuropathy Scale[b]						
Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to ankles or wrists	Symptoms extend to knees or elbows	Symptoms above knees or elbows or functionally disabling	
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis	
Autonomic symptoms	0	1	2	3	4 or 5	
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrists/ankles	Reduced up to elbows/knees	Reduced to above elbow/knee	
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrists/ankles	Reduced up to elbows/knees	Reduced to above elbow/knee	
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis	
Deep tendon reflex	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent	
Vibration sensation, % ULN	Normal to 125	126 to 150	151 to 200	201 to 300	>300	
Sural nerve SAP, % LLN	Normal/ reduced to < 5	76 to 95	51 to 75	26 to 50	0 to 25	
Peroneal nerve CMAP, % LLN	Normal/ reduced to < 5	76 to 95	51 to 75	26 to 50	0 to 25	
Eastern Cooperative Oncology Group Common Toxicity Criteria[c]						
Neurosensory	None	Mild paresthesias; loss of deep tendon reflexes	Mild or moderate objective sensory loss; moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	N/A	
Neurovision	None	N/A	N/A	Symptomatic subtotal loss of vision	Blindness	
Neurohearing	None	Asymptomatic, hearing loss on audiometry only	Tinnitus	Hearing loss interfering with function but correctable with hearing aid	Deafness, not correctable	
Neuromotor	None	Subjective weakness; no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis	
Neuroconstipation	None	Mild	Moderate	Severe	Ileus >96 hours	
WHO Toxicity Criteria[d]	None	Paresthesias and/or decreased deep tendon reflexes	Severe paresthesias and/or mild weakness	Intolerable paresthesias and/or motor loss	Paralysis	
Ajani Motor Neuropathy[e]						
Sensory neuropathy	None	Paresthesia and decreased deep tendon reflexes	Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional abnormality	Severe paresthesia, moderate objective, severe functional abnormality	Complete sensory loss, loss of function	
Motor neuropathy	None	Mild transient muscle weakness	Persistent moderate weakness but ambulatory	Unable to ambulate	Complete paralysis	

Note: ADL = activities of daily living; ULN = upper limit of normal; SAP = sensory action potential; LLN = lower limit of normal; CMAP = compound muscle action potential; N/A = not applicable. From [a]National Cancer Institute, 2009; [b]Cavaletti et al., 2003; [c]Oken, et al., 1982; [d]Miller, et al., 1981; [e]Ajani, 1990.

Table 3. Tools to measure patient-reported symptoms of CIPN

Name of tool	Author and year	Domains or factors (# of items)	Scaling	Scoring	Language
Peripheral Neuropathy Scale	Almadrones et al., 2004	Peripheral neuropathy (11)	1–4 (not at all–very much)	11 items are summed for a score of 11–44. Higher scores indicate higher degree of patient-reported peripheral neuropathy.	English
Functional Assessment of Cancer Therapy/ Gynecological Oncology Group-Neurotoxicity (FACT/ GOG-Ntx)	Calhoun et al., 2000, 2003	Physical well-being (7) Social well-being (7) Emotional well-being (6) Functional well-being (7) Additional concerns (related to neuropathy; 11)	0–4 (not at all–very much)	Scoring available at www.facit.org for additional charge.	English; many other language translations of this tool are available
Functional Assessment of Cancer Therapy-Taxane	Cella et al., 2003	Physical well-being (7) Social well-being (7) Emotional well-being (6) Functional well-being (7) Additional concerns (related to neuropathy; 11)	0–4 (not at all–very much)	Scoring available at www.facit.org for additional charge.	English; many other language translations or this tool are available

Note: CIPN = chemotherapy-induce peripheral neuropathy

the National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) as a measurement. Unfortunately, this instrument lacks standardization for administration and interpretation, allowing for wide variations in reports of CIPN across studies. Additionally, comorbid conditions associated with neuropathy, the use of multiple neurotoxic agents, and the treatment of advanced or recurrent cancer in a patient who has already received potentially neurotoxic chemotherapy all contribute to the difficulty of diagnosing and monitoring CIPN.

