Peripheral nerve function and symptom distress during biotherapy for malignant melanoma

By Constance G. Visovsky

Abstract

Studies of biotherapy-induced physiological changes are few, and systematic monitoring for neurotoxic effects are lacking. The purpose of this exploratory pilot study was to determine the change in peripheral nerve function and symptom distress during treatment with biotherapy for malignant melanoma. A convenience sample of 11 participants with malignant melanoma receiving interferon-alpha had measures of peripheral nerve function measured at baseline, four and 12 weeks of treatment. Data were analyzed using plots and regression slopes to determine change over time in sensation, gait/balance, vision, hearing, vibratory sense, muscle strength, deep tendon reflexes, blood pressure, and symptom distress. Declines in hearing, sensation, vibration, and muscle strength were found. Changes in visual acuity, and orthostatic blood pressure were noted, while gait/balance remained stable. Additionally, neuropathy symptoms were associated with symptom distress. The characterization of such changes can increase our understanding of the nature of the physiological effects associated with high-dose biotherapy treatment and aid clinicians to better prepare patients for anticipated changes in function and subsequent lifestyle adjustments. These findings can be used to provide information in a larger study of this phenomenon regarding important outcomes and measurement time-points of therapy-induced neuropathy and decreasing symptom distress in patients receiving cancer treatment with biologic agents.

Key words: peripheral neuropathy, biotherapy, clinical, measurement

Introduction

Each year, it is estimated that about 54,000 new cases of malignant melanoma will be diagnosed and more than 7,000 deaths will occur from the disease (American Cancer Society, 2003). The National Cancer Institute of Canada estimates that 2004 will see 4,200 new cases of melanoma resulting in 810 deaths (Canadian Cancer Statistics, 2004). The treatment of malignant melanoma often includes the use of biologic agents, particularly interferon alpha-2b. But while these agents can prolong life, they also have significant side effects. Increasing clinical evidence suggests that the treatment of cancer with biologic agents results in some degree of peripheral neuropathy (Irwin, 1987; Smith et al., 1991; Vial & Descotes, 1994; Merriggioli & Brown, 2000). Peripheral neuropathy is an impairment of peripheral, motor, sensory and autonomic

neurons that can predispose the individual to injury. Motor neuron deficits result in lower extremity muscle wasting and weakness. Damage to sensory neurons result in the classic "stocking and glove" sensory losses in the hands and feet. Clinical manifestations of peripheral neuropathy include a loss of touch sensation, impaired temperature perception, weakness, pain, numbness and tingling. Physical examination findings include a reduction or loss of deep tendon reflexes and diminished vibratory sensation. Associated damage to cranial nerves results in decreased hearing and visual perception (Visovsky, 2003).

Biologic agents such as interferon alpha have been associated with a predominantly sensory axonal neuropathy that appears weeks following the initiation of therapy and persists for months despite the cessation of treatment (Fatovich et al., 1996; Gastineau, Habermann, & Hermann, 1989; Manesis, Petrou, Brouzas et al., 1994; Quattrini, Comi, Nemni, Martinelli, Villa, Caimi, et al., 1997). Neuropathy related to the administration of interferon-alpha is known to be dose-related and cumulative (Armstrong, Rust, & Kohtz, 1997; Berger et al., 1997; Meyers, Scheibel, & Forman, 1991; Gastineau & Habermann, 1989; Gotaskie & Andreassi, 1994; Wilkes, 1996).

Most of the data on therapy-induced neuropathy have come from case studies, which are limited by the indirect, retrospective nature of the supporting data, and by lack of association of neuropathy with measurable differences in physiologic markers. Individuals receiving biologic agents for malignant melanoma have not been systematically monitored for long-term effects and associated symptom distress, even though peripheral neuropathy brings changes in function for which the individual and family are ill-prepared. This exploratory pilot study therefore examined peripheral nerve function over time in individuals undergoing treatment with biotherapy for malignant melanoma. Specifically, the study examined patterns of change in peripheral nerve function (vision, hearing, vibration, deep tendon reflexes, cutaneous sensation, gait, balance, muscle strength, orthostatic blood pressure) and looked at the relationships between peripheral neuropathy symptoms experienced and symptom distress over 12 weeks of treatment.

