



Review Article

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Chemotherapy-Induced Peripheral Neuropathy: Association with Increased Risk of Falls and Injuries

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Abstract

Background: Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a debilitating and degenerative side effect of many commonly used chemotherapy agents. Symptoms manifest as sensory and motor neuropathies. CIPN may necessitate chemotherapy dose reduction or discontinuation.

Objectives: This review intends to summarize literature linking CIPN to an increased risk of falls and injuries and provides recommendations to help maintain patient safety and maximize physical function.

Methods: A literature search was conducted using MEDLINE®, PubMed®, and ScienceDirect.

Findings: Assessment of CIPN and CIPN-related falls and injuries is vital in preventing related complications, and proper education of oncology nursing staff on CIPN assessment and management is necessary.

Keywords: Chemotherapy-Induced peripheral neuropathy; Functional impairment; Falls

Introduction

Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a common and potentially disabling side effect of several antineoplastic agents that treat cancer, such as platinum agents, taxanes, vinca alkaloids, thalidomide, and bortezomib [7]. Its pathophysiology is not well understood. Development of CIPN may necessitate chemotherapy dose reduction or cessation, leading to poorer cancer-related outcomes. A meta-analysis of 31 studies related to the prevalence of CIPN after treatment with various precipitating chemotherapy agents reported that CIPN prevalence was 68% within the first month of the end of chemotherapy, 60% within three months, and 30% at six months or later (Seretny *et al.*, 2014). Another study showed that 47% of female cancer survivors continued to report symptoms of CIPN six years after chemotherapy cessation (Winters-Stone, *et al.*, 2017). Clinical manifestations of CIPN can

include numbness, tingling, or burning; exaggerated sensations (Neuropathic Pain); decrease of muscle tone and coordination; and loss of balance. In general, CIPN begins distally in the fingers and toes and moves through the extremities (Toftagen, Visovsky, & Hopgood, 2013). CIPN seems to affect men and women equally (Winters-Stone, *et al.*, 2017). Complications stemming from CIPN symptoms include reduced quality of life, falls, and other injuries. This review aims to summarize literature linking CIPN to an increased risk of falls and injuries and provides several evidence-based suggestions for providers to help maintain patient safety and maximize physical function.

Methods

A literature review was conducted using MEDLINE®, PubMed®, and ScienceDirect to determine the risk of falling and other injuries



as a consequence of CIPN, as well as associated assessments, treatments, and interventions. Search terms included the following: chemotherapy-induced peripheral neuropathy, CIPN, assessment, falls, injuries, and functional impairment. A total of 15 articles published from 2013 to 2019 were selected from the 408 articles assessed (see Table 1). Articles that described injuries associated with falls among the general population were also included to explain the possible consequences of CIPN-related falls.

Risk of Falls

Based on the literature, patients with CIPN symptoms are significantly more likely to suffer injuries and falls compared to patients with cancer without neuropathic symptoms. Kolb, *et al.* (2016) found that those with CIPN were nearly three times more likely to report a fall or near fall than those without CIPN symptoms. Winters-Stone, *et al.* (2017) observed that greater neuropathic symptom severity is associated with increased disability and a higher fall risk, which can be as much as 1.8 times greater for individuals with CIPN symptoms compared to those without. Patients in a study by Gewandter, *et al.* (2013) completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy (EORTC QLQ-CIPN20), which has been shown to have internal reliability and test-retest reliability for CIPN [5]. Using the EORTC QLQ-CIPN20, 12% (n = 51) of 429 patients reported a fall in the past three months, with motor neuropathy being the only significantly associated factor (Gewandter, *et al.*, 2013). In addition, fallers more often reported high difficulty holding a pen, which made writing challenging, and high difficulty walking because of feet dropped downward than non-fallers; both are markers of functional impairment (Gewandter, *et al.*, 2013).

Preventing falls is a priority for all patients, particularly adults with cancer. A study of 5,880 patients reported that 46% of falls led to fractures, 33% led to superficial injuries, 8% led to open wounds, and 4% led to Traumatic Brain Injury (TBI) [2]. The most common types of fractures resulting from falls were hip (15%), elbow and forearm (9%), and shoulder and upper arm (7%) [2]. Falls are the leading cause of TBI in the United States, resulting in 79% of TBI-related Emergency Department (ED) visits, hospitalizations, and deaths in adults aged 65 years or older and 47% of all ED visits, hospitalizations, and deaths [6]. Falls not only affect morbidity and mortality but may also cause patients to restrict social contact and feel more lonely and isolated, which could be particularly troublesome for cancer survivors and individuals undergoing cancer treatment (Hajek & König, 2017). Fall prevention has even more significant implications in patients with cancer, who are at a 16%-17% greater risk of falling compared to those without cancer and, therefore, a higher risk of injury (Wildes, *et al.*, 2014).

