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The Role of Exercise in Chemotherapy-Induced Peripheral Neuropathy

Karen Y. Wonders and Brittany Stout

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurological side effect of chemotherapy and is characterized by damage to the nervous system that is a direct result of the medications associated with chemotherapy. Often, this damage to the central nervous system pain pathways results in neuropathic pain described as burning, paroxysmal, stabbing, or elective shock-like and accompanied by pins-and-needles sensations and itching. The presence and severity of neuropathic pain is often shown to be associated with impairments in walking, general activities, sleep, work, mood, enjoyment of life, and relationships with others. Treatment of neuropathic pain due to CIPN often requires a multidisciplinary approach due to the broad variety of symptoms and their negative impact on quality of life. To provide treatment strategies that are effective for patients, they should include a combination of pharmacological agents and exercise rehabilitation. Exercise rehabilitation programs should be designed in order to help patients familiarize themselves to changes in physical functioning. The goals of the program should target three main areas: maximize functional capacities, prolong or maintain independent function, and improve quality of life.

Keywords: Cancer, Exercise, Neuropathy, Chemotherapy, Rehabilitation

1. Introduction

Treating cancer requires an understanding of cellular kinetics [1]. DNA mutations that occur during DNA replication can aide in the development of cancer cells. Activation for DNA repair in a normal cell cycle uses checkpoints to facilitate the repair; however, checkpoint integrity is lost in tumor cells and DNA repair is bypassed [2]. The resulting mutations impact the regulatory mechanisms the restrict cell proliferation in a normal cell [3].

The use of chemotherapeutic agents works by disrupting the cell cycle to prevent cell proliferation before it begins [4]. The negative of systemic chemotherapeutic agents is that normal cells, as well as malignant cells, are disrupted. This leads to untoward effects and long-term morbidities [4] that negatively impact functional ability and quality of life. Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurological side effect of chemotherapy [5]. This condition is characterized by damage to the nervous system that is a direct result of the medications associated with chemotherapy. Often, this damage to the central nervous system pain pathways results in neuropathic pain [6], frequently described as burning, paroxysmal, stabbing, or elective shock-like [7], accompanied by pins-and-needles sensations and itching. The presence and severity of neuropathic pain is often shown to be associated with impairments in walking, general activities, sleep, work, mood, enjoyment of life, and relationships with others [2, 8].

Little is known about the mechanisms responsible for the development of CIPN [4]. The peripheral toxicity involved with CIPN is specific to each chemotherapy drug class and appears to be dose and duration dependent. However, it can evolve even after a single-drug application [9]. The type and cause of neuropathy are dependent on the chemotherapy agent administered, with vincristine, paclitaxel, and cisplatin being the most neurotoxic [10].

Currently, prophylactic and symptomatic treatments have been ineffective because the neurobiology underpinning CIPN is not fully understood [11]. Thus, the purpose of this chapter was to outline the differences in treatment options available to patients with CIPN and analyze the benefits of exercise in the management of symptoms related to this disorder.

2. Etiology of CIPN

In healthy individuals, peripheral and central nervous system pain pathways function in a protective and adaptive manner [12]. The transduction, conduction, and transmission of nociceptor activity involve these pathways when carrying out activity within the cell. Whether induced by cancer or its treatments, damage to these pathways can result in neuropathic pain [13]. Discontinuation of treatment can result in the development of acute and chronic neurotoxic effects, and these effects can be seen immediately or within weeks or months after discontinuation. Symptoms seen immediately following the first course of treatment can often be contributed to vincristine and oxaliplatin-based regimens. Though both regimens typically produce symptoms immediately following treatment, these symptoms vary between treatments. Vincristine use typically involves the cranial nerve and can lead to symptoms such as seizures, quadriparesis, and numbness. In contrast, oxaliplatin use often produces acute sensory symptoms seen in the mouth or throat that can be intensified by exposure to cold [14]. Regimens that do not present symptoms for up to several weeks after the final treatment may induce a length-dependent neuropathy on small fibers [15].