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Methods

Data were collected prior to the beginning of therapy (baseline), and at four and 12 weeks of treatment. Baseline measures were designed to identify pre-existing declines in peripheral nerve function unrelated to the course of chemotherapy. The four-week data collection point was chosen to coincide with the end of one month of high-dose induction therapy with the remaining 12-week measurement points to assess peripheral nerve functioning at standard lower doses.

Setting

This exploratory pilot study was conducted at a National Cancer Institute-designated cancer centre and a community-based ambulatory cancer centre located in the Midwestern United States. The sample consisted of 11 adults diagnosed with histologically confirmed malignant melanoma who were scheduled to receive interferon-alpha-2b as part of their treatment plan. The participants were all chemotherapy and biotherapy naïve and without any disease or disorder reducing peripheral nerve function. The sample consisted of seven women (63.6%) and four men (36.4%) with an average age of 53 years (SD = 18.9) with a range of 28 to 74 years. All study participants were Caucasian. One participant (9.1%) was diagnosed with Stage I disease, four (36.4%) participants had Stage II disease, four participants (36.4%) had Stage III disease and two (18.2%) participants were diagnosed with Stage IV disease. Five study participants underwent excision alone for their melanoma, while six participants had excision and lymph node dissection.

Measurement of variables and procedures

Following Institutional Review Board (IRB) approval, clinical nurses from the two sites referred subjects meeting eligibility criteria to the investigator who contacted subjects at the outpatient clinics regarding study participation. Following informed consent, each subject had all measures of peripheral nervous system function measured a total of three times: at baseline (prior to treatment with interferon alpha-2b), and at four and 12 weeks of treatment. Demographic data were collected once, at study enrolment. Clinical measures of peripheral nerve function were obtained, including visual acuity, hearing acuity, cutaneous sensation, vibratory sensation, reflexes, blood pressure, muscle strength and gait and balance. Symptom distress was measured using the Symptom Experience Index (Rhodes & McDaniel, 2000) that was adapted for this study to include 14 items reflecting symptoms associated with peripheral neuropathy. The instruments and scoring used in the study are outlined in Table One and briefly summarized below.

Vision. Visual acuity for each eye was tested using a hand-held Snellen chart. Higher values equate with worsening visual acuity. The Snellen letter chart provides a sensitive and reliable measure of changes in uncorrected vision (Bradley, Hook, & Haeseker, 1991). The results of each near vision screening were recorded as a fraction for each eye, with the denominator used as the score since the numerator of 20 is constant.

Hearing. Hearing was measured by the Rinne and Weber clinical hearing tests 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 being tested to verify air conduction. In this study, for the Rinne test of air conduction, each ear was tested separately. The Rinne test has a documented sensitivity of 0.84 regardless of hearing loss type or severity (Milteneburg, 1994). For the Weber test, the base of a vibrating tuning fork was applied to the top of the head at midline. A score of zero was given if the sound was heard only in one ear (laterally), an abnormal finding and a one if it could be perceived in both ears (centrally) a normal finding. A study using the Weber test found that it was sensitive in detecting the perception of normal and abnormal patterns of hearing-related bone conduction of sound (Haapaniemi, Suonpaa, Salmivalli, & Virolainen, 1996).

Cutaneous sensation. Touch was measured using the Semmes-Weinstein monofilaments. These calibrated nylon filaments bend when a specified amount of pressure is applied. With the participant's eyes closed, the filament is applied to specified locations on each hand (six locations) and foot (four locations) in a three-second sequence. A score is given when the corresponding monofilament is sensed, with higher scores indicating a lessened ability to sense touch. Using this standardized method, a 95% confidence interval has been reported for reliability (Birke & Sims, 1985).