Despite many studies of pharmacologic agents for the prevention or treatment of CIPN, there are no evidence-based recommendations currently available (Visovsky, Collins, Abbott, Ashenbrenner, & Hart, 2007). Efforts to prevent CIPN must include careful attention to maintaining the efficacy of the chemotherapy so that antitumor activity is not interrupted. However, increasing symptoms of CIPN can lead to chemotherapy dose reduction, delays, or treatment discontinuance, potentially impacting survival. With no gold standard for assessing or monitoring CIPN, available options include clinical neurologic examination, clinical grading scales, neuropathy-specific questionnaires, and laboratory assessments.

Role of the Advanced Oncology Practitioner in CIPN Assessment

Advanced practitioners in oncology are at the forefront of patient symptom assessment and monitoring of chemotherapy-induced neurologic toxicities. As noted previously, not only is there a lack of standardized, evidence-based CIPN assessments, there is no consensus as to when assessment or monitoring of CIPN should take place. Due to the agent-related variable nature of CIPN, it may be best to base assessments upon the recognized patterns of neurotoxicity of the chemotherapeutic agents/regimens received. Therefore, patient-reported symptoms of CIPN, as well as careful physical assessment, are critical in the detection of neurotoxicity. Recently, the National Comprehensive Cancer Network (NCCN) Task Force issued a report on the management of neuropathy in cancer (Stubblefield et al., 2009). Some of the Task Force recommendations will be highlighted in this article.

Assessment of CIPN

Neurophysiologic testing using electromyography, nerve conduction assessment, quantitative sensory testing, and skin biopsy of nerve-fiber

density has been conducted to quantify CIPN. However, these tests have limitations in terms of cost, invasiveness, availability, and inconsistency with patient-reported symptoms. A targeted neurologic history and clinical examination are the cornerstones for detecting and monitoring CIPN.

PATIENT NEUROLOGIC HISTORY

Assessment of CIPN begins with a review of pre-existing peripheral neuropathy. The advanced practitioner should inquire about a personal or family history of diseases or disorders that would predispose patients to peripheral neuropathy, such as diabetes, alcoholism, Charcot-Marie-Tooth disease, paraneoplastic syndromes, human immunodeficiency virus, and vitamin B deficiencies. Previous treatment with neurotoxic agents should be noted, as the baseline clinical examination may reveal neurologic deficits as a result of prior treatment for cancer or other illnesses. In addition, the advanced practitioner must consider other potential causes of neuropathy, such as cancer-related paraneoplastic syndromes. If CIPN is already present, the temporal profile of the chemotherapy agent, dose, treatment duration, characteristics, location, and duration of symptoms should be documented (Stubblefield et al., 2009).

PATIENT-REPORTED NEUROPATHIC SYMPTOMS

Assessment of neuropathic symptoms should 1) begin before the administration of neurotoxic chemotherapy to provide a baseline assessment; 2) continue throughout the course of treatment; 3) persist for several months after treatment concludes (Stubblefield et al., 2009). A number of instruments are available to assess patient-reported symptoms associated with CIPN (Table 3). Tools that assess neuropathic symptoms, including pain and physical functioning, can provide important information concerning the effects of neurotoxicity on daily living, information that can be used in making toxicity-related treatment decisions. These instruments are often available at no or minimal cost and can be easily completed by the individual patient.

If a standardized tool is not used, the advanced practitioner can systematically ask throughout treatment about a patient's weakness, experience of numbness and tingling in the extremities, perception of symptoms as bothersome or worsening, difficulty walking or climbing stairs, and experience of symptoms that interfere with activities of daily living (such as dropping items or falling). Because CIPN can adversely affect physical functioning, it is also important to inquire about the patient's ability to engage in activities of daily living, such as writing, buttoning clothing, or ambulating. In addition, pain is often present in CIPN, making consistent pain assessment a necessity. Pain assessment tools recommended by the NCCN Task Force include the Brief Pain Inventory (Cleeland & Ryan, 1994), the Neuropathic Pain Scale (Galer & Jensen, 1997), and the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (Bennett, 2001).