Incidence of CIPN is estimated to range anywhere from 10 to 100%, depending on the antineoplastic agent, dose, and other factors as presented by the patient [16]. Patients previously affected by diabetes, alcoholism, or inherited neuropathies may be at an increased risk

for CIPN [1, 16]. Clinical diagnosis of CIPN is complex, as there is often more than one contributing mechanism [17]. Therefore, testing is multi-faceted and includes neurological examination, quantitative sensory testing, nerve conduction studies, and toxicity grading. Positive symptoms include hypersensitivity to innoculous and noxious stimuli, such as gentle and/or blunt pressure and pinprick [18, 19].

3. Impact on quality of life

Neuropathic pain negatively affects health-related quality of life. Specifically, decrements to physical [20–22], emotional [20, 21, 23], and social functioning [21, 22, 24] are noted in patients with CIPN. In addition, sleep [20, 21, 24, 25] and global quality of life [3, 26] are disturbed. The presence and severity of pain was reported to cause depression and anxiety in patients [20, 21, 23].

4. Treatment strategies

Treatment of neuropathic pain due to CIPN often requires a multidisciplinary approach due to the broad variety of symptoms and their negative impact on quality of life. To provide treatment strategies that are effective for patients, they should include a combination of pharmacological agents and exercise rehabilitation.

4.1. *Pharmacological agents*

There has been much effort put into exploring pharmacological therapies to effectively reduce CIPN. To date, research has shown that some of these therapies provide modest improvements in neurological function. Unfortunately, in some cases, these agents have been shown to have additional negative side effects for cancer patients. The following text provides a discussion of some of these agents, their mechanism of action, and possible side effects.

Alpha-lipoic acid is a cyclic disulfide broad-spectrum antioxidant [27] that has been recently used in research for treatment of CIPN. It has been shown to be effective in animal subjects of CIPN treated with oxaliplatin, cisplatin, and vincristine. Alpha-lipoic acid has the ability to enter all parts of a nerve because it displays the unique capability of functioning in both water and fat. They utilize this ability and other mechanisms by involving the regulation of acetyl-CoA, acetylation of tubulin, and increasing NGF-induced histone acetylation [28]. Alpha-lipoic acid also increases the formation of glutathione and is involved in the recycling of antioxidants such as glutathione, vitamin C, and vitamin E [29]. A few possible side effects of the treatment includes headache, tingling, pins-and-needles sensation, rash, and muscle cramps.

Another possible treatment for CIPN is carbamazepine; a sodium-channel inhibitor prescribed in the treatment of epilepsy. Sodium channel dysfunction is linked to oxaliplatin-induced peripheral neuropathy [30] and carbamazepine has been reported to be an effective treatment against certain forms of pain associated with oxaliplatin. The reported areas of

effectiveness with carbamazepine have been against the lancing and shooting pain components with less effectiveness seen in burning pain sensations [31]. Side effects of using carbamazepine include dizziness, drowsiness, and headache, as well as cardiac conduction defects, abnormalities in antidiuretic hormone secretion, loss of balance, and diplopia [9].

Another solution used in the treatment of epilepsy that has been recently acknowledged for its role in treating neuropathic pain is gabapentin. Gabapentin has been found to be effective in painful diabetic neuropathy [32] by binding with subunits of the calcium channel [33]. It was originally developed as a γ-aminobutyric acid (GABA) analogue and has been associated with symptoms such as fatigue, blurred or double vision, muscle pain, swelling in extremities, tremor, and drowsiness [34].

Previously, it has been reported that individuals with cancer more often than not have shown reduced levels of glutamine. Glutamine is an amino acid that functions as the primary energy source for rapidly proliferating cells. It also plays a significant role in the upregulation of nerve growth factor, mRNA [35]. Additionally, studies involving human subjects report reduced levels of nerve growth factor during therapy [36]. Together, these findings provide support the use of glutamine as a neuroprotective agent in individuals with cancer.