Because no evidence-based methods for the prevention of CIPN exist, dutiful treatment of CIPN symptoms should be a priority in the symptomatic patient's plan of care. It is imperative to take steps, in the healthcare setting and in the home, to prevent patients with CIPN from experiencing falls and other injuries.

Assessment and Grading

Because proven strategies to prevent and treat CIPN are limited, regular CIPN assessment allows for the early treatment of symptoms to prevent further nerve damage and functional decline. There are several grading tools to help providers assess CIPN, including the Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status, the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), and the Total Neuropathy Score (TNS). The ECOG Scale of Performance Status and the CTCAE rely on the patient's self-reported sensory and/or motor symptoms, whereas the TNS is a formal neurologic scale of subjective and objective measures. The Functional Assessment of Cancer-Gynecologic Oncology Group-Neurotoxicity subscale (FACT/GOG-Ntx) assesses the impact of CIPN on functional capacity [7]. The FACT/GOG-Ntx is made up of 11 questions that evaluate CIPN severity and its effect on functional capacity and Activities of Daily Living (ADLs). It asks about subjective experiences of weakness, numbness, and discomfort, as well as the patient's perceived ability to complete tasks, such as buttoning buttons, feeling the shape of small objects, and walking. The instrument is a Likert-type scale ranging from 0 to 4, with total scores ranging from 0 to 44; higher scores indicate greater levels of impairment [4].

Prevention and Treatment Despite placebo-controlled trials testing various substances including alpha-lipoic acid (Guo, *et al.*, 2014), glutathione (Leal, *et al.*, 2014), and IV magnesium and calcium (Loprinzi, *et al.*, 2014), none yielded any statistical superiority over placebos in the prevention of CIPN. Similarly, numerous trials have attempted to find an effective pharmacologic treatment for established CIPN, but few options have shown promise. One agent shown to have reliable efficacy for CIPN is the antidepressant duloxetine given at 60 mg per day (Lavoie Smith, *et al.*, 2013). A study comparing 40 mg duloxetine and 1.5 mg vitamin B12 per day yielded similar results (Hirayama, *et al.*, 2015). Gabapentin has been shown to be effective in reducing neuropathy symptoms, pain, and neurologic deficit at a dose of 300 mg three times per day (Magnowska, *et al.*, 2018). Although opioids are often the firstline treatment for severe pain, there is no evidence that opioids are beneficial for CIPN-specific neuropathic pain (Majithia, Loprinzi, & Smith, 2016). A topical combination of 2% ketamine and 4% amitriptyline has not been shown to be beneficial in treating CIPN; however, toxicity is minimal, so its use may be considered in individual patients (Gewandter, *et al.*, 2014). Several nonpharmacologic interventions exist for the palliation of CIPN symptoms. Physical therapy and exercise have been shown to improve balance, strength, and Ability To Complete ADLs (Duregon, *et al.*, 2018). Acupuncture as a complementary strategy requires additional research to demonstrate its efficacy as a treatment for CIPN [3]. Sensorimotor training, a type of balance exercise on unstable surfaces, and whole-body vibration training, an exercise in which patients stand barefoot on a vibrating platform, were shown to significantly improve peripheral deep sensitivity, Achilles tendon reflex, and patellar tendon reflex, as well as pain, in patients with CIPN (Streckmann, *et al.*, 2019). Whole-body vibration training was shown to be more effective in

controlling pain, whereas sensorimotor training was determined to be superior in terms of increased deep tendon reflexes. Sensorimotor training and whole-body vibration training are being studied in CIPN prevention (Streckmann, et al., 2018). Another strategy to treat CIPN involves the patient's wearing of a wristband that generates low-frequency stimulation and photobiomodulation therapy, also known as low-level laser therapy, to promote the functional recovery of damaged peripheral nerves [1], Jan, g et al., 2018).

Falls and Injuries

When a patient is diagnosed with CIPN, providers can initiate strategies to prevent falls and injuries. Risk assessment is the first step to identify individuals who are most at risk for experiencing adverse effects of CIPN; this can be done by performing functional assessment of lower extremity function, upper extremity function, and fine motor skills on all patients through the course of treatment. Brief assessments of lower extremity function include the Romberg test, the sharpened Romberg test, the Timed Up and Go Test, and the Unipedal Stance Time (Toftagen, et al., 2013). The Maximum Step Length Test also can be used because it assesses dynamic balance and leg strength; a decrease in maximum step length may suggest an increased fall risk (Marshall, Zipp, Battaglia, Moss, & Bryan, 2017). Women with CIPN symptoms can have a significantly more conservative gait pattern compared to women without CIPN symptoms: shortened steps, slower walk, and increased time spent standing to maintain a stable gait (Winters-Stone, et al., 2017).