PHYSICAL ASSESSMENT

To date, correlations between clinical or laboratory findings, physician examination, and patient-reported symptom severity in CIPN have been poor. As noted previously, barriers regarding examination standards and toxicity-grading scales may have influenced these findings. An important consideration in the clinical examination of CIPN is that assessments must be clinically feasible, practical, and reproducible across time (Dunlap & Paice, 2006). Therefore, careful neurologic examination using a standardized procedure is recommended. Because CIPN can cause impairments in deep tendon reflexes, vibration, proprioception, and touch sensation, the addition of objective clinical measures should serve as an adjunct to patient reports of neuropathic symptoms (Shy et al., 2003; Cavaletti et al., 2003). For instance, in a study by Cavaletti et al. (2004), changes in vibration and DTRs were found to be early predictors of CIPN outcomes in combination chemotherapy with cisplatin and paclitaxel.

Deep tendon reflexes. Deep tendon reflexes are involuntary responses elicited by tapping the tendon of a stretched muscle, which generates an impulse that travels in peripheral nerve fibers and results in contraction of the muscle and flexion of the extremity. With CIPN, the loss of the distal (ankle) reflex precedes the loss of the patellar reflex. With the patient sitting or lying, the examiner gently dorsiflexes the foot and uses a reflex hammer to strike the Achilles tendon bilaterally, leading to plantar flexion. If plantar flexion is absent, the use of a reinforcement technique (having patients attempt to separate their fingers) can be done just be-

fore striking the tendon. Reflexes are graded using the National Institute of Neurological Disorders and Stroke (NINDS) Myotatic Reflex Scale (0 = absent; 1 = decreased [trace response]; 2 = normal; 3 = increased; 4 = greatly enhanced/clonus).

Touch. The sensory perception of touch can be clinically measured using a 5.07/10-g Semmes-Weinstein monofilament, which bends when applied with pressure. Use of such monofilaments has been validated in diabetic peripheral neuropathy (Boulton et al., 2005). The examiner performs this assessment by first asking the patient to close his or her eyes. The examiner then applies the filament to four locations bilaterally on the patient's foot (Figure 1) in a 3-second sequence (Mueller, 1996). The patient reports any detection of the monofilament, and the examiner notes if the monofilament was or was not sensed at each tested area. Ulcers, calloused areas, and scars on the foot should be avoided.

Vibratory Sense. Vibratory sense is measured clinically using a 128 Hz tuning fork. The tuning fork is a simple, non-invasive approach that is widely employed in clinical practice for testing vibratory sensation. Vibration perception thresholds are a reliable and validated method of evaluating peripheral neuropathy, and results with this method are highly correlated with nerve-conduction velocity testing (Klima, Weigand, & DeLisa, 1991; Rendell, Katims, Richter & Rowland, 1989). Following standard clinical procedure, the tuning fork is struck on the ulnar border of the palm, causing the tines to vibrate. Evidence suggests that striking the tines with force sufficient to produce a "clanging" sound standardizes the stimulus and the number of seconds the tuning fork vibrates (Oyer, Saxon, & Shah, 2007). The examiner should demonstrate the vibration sensation for the patient using the nail bed before proceeding with the exam.

Testing is performed bilaterally at the bony prominence at the dorsum of the big toe and medial malleolus. The examiner places the vibrating tuning fork at the specified site while placing the index finger of the opposite hand under the toe or alongside the malleolus to determine the accuracy of the patient response (Figure 2). The patient is asked to state when and where the vibration was felt and to indicate when the vibration ceases. To quantify changes in vibration over time, Perkins et al (2001) suggest using a watch to record the number of seconds a vibration is felt by the examiner after the patient can no longer detect it. The number of seconds counted for each big toe is then summed. A difference between perceived and actual vibration that is less than 20 seconds (10 seconds per toe) is considered normal; a difference that lasts longer than 40 seconds (20 seconds per toe) indicates the presence of neuropathy.

Proprioception. Proprioception refers to the sense of the relative position of parts of the body. The proprioceptive sense is believed to be composed of information from sensory neurons located in the inner ear (motion and orientation) and in the stretch receptors located in the muscles and the joint-supporting ligaments (stance). The Romberg test is primarily a test of position sense, and it is useful in determining the loss of motor coordi-