Vibratory sensation. Vibration was tested using a 128-Hz tuning fork that was struck and applied to the right and left lateral knee and ankle sites and measured according to widely used clinical procedures. Since vibratory deficits are among the earliest manifestations of axonal neuropathies, screening for deficits allows for early detection. Vibration perception thresholds have been demonstrated to be a reliable and valid method of evaluating peripheral neuropathy, and results are highly correlated with nerve conduction velocity testing (Klima, Weigand, & DeLisa, 1991; Rendell, Katims, & Richter, 1989).

Deep tendon reflexes. Deep tendon reflexes (DTRs) were measured at the knee and ankle using a standardized clinical procedure and one Babinski reflex hammer. Reflexes were graded using the National Institute of Neurological Disorders and Stroke (NINDS) Myotatic Reflex Scale, which ranges from one to four. Each reflex was scored separately and the ordinal scores summed over the four sites tested. This total score could range between 0 (areflexia) and 16 (hyperreflexia).

Orthostatic blood pressure. Peripheral nervous system damage interferes with signaling of position-related blood pressure changes, resulting in a delayed or lessened sympathetic nervous system response to changes in position. Indirect blood pressure (BP) measurement is a well-established clinical measure of arterial pressure, which is stable with changes in body position, unless underlying pathology exists (Quaal, 1997). Blood pressure measures were taken using one Medwave Vasotrac® (Medwave, Inc., St. Paul, MN) automated, calibrated blood pressure device. Measurements were done in lying, sitting and standing positions. The Vasotrac® has a non-invasive sensor that is placed over the radial artery using a Velcro strap and information is then measured from the radial pulse. Systolic, diastolic and mean arterial pressure readings are recorded in mmHg. Vasotrac® BP readings have a mean correlation of 0.97 to an arterial line, providing the accuracy necessary to detect changes (Belani, Ozaki, Hynson, Hartmann, Reyford, Martino, et al., 1999). Orthostatic blood pressure change between lying and standing positions was measured on a continuous scale of mmHg.

Muscle strength. Muscle strength of the knee and hip flexors and extensors was measured using a hand-held dynamometer. The dynamometer is placed above the knee and ankle as the patient moves

through range of motion while in a weight-bearing position. A reading is then recorded. In previous studies, the validity of the dynamometer was established against other tasks requiring the same amount of force. Hand-held dynamometry intratester correlation coefficients ranged from 0.82 to 0.96 for subjects with pre-existing neuropathies and control subjects (Bohannon & Andrews, 1987). In this study, intratester reliability for the dynamometer ranged from .88 to .90.

Gait and balance. Gait was assessed using the gait portion of the Tinetti Performance-Oriented Assessment of Balance and Gait instrument (Tinetti, 1986). This 17-item assessment for mobility requires the person to perform manoeuvres reliant on stability. Gait was observed from three aspects: walking away from and toward the researcher, and in a perpendicular plane. Gait items were scored zero to one, with

