Clinical Tests Can Assess Chemotherapy-Induced Neuropathy

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An estimated 1,368,000 new cases of invasive cancer were diagnosed and 563,700 cancer-related deaths occurred in the United States in 2004.## Chemotherapy-based cancer treatment continues to evolve as new agents and more dose-intensive treatment schedules are used, thus increasing survival times of persons in whom the disease is diagnosed. The treatment of most cancers requires use of chemotherapeutic agents to cure, control, or palliate symptoms. While chemotherapy can prolong life, such drugs are associated with significant side effects, and certain chemotherapeutic drugs are associated with peripheral neuropathy.##

Peripheral neuropathy results from impairment of peripheral, motor, sensory, and autonomic neurons that causes motor and sensory deficits. Motor neuron involvement results in lower extremity muscle wasting accompanied by weakness. It begins in the distal lower extremities and spreads in a proximal fashion. Sensory neuron dysfunction produces the classic "stocking and glove" distribution of loss of touch sensation in the extremities. In early studies, it was hypothesized that neurotoxic chemicals caused axons to die back from nerve terminals by interfering with neuronal soma metabolism. More recently, it has been hypothesized that neurotoxic chemicals directly damage nerve fibers by deactivating components required to maintain the metabolic needs of the axon. The longer and larger distal axons are affected first, and the result is interruptions of axonal transport and degeneration of myelinated nerve fibers and unmyelinated axons.

Symptoms such as numbness, tingling, and/or pain in the extremities, as well as declines in cutaneous sensation, vibration sensation, and muscle strength, are experienced. Treatment-associated changes in muscles also result in a reduced ability of the muscle to generate force, causing muscle weakness and a decline in functional performance. Autonomic dysfunction is caused by damage to unmyelinated nerve fibers that occurs secondary to neurotoxic chemotherapy. Clinical manifestations of autonomic neuropathy include hypotension, cardiac conduction irregularities, impotence, and bowel and bladder dysfunction. Postural hypotension is the most common cardiovascular manifestation of peripheral neuropathy.

**IMPLICATED AGENTS**

Platinum-based compounds such as cisplatin are known to induce peripheral neuropathy. These heavy metals bind to DNA and possibly act as precursors to axonal degeneration. Cisplatin therapy is associated with ototoxicity, retinal toxicity, and sensory neuropathy. Large-fiber nerves are primarily affected. Vinca alkaloids, such as vincristine and vinblastine, induce paresthesias of the hands and feet in approximately 57% of patients, and weakness, footdrop, and gait disturbances in 23% to 36%.

Antimitotics, such as paclitaxel and docetaxel, are associated with a decrease in or loss of deep tendon reflexes (DTRs). Docetaxel is a semisynthetic taxane that induces sensory neuropathy in 50% of treated patients. Sensory loss can be distinguished even after the first dose is administered. Many chemotherapeutic regimens require the administration of 2 neurotoxic agents, resulting in higher grades of neurotoxicity.

A variety of toxicity grading scales have been used to detect and monitor chemotherapy-induced peripheral neuropathy (CIPN). The 2 most commonly used CIPN grading scales are the Eastern Cooperative Oncology Group (ECOG) scale and the World Health Organization (WHO) scale. The ECOG scale contains a motor component (to assess DTRs), a sensory component (to assess paresthesias), and an autonomic component (to assess such symptoms as constipation). However, this scale is limited by the use of a single item as the determinant of the presence or absence of neuropathy. In addition, this scale contains undefined terms such as "mild weakness" and "disabling
sensory loss,” which encourages subjective and inconsistent interpretation by the examiner. The WHO scale rates peripheral neuropathy from grade 0 (none) to grade 4 (paralysis). This scale follows the progression of paresthesia (sensory function) and motor function (weakness), but DTRs are not assessed beyond grade 1. Like the ECOG scale, the WHO scale has similar undefined terms such as “marked motor loss” that could lead to inconsistent grading of neuropathy. Neither scale is able to determine the impact that neurologic changes may have on the patient.

DETECTING CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

A decided lack of consensus exists concerning the grading of neuropathy because guidelines for the standard use of toxicity grading scales have not been developed. This lack of consensus makes it difficult to compare neurotoxicity results across studies. Therefore, I conducted a pilot study using an exploratory design to characterize patterns of change in peripheral nerve function over time in 16 persons undergoing treatment with neurotoxic chemotherapy (carboplatin/paclitaxel) or biotherapy (interferon alpha-2b).17

The mean age of study participants was 59 years (range, 28 to 79) and consisted of 8 women and 8 men. All were white. Seven (44%) of the participants were being treated for malignant melanoma, 4 (25%) for ovarian cancer, and 5 (31%) for nonsmall-cell lung cancer. Persons with any illnesses that were associated with peripheral neuropathy (eg, diabetes, HIV infection, alcoholism) were excluded from study participation.

Measures of peripheral nerve function were obtained before the start of treatment and at 4, 8, and 12 weeks. These included results of tests of hearing, vision, touch, vibratory sensation, DTRs, gait and balance, and muscle strength.

Hearing was measured by the Rinne clinical test of air and bone conduction using a calibrated 250-Hz tuning fork. The tines of the tuning fork were struck and placed against the right and left mastoid processes to verify bone conduction. The tuning fork was then placed with the tines forward toward the front of the ear to verify air conduction.

Visual acuity for each eye was tested using a handheld Snellen chart. Analysis was based on the denominator, with the numerator (20) held constant. Higher values signify worsening visual acuity. Touch was measured using the Semmes-Weinstein monofilaments. These calibrated nylon filaments of varying size bend when a specified amount of pressure is applied. With the participant’s eyes closed, the finest filament was applied perpendicularly in a random manner to specified locations on each hand (6 locations) and foot (4 locations) in a 3-second sequence.