This abnormal gait pattern has been associated with an increased fall risk in other neuropathic populations, specifically diabetic neuropathy (Winters-Stone, et al., 2017). Fine motor skills can be tested using simple tasks, such as buttoning buttons on a shirt, signing one's name, or tying shoelaces. Upper extremity function can be evaluated via numerous tests developed to assess functionality during performance of ADLs: the Action Research Arm Test, the Fugl-Meyer Assessment, the Jebsen-Taylor Hand Function Test, and the Wolf Motor Function Test (Webber, Shin, & Kaufman, 2018). It is important to note that these measures were originally designed to assess motor and functional recovery poststroke and have not been validated for CIPN-related impairments.

Regular assessments using a single scale to avoid interscale differences is imperative, particularly in patients demonstrating greater impairments because they are at a higher risk for falling and sustaining injuries (Gewandter, et al., 2013; Kolb, et al., 2016; Winters-Stone, et al., 2017). After assessing patients for physical limitations, plans for interventions inside and outside of the healthcare setting can be made to prevent further complications and falls. Interventions Within the Healthcare Setting For individuals receiving their cancer treatment as inpatients, the healthcare team can consult physical or occupational therapists before discharge to assess patient limitations, as well as to provide muscle-strengthening exercises patients can perform in the hospital and at home (Duregon, et al., 2018). Because nursing staff are at the front lines of patient care, they are the predominant providers to assess for CIPN and its severity. A survey of 408 oncology nurses found that although

oncology nurses frequently or always assess for CIPN during neurotoxic chemotherapy infusion visits and when patients report neuropathic symptoms, they less frequently perform focused physical examinations or use toxicity grading scales and patient-reported outcome measures (Lavoie Smith, et al., 2014).

Most nurses in this survey reported perceived barriers that prevented them from assessing CIPN, as well as a knowledge gap in what chemotherapy agents are neurotoxic and what evidence-based treatment and prevention methods exist for CIPN (Lavoie Smith, et al., 2014). Interventions Within the Home Most falls occur outside the healthcare setting [2]. Strategies to prevent falls at home can reduce the risk of falls and injuries. Toftagen et al. (2013) reported the following strategies to prevent falls at home:

- a) In the bedroom, do not use furniture with wheels; clear clutter from walkways through the bedroom; secure cords along the edge of the floor with electrical tape; and remove furniture and objects with sharp edges or corners.
- b) In the kitchen, use rubber gloves for dish washing; check water temperature with a thermometer and ensure it is less than 110°F; use lightweight, nonbreakable glasses, utensils, and plates; and use oven mitts to handle hot items.
- c) Outside, store gardening equipment off of the floor; place nails, screws, and other hardware in containers with lids; and wear rubber shoes or work boots when working in the garage or garden.
- d) Keep rooms, hallways, and staircases well lit; keep a night-light on; and use a flashlight when lighting is inadequate.
- e) Always use handrails on the stairs, and cover hardwood stairs with a nonslip material.
- f) Wear closed-toe shoes that fit well; avoid walking barefoot and wearing slippery or seamed socks; wear gloves and warm socks when it is cold; and avoid jewelry and clothing that need fastening.

Conclusion

Patients with cancer and cancer survivors are already a vulnerable population, and the development of CIPN can be devastating to these individuals, particularly if they already are experiencing decreasing functional capacity; consequently, preventing further impairments should be a priority for nurses and other healthcare providers. Many assessment strategies exist to ascertain the severity of CIPN as well as its impact on physical functioning. Although research into pharmacologic and nonpharmacologic CIPN prevention and treatment methods has proved relatively futile, there are numerous novel prevention and treatment methods actively being studied. As new research becomes available, providers should remain aware of the most promising methods to mitigate the effects of CIPN. By treating CIPN early and aggressively, providers can help to prevent falls and its sequelae of injuries among patients with cancer. Interventions should involve the entire healthcare team, including doctors, nurse practitioners, nurses, physical therapists, occupational therapists, and home health services staff. Patient and

provider education is vital in preventing falls and other complications, as well as in maintaining patients' quality of life and physical functioning. Future research should focus on identifying risk factors for CIPN, examining differences in symptom presentation and physical functioning between men and women with CIPN, and finding more effective means of prevention and treatment.

Acknowledgement

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Conflict of Interest

None.

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