Table One: Summary of instruments and scoring

Variable and Measure	Procedure	Range of Scores
Vision Hand-Held Snellen Chart	The participant read the chart from a distance of 14 inches, covering the opposite eye.	20/20 – 20/800
Hearing Weber Test Rinne Test The base of a vibrating tuning fork was applied to the top of the head at midline.	The base of a vibrating tuning fork was applied to the mastoid process (bone conduction) until it could no longer be heard. The tuning fork was then placed forward toward the ear being tested (air conduction). 0 if sound heard laterally (abnormal) 1 if sound heard centrally (normal)	0 = sound not perceived 1 = sound perceived.
Cutaneous Sensation Semmes Weinstein Monofilaments	Calibrated nylon filaments of varying thickness were applied to specified sites on the hands and feet.	Hands were scored from one (finest filament) to five (thickest filament) for each of the six hand sites tested. Feet were scored from one (finest filament) to three (thickest filament) for each of the four foot sites tested. Scores were summed over the 20 tested sites ranging from 20 (most discriminating feeling) to 96 (least discriminating feeling).
Vibration 128-Hz tuning fork	The tuning fork was struck and placed over the lateral knee and ankle sites of both lower extremities.	Vibration was scored as 0 = unable to sense vibration start or stop or 1 = able to sense vibration start or stop.
Deep Tendon Reflexes Babinski Reflex Hammer	Reflexes were elicited by tapping the tendon of a stretched muscle using standard clinical procedures.	0 = reflex absent 1 = reflex trace, less than normal 2 = reflex in lower half of normal range 3 = reflex in upper half of normal range 4 = reflex enhanced
Orthostatic Blood Pressure Medwave Vasotrac®	A sensor is placed over the radial artery and secured with a Velcro strap. Systolic, diastolic and mean arterial pressure were calculated.	Blood pressure was measured in mm Hg.
Muscle Strength Hand-held Dynamometer	The dynamometer is placed on the bilateral knee and ankle sites as the patient moves through ROM in a weight-bearing position, and a reading is then recorded.	Measures peak force in kg.
Gait Tinetti Performance-Oriented Assessment of Balance and Gait instrument (Tinetti, 1986).	Gait was observed and recorded from three aspects: walking away from and toward the researcher, and in a perpendicular plane.	0 (abnormal gait) 1 (normal gait)
Balance Tinetti Performance-Oriented Assessment of Balance and Gait instrument (Tinetti, 1986).	Balance maneuvers performed included: sitting balance, arising from chair, immediate standing balance, neck turning, reaching up, bending down, and sitting down.	0 = abnormal balance 1 = compensatory balance 3 = normal balance
Symptom Distress Symptom Experience Index (SEI) (Rhodes & McDaniel et al, 2000).	The SEI is a 48-item self-report Likert-type ordinal scale that assesses 15 symptoms: nausea, vomiting, pain, anorexia, sleep, fatigue, bowel elimination, breathing, coughing, concentration, body image, lacrimation, body temperature, neuropathy and restlessness.	This instrument was scored from zero (no occurrence) to four (greatest occurrence) and provides measures of the total symptom experience, symptom occurrence and symptom distress.

a score of zero considered abnormal, indicating the subject is unable to walk, or requires assistance in walking. Normal gait was scored as one. Gait items included initiation of gait, step height, step length, step symmetry, step continuity, path deviation, trunk stability, walk, stance, and turning while walking. Individual items were summed to obtain the gait score, which ranged from zero to nine, with nine equaling normal gait.

Dynamic balance was assessed using the balance portion of the Tinetti instrument (Tinetti, 1986). Items addressed included sitting balance, arising from a chair, immediate standing balance, neck turning, reaching up, bending down, and sitting down. Balance was scored zero to two. A score of zero was considered abnormal, indicating that the person was unable to compensate for the loss of balance function. A score of one indicated that the person has a normal response with assistance, but was able to use compensatory means of maintaining balance. A score of two for each item represented normal balance. The ratings were summed for a total score, ranging from zero to 16, with lower scores indicating less postural stability. Interrater and test-retest reliability are > 0.95 (Spellbring & Ryan, 1997). Clinical indications of gait and balance disturbances are particularly important to assess because these disturbances in gait and balance may be amenable to interventions aimed at improving functional health.

Symptom Distress. Symptom distress was measured using the newly revised Symptom Experience Index (SEI) which was expanded from the original 34 items to 48 items (Rhodes, McDaniel, Homan, Johnson, & Madsen, 2000). The original SEI is a self-report Likert-type ordinal scale that assesses 15 symptoms: nausea, vomiting, pain, anorexia, sleep, fatigue, bowel elimination, breathing, coughing, concentration, body image, lacrimation, body temperature, and restlessness. The items are categorized into six symptom experience subscales (respiratory, pain/discomfort,

Table Two: Patterns over time for peripheral nerve function.