Vibratory sensation was tested using a 128-Hz tuning fork that was struck and applied bilaterally to lateral knee and ankle sites. DTRs were measured at the knee and ankle using the standardized clinical procedure and 1 Babinski reflex hammer. Reflexes were graded using the National Institute of Neurological Disorders and Stroke Myotatic Reflex Scale (0 = reflex absent; 1 = reflex small, less than normal, a trace response; 2 = reflex in lower half of normal range; 3 = reflex in upper half of normal range; 4= reflex enhanced, more than normal).

Gait and balance were assessed using the Tinetti Performance-Oriented Assessment of Balance and Gait instrument. This mobility assessment requires an individual to perform maneuvers that rely on stability. Gait items were scored 0 to 1. A score of 0 indicated an inability to walk or a need for assistance in walking. Balance was scored on a 0-to-2 scale. A score of 0 (abnormal) for balance indicated that the participant was unable to compensate for the degree of peripheral neuropathy. A score of 1 indicated that the person performed the task with adaptation. A score of 2 represented normal balance.

Muscle strength was measured using a handheld dynamometer. The device was placed above the knees and above the anterior and posterior aspects of the ankles as the patient moved through his or her range of motion in a weight-bearing position. A reading in kilograms was then recorded. All measures are feasible, noninvasive, and widely used in the clinical setting.

RESULTS

Data were analyzed using descriptive statistics, and individual regression slopes were calculated as change scores of peripheral nerve function over time. Pearson correlation coefficients were used to determine the relationship between muscle strength measures of dynamometry and manual muscle strength testing results.

The Table displays actual scores for each measure. Changes occurred in several measures over time, although the magnitude of change was relatively small and was not statistically significant. Results were consistent between the interferon-alpha and carboplatin/paclitaxel groups.

Mean visual acuity scores declined by 8% from baseline after 12 weeks of therapy. No changes occurred in hearing-related bone conduction as measured by the Rinne test. It is possible that the Rinne test was not sensitive enough to capture declines in hearing during the relatively short study.
period. Lower extremity DTR scores declined only 6% from baseline measures—a change that was not clinically significant.

In tests of vibratory sensation, all participants received a normal score of 7.9 at baseline. However, the ability to sense vibration declined 10% over the 12-week study period. While this decline appears small, it is important to note that this finding supports previous studies of vibratory sensation declines using regimens containing cisplatin or paclitaxel and is congruent with case study evidence supporting a decline in vibration sensation with administration of interferon alpha-2b.\textsuperscript{18,19}

Cutaneous sensation remained relatively stable during the study period, declining only 3% from baseline measures in the hands and feet. All participants scored at the highest level for gait and balance at baseline, indicating no disturbance in either gait or balance before treatment. No observable change remained in gait from baseline to 12 weeks of therapy. Balance declined 18% from baseline measures over the study period, which is clinically significant as a risk factor for falls. The mean summed dynamometry muscle strength score for the lower extremities was 40 kg at baseline, which declined to 36 kg by week 12, indicating that a steady decline in muscle strength was associated with the administration of cytotoxic agents.

**IMPLICATIONS FOR PRACTICE**

This was the first prospective study to measure peripheral nerve and muscle changes resulting from combination chemotherapy or a biotherapy regimen in a comprehensive manner using only clinical measures that can easily be applied in almost any setting. Alterations in vision, hearing, DTRs, vibration sensation, cutaneous sensation, balance, and muscle strength were noted as treatment progressed. Gait remained unchanged.

A comprehensive assessment of peripheral neuropathy is feasible and can easily be performed in the clinical environment. A general trend of decline in peripheral nerve function with cumulative drug dosing was observed throughout the study period. The decline may not be detected using current clinical practice methods, which vary in the assessment and grading of peripheral neuropathy. Methodologic issues associated with the use of clinical measures need to be addressed to incorporate a comprehensive neuropathy assessment into clinical practice. For example, the Rinne test for hearing failed to capture changes, suggesting a need for further testing and refinement of clinical hearing testing measures. Portable audiometry may provide a more accurate assessment of hearing decline that cannot be captured by standard tuning fork hearing assessments. Also, an inherent intrasubject variability is present in clinical measures, such as DTR assessment, when performed repeatedly over time, because such measures require subjective interpretation of observed phenomena. Standardization of clinical assessment procedures to enhance accuracy will be essential in ensuring greater precision in these clinical measurements.

Although this study provides evidence to support the need for careful, ongoing assessment of treatment-induced peripheral neuropathy, a great deal more work is needed to fully describe the incidence and pattern of neuropathy. Specifically, clinical practice procedures need to be developed that address how often patients should be evaluated for signs and symptoms of peripheral neuropathy while undergoing cancer treatment and how long they should be periodically evaluated after treatment is completed.

A need still exists to determine the amount of sensory or motor nerve changes that is significant enough to warrant a reduction in drug dose and/or signal a need for a rehabilitation evaluation by a physical or occupational therapist. Although dose reductions are prudent in the event of severe neuropathy, the effect on cell kill and drug efficacy in eradicating or controlling disease remains a concern.

Newer agents that are intended to be less neurotoxic and have fewer side effects are being developed. Until then, clinicians need to educate their patients about the functional changes they may experience as a result of neurotoxic chemotherapy, and they need to assist patients in developing strategies to manage limitations resulting from peripheral neuropathy.\textsuperscript{*}

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**REFERENCES**


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