Glutathione is an antioxidant and antiviral tripeptide. It has been reported that concurrent administration of glutathione and cisplatin results in a reduction of CIPN. This is thought to be due to a reduction in platinum deposits, as glutathione has a high affinity for heavy metals [37, 38]. However, increased levels of glutathione have been linked to chemotherapy resistance in bone marrow, breast, colon, larynx, and lung cancers [39].

Lamotrigine is a neuroprotective agent that stabilizes sodium channels. In vitro studies suggest that lamotrigine modulates the release of glutamate. Studies examining its efficacy have reported positive effects on diabetic neuropathy [40] and neuropathic pain in the elderly [41]. Adverse effects include loss of balance, dizziness, fatigue, memory and cognitive problems, and drowsiness [40].

Phenytoin is an anticonvulsant drug that works as a sodium channel stabilizer, which works to reduce neuronal excitability. Phenytoin has recently been seen to be effective at decreasing visual analogue scale pain scores [42]; however, excessive use of the drug has been associated with neurological problems such as horizontal gaze. Other associated problems include loss of balance, drowsiness, dizziness, and inhibited insulin release.

Valproic acid has been used quite extensively in the management of neuropathic pain [43]; however, there is little evidence to support its clinical use currently. It is believed to increase levels of GABA in the brain, yet its mechanism of action is unknown. Side effects reported with use of the drug include a decrease in blood clotting mechanisms, which may lead to excessive bleeding. Valproic acid has also been associated with side effects such as drowsiness, dizziness, nausea, vomiting, and tremors [43].

Venlafaxine is a drug that has traditionally been used as an antidepressant, but is currently being looked at for its beneficial effects in cancer patients. Venlafaxine works in the selective reuptake of serotonin and norepinephrine and has been recently found to lessen the hyperex-

citability of peripheral nerves [44]. However, reported side effects with venlafaxine can include headaches, anxiety, drowsiness, and increased blood pressure.

Vitamins have also been studies as a possible means of controlling symptoms of neuropathy. Vitamin E is a fat-soluble antioxidant that prevents the peroxidation of polyunsaturated fatty acids. Typically in patients with peripheral neuropathy, there is usually an accompanied deficiency of vitamin E [45] and a greater chance of developing fat-malabsorption disorders. Vitamin E supplementation during treatment with paclitaxel or cisplatin [46, 47] has demonstrated evidence of neuroprotection in clinical trials. These same trials have indicated that Vitamin E supplementation may reduce mortality rates associated with certain forms of cancer [48].

Other prophylactic agents that have been identified as potential neuroprotective agents in CIPN include amifostine, corticosteroids, diethyldihiocarbamate, electrolyte infusions, recombinant human leukemia inhibitory factor, nimodipine, and ORG-2766. These agents have only been tested in animal populations; however, human studies have shown little or no evidence of neuroprotection [49–55].

4.2. *Exercise rehabilitation*

Most preventative and treatments option thus far have come accompanied with a variety of side effects. Due to this, options other than the use of pharmacological interventions that target CIPN should be considered. Exercise rehabilitation is a potential avenue for preventative measures as well as alleviating CIPN symptoms in cancer patients. Many previous research trials have shown beneficial effects of exercise in offsetting countless cancer treatment-related toxicities as well as enhancing the quality of life of the patients. However, clinical trials examining the role of exercise in preserving neurological function following chemotherapy are limited. One recent investigation on the current exercise behaviors of breast cancer patients diagnosed with CIPN patients reported that those individuals who met the amount of recommended physical activity levels reported a significantly higher quality of life and experienced significantly less pain than their sedentary counterparts [56]. A follow-up investigation examined the effect of 12 weeks of supervised exercise training on symptoms of CIPN and found that exercise training positively impacted neurological function. Specifically, unpleasant skin sensations and sensitivity related to neuropathic pain were attenuated following chronic exercise training [57].