fatigue/restlessness, gastrointestinal, concentration and appearance) and are scored from zero (no occurrence) to four (greatest occurrence). This instrument provides measures of the total symptom experience, symptom occurrence and symptom distress. Cronbach's alpha was .91 for the total symptom experience, .76 for the total distress, and .90 for total symptom occurrence. Reliability of the subscales ranged from .64 to .84 (concentration) with the exception of appearance at .38. Test-retest scores were strongly correlated ($r = .92$). Validity of the instrument was supported by the Kruskal-Wallis test and by content validity by including symptoms identified by patients. The original instrument was revised in collaboration with Drs. Rhodes and McDaniel, the instrument authors, to include 14 items reflecting symptoms associated with peripheral neuropathy such as burning, numbness, and tingling. For this study, the Cronbach's alpha scores for the peripheral neuropathy subscale were 0.66 at baseline, 0.62 at four weeks and 0.79 at 12 weeks. The reliability of scores increases as the severity and frequency of symptoms increases.

Results

Patterns of change

Changes in peripheral nerve function are presented in a head-to-toe approach to assessment of the outcome variables. Graphic representation of patterns of changes in peripheral nerve function can be seen in Table Two. The mean visual acuity score was 20/86 at baseline and decreased to 20/57 by four weeks and to 20/39 by 12 weeks of therapy. There were no detectable changes in hearing-related air and bone conduction of sound using the Rinne test. However, the Weber test detected alterations in bone sound conduction. At baseline, 82% of the participants were able to hear sound conducted centrally, a normal hearing pattern. By four weeks of therapy, only 54% of the participants reported hearing sound conducted centrally, and this figure remained stable at the 12-week data collection point.

The cutaneous sensation mean score for the hands and feet was 27 at baseline, slightly above the score considered most discriminating, but still normal. The mean score increased to 30 by four weeks and to 32.5 by 12 weeks of treatment, indicating a 6% decline in touch sensation. The mean score for vibratory sensation measures at the bilateral knee and ankle sites was 7.6 at baseline; this remained stable at four weeks, but declined to 6.8 by week 12, representing a 10% change from baseline. The mean score for lower extremity deep tendon reflexes was 5.7 at baseline, this declined to 4.6 (19%) by week four, but returned to 5.5 by week 12 for an overall decline of 4% in reflex response.

Table Three: Correlations between peripheral neuropathy symptoms and symptom distress

Symptom Distress	Four Weeks	12 Weeks
Total peripheral neuropathy symptoms	0.76	0.76
Changes in body temperature	0.88	No correlation
Pain, numbness, tingling of extremities	0.91	0.88
GI disturbances	0.71	No correlation
Hearing acuity	-0.67	No correlation
Orthostatic blood pressure changes	0.73	No correlation

The mean orthostatic change score from lying to standing position was 6.2 mm Hg at baseline; this figure increased to 13.4 mm Hg by week four, before declining to below baseline, at 3.1, by week 12. The mean score for gait at baseline was nine, the highest possible score. This score remained stable throughout the study period. The mean score for the balance was 15.5 at baseline, declining to 14.3 by week four and remaining stable at 12 weeks of treatment. The mean score for lower extremity muscle strength was 41.2 at baseline, declining to 39.5 by week four and declining further to 37.1 by 12 weeks of treatment.

The Symptom Experience Index revealed that self-reported symptoms of neuropathy were correlated with symptom distress both at four and 12 weeks of treatment (Table Three). Self-reported changes in body temperature, such as feeling cold, were correlated with symptom distress at four weeks of treatment. Self-reported classic neuropathy symptoms (pain, numbness, and tingling in the extremities) were correlated with symptom distress at four and 12 weeks; clearly as changes occurred in the extremities, symptom distress increased. Gastrointestinal disturbances, specifically constipation, were correlated with symptom distress at four weeks, but had resolved by 12 weeks. Self-reported alterations in hearing were negatively correlated with symptom distress at four weeks, but not at 12 weeks. The orthostatic changes in blood pressure observed at four weeks appeared to cause distress, but this had resolved by 12 weeks of therapy. Self-reported disturbances in gait were negatively correlated with symptom distress at 12 weeks only. Table Four summarizes the changes in peripheral nerve function over the 12-week study period.