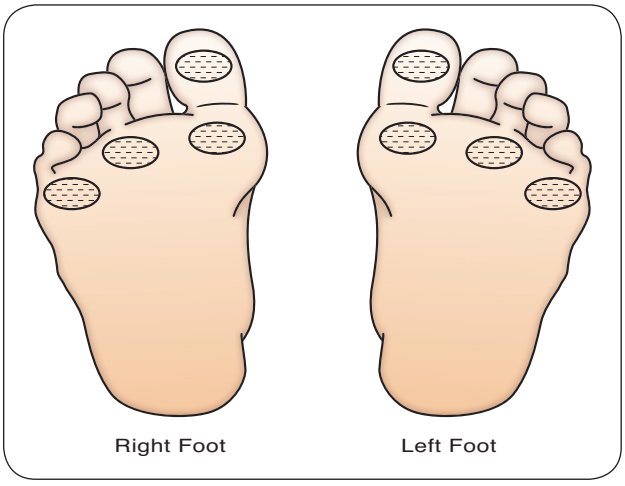

Figure 1. Testing sites on the feet using a monofilament.

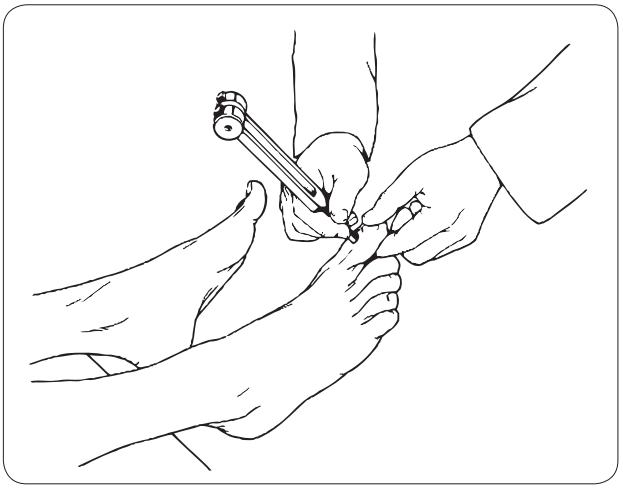

Figure 2. Vibratory sense testing using a tuning fork. Adapted from Walker et al., 1990.

nation (ataxia). To conduct the test, the examiner first instructs the patient to stand with heels together and maintain balance with eyes open. The patient is then asked to maintain balance with eyes closed. (The examiner should be positioned close to the patient as a safety precaution against a loss of balance.) A positive Romberg test, when swaying or an obvious loss of balance is observed when the patient's eyes are closed, suggests that disturbances in motor coordination are sensory, stemming from the loss of proprioception.

Implications for Clinical Assessment

Advanced oncology practitioners are in an ideal position to perform baseline assessments and to monitor patients at risk for CIPN. Until evidence-based assessments are established, the neurotoxicity profile of individual agents in a chemotherapy regimen should serve as a guide for CIPN assessment. As CIPN tends to be dose-related and cumulative, routine assessments should be performed throughout therapy. Baseline and ongoing assessment can assist with 1) determining the severity of symptoms over time; 2) instituting appropriate interventions (i.e., pain control); and 3) determining whether symptoms are severe enough to modify or discontinue treatment. Depending on assessment findings, advanced oncology practitioners should provide necessary referral to rehabilitation services for orthotics, walking aids, or physical therapy. If neuropathic pain control becomes problematic, referral to a pain management service would also be appropriate.

REFERENCES

Ajani, J. A., Welch, S. R., Raber, M. N., Fields, W. S., & Krakoff, I. H. (1990). Comprehensive criteria for assessing therapy-induced toxicity. *Cancer Investigation, 8,* 147–159.

Almadrones, L., McGuire, D., Walczak, J., Florio, C., & Chunqiao, T. (2004). Psychometric evaluation of two scales assessing functional status and peripheral neuropathy associated with chemotherapy for ovarian cancer: A Gynecologic Oncology Group study. *Oncology Nursing Forum*, *31,* 615–623.

Antonacopoulou, A. G., Argyriou, A. A., Scopa, C. D., Kottorou, A., Kominea, A., ... Kalofonos, H. P. (2010). Intergrin beta-3 L33p: A new insight into the pathogenesis of chronic oxaliplatin-induced peripheral neuropathy? *European Journal of Neurology*. Advance online publication. doi:10.1111/j.1468-1331.2010.02966.x

Bennett, M. (2001). The LANSS Pain Scale: The Leeds Assessment of Neuropathic Symptoms and Signs. *Pain, 92*, 147–157.