While the mechanisms underlying the role of exercise in neuroprotection are unclear, several theories have been circulated. With neuropathy, muscle mass atrophies cause significant decreases in muscular strength [24]. This decline in strength appears to be slow and progressive. It also appears to affect distal muscle groups more so than proximal muscles. Researchers have indicated that this muscle weakness translates into impaired motor performance skills and a reduced exercise capacity [29]. However, several studies have reported improvements in muscular strength following moderate resistance exercise programs in patients with hereditary motor and sensory neuropathies [20, 21], as well as diabetic neuropathies, and those associated with fibromyalgia and chronic fatigue [3, 26–28, 39, 40]. In light of these findings, many researchers recommend that exercise training serve as an important component in the

comprehensive treatment plan for patients with peripheral neuropathy [3, 23, 27]. Moderate to intense strength training and aerobic exercise appears to be well tolerated by these patients [23] and is associated with improvements in motor function and nerve conduction velocity [26, 28], as well as improved muscle reinnervation and increased axon regeneration [22]. In addition, one investigation reported that low intensity treadmill exercise promoted Schwann cell proliferation in the injured peripheral nerve [25]. In light of these findings, it is feasible to assume that an individual who has experienced a reduction in muscular strength and functional ability due to CIPN may experience similar improvements following an exercise program.

Those affected by CIPN typically experience large amounts of pain associated with peripheral neuropathy and can be severe enough that it interferes with an individual's quality of life [13]. This type of pain has long been recognized as one of the more difficult types of pain to treat; however, exercise rehabilitation may be able to reduce the amount of pain accompanying peripheral neuropathy. In healthy individuals, studies have shown that acute exercise can temporarily decrease pain perception; a condition known as exercise-induced hypoalgesia (EIH). Specifically, there have been reported increases in pain thresholds and pain tolerance levels both during and after exercise. Even further, there appears to be a decrease in intensity ratings of pain following exercise. To date, research in these areas has yet to determine the optimal intensity of aerobic exercise needed to produce a hypoalgesic effect [58–63]. Typically, exercising at intensities between 60 and 75% of maximum heart rate has been found to produce EIH [58, 59]. Thus far, it has been reported that women tended to experience hypoalgesia following aerobic exercise at 85% HR_{max} [60]. In most research that has been performed, subject has self-selected their aerobic exercise intensities in which they reported EIH following the exercise bout [61, 62]. EIH has also been observed following resistance exercise training, though reports are limited in this area. In a study conducted by Koltyn and Arbogast [63], it was shown that following 45 min of resistance exercise at 75% of the subject's 1-RM, increases in pain thresholds were observed.

Exercise rehabilitation programs should be designed in order to help patients familiarize themselves to changes in physical functioning. Further, goals of the program should target three main areas: maximize functional capacities, prolong or maintain independent function, and improve quality of life. For example, studies performed using populations with hereditary motor and sensory neuropathy have shown that a minimum of 12 weeks of low to moderate resistance training (approximately 30% overload) resulted in strength gains [64–66] that improved function ability [67]. An important area of concern for resistance training is watching for signs that indicate the muscles are being over-worked or exhausted. Symptoms of muscle exhaustion include, but are not limited to, muscle weakness within a half hour of completion of the exercise and excessive muscle soreness between 24 and 48 h after exercise [76, 77]. Training programs should also target aerobic exercise due to its associated benefits with cardiovascular performance and pain tolerance as well as decreased fatigue and depression scores. Currently, research suggests that endurance-based programs should be low impact or utilize approximately 50% of the patient's heart rate reserve [68, 69]. Studies in this area also suggest including a proper warm up and cool down component.

5. Summary

In closing, CIPN is a dose-limiting effect of cancer therapy that has negative implications on a patient's quality of life. While much effort has been made to explore pharmacological therapies aimed at cancer patients. However, exercise rehabilitation is one lifestyle modification that positively impacts the lives of patients with CIPN.

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