Discussion

This is the first known study to comprehensively examine the neurotoxic effects of a biotherapy regimen for malignant melanoma. Many of the physiologic parameters examined in

Table Four: Changes in peripheral nerve function

Measures	Baseline X (SD)	Four Weeks X (SD)	12 Weeks X (SD)
Visual acuity	20/86 (76)	20/56 (59)	20/39 (16)
Hearing			
Rinne test	3.8 (.40)	3.5 (.52)	3.7 (.75)
Weber heard centrally	9 (82 %)	6 (54.5 %)	6 (54.5 %)
Weber heard laterally	2 (18 %)	5 (45.5 %)	5 (45.5 %)
Cutaneous sensation	27 (8.4)	30 (8.7)	32 (10.4)
Vibration	7.6 (1.2)	7.6 (.70)	6.8 (1.6)
Lower extremity deep tendon reflexes	5.8 (2.2)	4.7 (2.5)	5.4 (2.8)
Orthostatic BP	6.2 (13.5)	13.4 (13.0)	3.1 (8.6)
Muscle strength	41.2 (9.0)	39.5 (9.1)	37.1 (6.4)
Gait	9.0	9.0	8.8
Balance	15.5	14.3	14.7
Symptom distress	4.2	9.7	9.1

this study are not part of the routine toxicity assessment done by oncology nurses, but have implications for translation into clinical practice. Oncology nurses using clinical measures such as deep tendon reflexes, hearing or vision testing for assessment of toxicity must be skilled in the conduct and interpretation of these measures for accuracy of results. In using clinical measures for research, issues of measurement need to be taken into consideration. There is a need for more accurate means of assessing vision and hearing in the clinical setting. For example, this study used a hand-held vision card as a more practical means of assessing visual acuity in a busy oncology practice. However, using this approach, the chance of measurement error increases since the person can manipulate the distance from which the card is held, moving it closer to the visual field than recommended for testing, making results inaccurate. In this study, visual acuity appeared to improve, a finding that is contrary to published case reports of the effect of interferon alpha on vision. Likewise, tuning fork tests of hearing-related air and bone conduction appear to be limited in their ability to detect declines in hearing. The results of the Weber test performed in this study suggest that hearing is affected by interferon alpha during the dose-intensive phase of treatment while the Rinne test showed no change from baseline in hearing-related air and bone conduction. For the clinical assessment of interferon-alpha hearing-related toxicity, it appears that the Weber test would provide more accurate assessment of hearing, and is a very feasible test to perform at the bedside. However, using a stopwatch to record the length of time sound is heard and using a range of tuning forks, especially those with higher range frequencies, may improve the sensitivity of the Rinne test in the clinical setting.

Findings from this study suggest that there are dose-related declines in cutaneous sensation, vibration, and muscle strength that occur in conjunction with high-dose interferon-alpha regimens. Due to the pilot nature of this study and the relatively short follow-up time, it is not clear whether these declines persist, worsen or resolve over the typical one-year interferon-alpha treatment regimen. Deep tendon reflexes (DRY) in the lower extremities were unchanged throughout the study period. The interpretation of DTR is highly subjective, and presents difficulties for accurate interpretation, even by skilled nurse clinicians.