Boulton, A., Vinik, A. I., Arrezzo, J. C., Bril, V., Feldman, E. L., Freeman, R., ... Ziegler, D. (2005). Diabetic neuropathies: A statement by the American Diabetes Association. *Diabetes Care, 28*, 956–962.

Burstein, H. J., Manola, J., Younger, J., Parker, L. M., Bunnell, C. A., Scheib, R., ... Winer, E. P. (2000). Docetaxel administered on a weekly basis for metastatic breast cancer. *Journal of Clinical Oncology, 18*, 1212–1219.

Calhoun, E. A., Fishman, D. A., Roland, P. Y., Lurain, J. R., Chang, C. H., & Cella, D. (2000). Validity and selective sensitivity of the FACT/GOG-Ntx. *Proceedings of the American Society of Clinical Oncology, 19,* 446a.

Calhoun, E. A., Welshman, E. E., Chang, C. H., Lurain, J. R., Fishman, D. A., Hunt, T., & Cella, D. (2003). Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *International Journal of Gynecological Cancer*, *13,* 741–748.

Cavaletti, G., Bogliun, G., Marzorati, L., Zincone, A., Piatti, M., Colombo, N., ... Zanna C. (2003). Grading of chemotherapy-induced peripheral neurotoxicity using the Total Neuropathy Scale. *Neurology, 61,* 1297–1300.

Cavaletti, G., Bogliun, G., Marzorati, L., Zincone, A., Piatti, M., Colombo, N., ... Zanna, C. (2004). Early predictors of peripheral neurotoxicity in cisplatin and paclitaxel combination chemotherapy. *Annals of Oncology, 15,* 1439–1442.

Cella, D., Peterman, A., Hudgens, S., Webster, K., & Socinski, M. A. (2003). Measuring the side effects of taxane therapy in oncology: The Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane). *Cancer, 98,* 822–831.

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: Global use of the Brief Pain Inventory. *Annals of Academy of Medicine Singapore, 23*, 129–138.

Dunlap, B., & Paice, J. A. (2006). Chemotherapy-induced peripheral neuropathy: A need for standardization in measurement. *Journal of Supportive Oncology, 4*, 398–399.

Dougherty, P. M., Cata, J. P., Cordella, J. V., Burton, A., & Weng, H. R. (2004). Taxol-induced sensory disturbance is characterized by preferential impairment of myelinated fiber function in cancer patients. *Pain, 109*, 132–142.

Galer, B. S., & Jensen, M. P. (1997). Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. *Neurology, 48*, 332–338.

Gradishar, W. J., Tjulandin, S., & Davidson, N., Shaw H., Desai N., Bhar P., ... O'Shaughnessy, J. (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *Journal of Clinical Oncology, 23,* 7794–7803.

Hauscheer, F. H., Schilsky, R. L., Bain, S., Berghorn, E. J., & Lieberman F. (2006). Diagnosis, management and evaluation of chemotherapy-induced peripheral neuropathy. *Seminars in Oncology, 33*, 15-49.

Jagannath, S., Barlogie, B., Berenson, J., Siegel, D., Irwin, D., Richardson, P. G., ... Anderson, K. C. (2004). A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. *British Journal of Haematology*, *127,* 165–172.

Klima R. R., Weigand, A. H., DeLisa, J. A. (1991). Nerve conduction studies and vibration perception thresholds in diabetic and uremic neuropathy. *American Journal of Physical Medicine & Rehabilitation, 70,* 86–90.

Lee, J. J., & Swain, S. M. (2006). Peripheral neuropathy induced by microtubule-stabilizing agents. *Journal of Clinical Oncology, 24*, 1633–1642.

Miller, A. B., Hoogstraten, B., Staquet, M., & Winkler, A. (1981). Reporting results of cancer treatment. *Cancer, 47,* 207–214.

National Cancer Institute. (2009). *Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.* U. S. Department of Health and Human Services: National Cancer Institute: Bethesda.

Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T., & Carbone, P. P. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology, 5,* 49–55.

Oyer, D. S., Saxon, D., & Shah, A. (2007). Quantitative assessment of diabetic peripheral neuropathy with use of the clanging tuning fork test. *Endocrine Practice, 13*, 5–10.