Alterations in positional blood pressure were noted during the first four weeks of treatment that may predispose the individual to injury from falls during this period. The alterations in positional blood pressure may be the result of autonomic cardiovascular mechanisms affecting sympathetic control of blood pressure. These findings support the need for oncology nurses to monitor orthostatic blood pressure parameters throughout the first month of therapy. It is possible that during the first few weeks of treatment, patients may experience symptoms such as nausea, vomiting, decreases in appetite and fluid intake that contribute to fluid volume depletion and make patients more vulnerable to orthostatic changes in blood pressure. Routine nursing assessment of weight, intake and output, skin turgor and mucous membranes would provide information related to the fluid volume status of patients during this critical time. Following the first month of treatment, the factors contributing to volume depletion are likely to have been addressed by clinicians. Patients with symptoms of lightheadedness or dizziness should be instructed by oncology nurses to use behavioural adaptations, such as rising slowly to allow for physiologic adjustment of blood pressure, especially during the dose-intensive phase of treatment. Subjective

reports of symptoms associated with orthostatic changes are not part of routine monitoring in this population, and there is a need for additional research to better understand this phenomenon.

Gait and balance scores using the Tinetti Performance-Oriented Assessment of Balance and Gait instrument (Tinetti, 1986) were largely unchanged during the study period. Each study participant scored at the highest level (nine) of the instrument at baseline, reflecting the relatively high performance status of individuals normally considered for outpatient cancer treatment. While no change in gait scores was detected, the study period may not have been long enough to capture the effects of neurotoxic therapy on parameters of gait. Other studies that included gait as a variable relied on investigator evaluation of observed walking ability and assessment of Romberg's sign, or patient-reported gait difficulties (Postma, Hoekman, van Riel, Heimans, & Vermorken, 1999). No previous studies included a systematic evaluation of gait using the Tinetti instrument, so comparisons between studies were not possible. Balance declined 5% from baseline over the course of treatment. Balance has not been evaluated in studies examining the effects of biotherapy, and further evaluations of balance are needed, especially in older individuals who may have age- or disease-related declines in muscle strength and peripheral nerve function. Individuals receiving high-dose interferon alpha may require educational interventions and/or an assistive device for safe ambulation, thus, appropriate referrals to physical therapy for evaluation of gait and balance should be instituted if balance becomes impaired.

This study used the newly revised Symptom Experience Index to measure symptom distress associated with symptoms of peripheral neuropathy. Distress related to sensations of feeling cold and constipation may be the result of diminished autonomic nervous system responsiveness during the four-week, dose-intensive therapy. Subjective reports of declines in hearing from baseline to four weeks of treatment may represent a short-term phenomenon associated with the high dose intravenous administration of interferon alpha, and warrants further investigation. Self-reports of gait impairment were noted at 12 weeks of therapy, indicating that alterations in gait/balance may happen later in the treatment phase that may require nursing interventions to prevent falls.

This study is limited by its small, convenience sample and lack of racial diversity. However, it should be noted that the majority of individuals who develop malignant melanoma are fair-skinned Caucasians, as reflected in the study sample. This study clearly points to the need for consistent, ongoing neurological monitoring of patients receiving biotherapeutic agents. Gait and balance disturbances may not be noted in the earlier phase of treatment, but as patients report symptoms of gait disturbances at 12 weeks of treatment, assessment of gait and balance should be monitored throughout the duration of therapy.

In summary, there are changes in cutaneous sensation, vibration, muscle strength and blood pressure in the first 12 weeks of high-dose interferon-alpha 2b administration. While the use of clinical measures to assess the onset and severity of neuropathy is both economical and feasible in this population, there are challenges associated with their use for clinical toxicity monitoring or research. Commonly used clinical measures may not be effective in detecting early neurological dysfunction. Not only do clinical measurements require a highly trained examiner to perform them consistently and accurately, the particular measure chosen and subjective nature of some measures limit the accuracy in interpretation

of the results obtained. Studies that include prospective, long-term follow-up of peripheral neuropathy as a complication of cancer treatment are few, and are largely confined to the monitoring of symptoms during pharmacologic trials. The measurement of peripheral neuropathy in conjunction with cancer

and cancer treatments remains unstandardized. A comprehensive, standardized nursing assessment will improve detection of treatment-induced neuropathy and could provide a template for neurological monitoring of patients at risk of developing treatment-induced peripheral neuropathy.

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