Pace, A., Bove L., Nitisco, C., Ranuzzi, M., Innocenti, P., Pietrangeli, A., ... Jandolo, B. (1996). Vinorelbine neurotoxicity: clinical and neurophysiological findings in 23 patients. *Journal of Neurology Neurosurgery and Psychiatry, 61,* 409–411.

Perkins, B. A., Olaleye, D., Zinman, D., & Bril, V. (2001). Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care, 24*, 250–256.

Plasmati, R., Pastorelli, F., Cavo, M., Petracci, E., Zamagni, E., Tosi, P., ... Tassinari, C. A. (2007). Neuropathy in multiple myeloma treated with thalidomide: A prospective study. *Neurology*, *769,* 573–581.

Quastoff, S., & Hartung, H. P. (2002). Chemotherapy-induced peripheral neuropathy. *Journal of Neurology, 249*, 9–17.

Rendell, M. S., Katims, J. J., Richter, R. & Rowland, F. (1989). A comparison of nerve conduction velocities and current perception thresholds as correlates of clinical severity of diabetic sensory neuropathy. *Journal of Neurology, Neurosurgery, and Psychiatry, 52,* 502–511.

Richardson, P. G., Blood, E., Mitsiades, C. S., Jagannath, S., Zeldenrust, S. R., Alsina, M., ... Anderson, K. C. (2006). A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood, 15*, 3458–3464.

Rowinsky, E. K., McGuire, W. P., Guarnieri, T., Fisherman, J. S., Christian, M. C., & Donehower, R. C. (1991). Cardiac disturbances during the administration of Taxol. *Journal of Clinical Oncology, 9,* 1704–1712.

Shah-Khan, K. & Shah, P. (2008). Loss of bladder sensation following taxane therapy. *Chemotherapy, 54*, 425–426.

Shy, M. E., Frohman, E. M., So, Y. T., Arezzo, J. C., Cornblath, D. R., Giuliani, M. J., ... Weimer, L. H.; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. (2003). *Neurology, 60,* 898–904.

Stubblefield, M. D., Burnstein, H. J., Burton, A. W., Custodio, C. M., Deng, G. E., Ho, M., ...Von Roenn, J. H. (2009). NCCN Task Force report: Management of neuropathy in cancer. *Journal of the National Comprehensive Cancer Network, 7*, S1–S26.

Taieb, S., Trillet-Lenoir, V., Rambaud, L., Descos, L., & Freyer, G. (2002). Lhermitte sign and urinary retention: Atypical presentation of oxaliplatin neurotoxicity in four patients. *Cancer. 94*, 2434–2440.

Verstappen, C., Heimans, J. J., Hoekman, K. & Postma, T. J. (2003). Neurotoxic complications of chemotherapy in patients with cancer. *Drugs, 63,* 1549–1563.

Verstappen, C. C., Koeppen, S., Heimans, J. J., Huijgens, P. C., Scheulen, M. E., Strumberg, D., ...Postma, T. J. (2005). Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. *Neurology. 64,* 1076–1077.

Visovsky, C., Collins, M., Abbott, L., Ashenbrenner, J. & Hart, C. (2007). Putting evidence into practice: Evidenced-based interventions for chemotherapy-induced peripheral neuropathy. *Clinical Journal of Oncology Nursing, 11*, 901–913.

Walker, H. K., Hall, W. D., Hurst, J. W. (1990). Clinical methods: The history, physical and laboratory examinations. Oxford, UK: Butterworth-Heinemann.

Wiernik, P. H., Schwartz E.L., Strauman J. J., Dutcher, J. P., Lipton, R. B., & Paietta E. (1987). Phase I clinical and pharmacokinetic study of Taxol. *Cancer Research, 47,* 2486–2493.

Wilson, R. H., Lehky, T., Thomas, R. R., Quninn, M. G., Floeter, M. K., & Grem, J. L (2002). Acute oxaliplatin-induced peripheral nerve hyperexcitability. *Journal of Clinical Oncology, 20,* 1767–1774.

Windebank, A., & Grisold, W. (2008). Chemotherapy-induced neuropathy. *Journal of the Peripheral Nervous System, 13*, 27–46.

Wolf, S., Barton, B., Grothey, A., & Loprinzi, C. (2008). Chemotherapy-induced peripheral neuropathy: Prevention and treatment strategies. *European Journal of Cancer, 44*, 1507–1515.