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Review Article

Assessment and Treatment of Chemotherapy-induced Peripheral Neuropathy: A Physical Therapy Perspective

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Abstract

Chemotherapy is recognized as a mainline treatment for all types of cancer, and its most debilitating and dose-limiting complication is Chemotherapy-induced peripheral neuropathy (CIPN), the mechanisms of nerve damage of which depends upon the specific chemotherapeutic agent used. Use of non-invasive treatment methods such as physical therapy may provide a valuable therapeutic adjunctive option in patients with CIPN. Physical therapy treatment methods had been shown to produce effective symptom control and enhance quality of life in palliative care. A detailed evidence-based update of literature is provided under evaluation and management of CIPN with a special perspective of physical therapy management using a proposed clinical reasoning-based treatment decision making algorithm so that an 'out of the box' self-reflective evidence-informed critical thinking process is applied along a collaborative multidisciplinary biopsychosocial approach.

Keywords: Chemotherapy-induced neurotoxicity; Chemotherapy-induced neuropathy; Physical therapy; Palliative rehabilitation

Introduction

Chemotherapy is recognized as a mainline treatment for all types of cancer, and its most debilitating and dose-limiting complication is Chemotherapy-induced peripheral neuropathy (CIPN), the mechanisms of nerve damage of which depends upon the specific chemotherapeutic agent used [1,2]. Depending on the substance used, a pure sensory and painful neuropathy (with cisplatin, oxaliplatin, carboplatin) or a mixed

sensorimotor neuropathy with or without involvement of the autonomic nervous system (with vincristine, taxol, suramin) can ensue [3].

CIPN occurs secondary to use of many chemotherapeutic agents like plant alkaloids, interferons, antimetabolites [4] platinum compounds/analogues (cisplatin, oxaliplatin, carboplatin), taxanes (paclitaxel, docetaxel), epothilones, vinca alkaloids (vincristine), thalidomide, lenolidamide and newer agents such as bortezomib [5], and it affects both adult and pediatric population [6].

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The Chemotherapy-induced neurotoxicity (CIN) affects the peripheral nerves and can affect the nerve fibers and neuronal cell bodies especially the dorsal root ganglia [7], the axonal transport system, the myelin

sheath and glial support structures [8]. In the central nervous system, the chemotherapy-induced neurotoxicity induces polymorphisms in folate metabolizing enzymes and apolipoprotein E, and in blood-brain barrier transporter genes [9], reduces the efficiency of cellular efflux pumps, causes DNA damage, telomere shortening, alteration of cytokine regulation, defects in neural repair, and increases oxidative stress [10]. Acute exacerbation of CIN is seriously bothersome, with symptomatic manifestations such as sleep disturbances and severe pain/dysaesthesia [11].

The importance of understanding and recognition of CIPN by healthcare professionals was explored by Binner et al. [12] in their survey of 39 oncology nurses who found that the participants had knowledge deficits pertaining to CIPN and lacked training, proficiency, and confidence in neurologic physical assessment; and by Kuroi et al. [13] who found that physicians felt the need to assess peripheral neuropathy in patients undergoing chemotherapy.

Presently, the modification of chemotherapy is the only available approach to limit the severity of neuropathy in majority of patients, with most of them with a possibility of delayed worsening after treatment withdrawal, and thus delay important treatment modification decisions [14]. To date, no drugs have been proven to prevent this neurotoxicity [15].

Windebank and Grisold [16] stated, "The neurologist managing the cancer patient who develops neuropathy must answer a series of important questions as follows: (1) Are the symptoms due to peripheral neuropathy? (2) Is the neuropathy due to the underlying disease or the treatment? (3) Should treatment be modified or stopped because of the neuropathy? and (4) What is the best supportive care in terms of pain management or physical therapy for each patient?" Their last statement reflected the importance of physical therapy in symptom control and quality of life of patients with CIPN.

Use of non-invasive treatment methods such as physical therapy may provide a valuable therapeutic adjunctive option in patients with CIPN. Physical therapy treatment methods had been shown to produce effective symptom control and enhance quality of life in palliative

care [17]. The objective of this paper was to provide an evidence-informed update on the CIPN as a clinical condition- its assessment and treatment options, with a focused perspective on physical therapy management.

Definition

Chemotherapy-induced peripheral neuropathy (CIPN) is defined as a disease or dysfunction of peripheral nerves secondary to chemotherapy which leads to severe chronic disabling pain, altered painful sensations, sensory deficits, muscle weakness, impaired daily functional activities and reduced quality of life [1,2].

Diagnostic criteria

The American Cancer Society (ACS) through the National Cancer Institute and Neuropathy Association has listed the following features as indicative of CIPN; "Presence of symptoms and signs indicative of neuropathy after initiation of chemotherapy regime, and amelioration or reduction in symptoms upon altering the chemo-dose" [18].

Epidemiology

The incidence and degree of neuropathy depends on the type of cytotoxic drug, the duration of administration, cumulative dose and pre-existing peripheral neuropathy [19]. The incidence of CIPN was 15.3, 21.5 and 18.3 per 1000 person-years for breast, ovarian and lung cancer respectively [20]. The incidence of CIPN is increasing because more neurotoxic drugs have been developed and because patients are living longer and receiving multiple chemotherapy regimens [21].

Impact on healthcare costs and work loss burden

Pike et al. [22] found that average healthcare costs were \$17,344 higher for CIPN especially for out-patient settings with more visits and longer hospital stay and greater work loss. The burden of CIPN is not only physical and but also physiological, with the perceived discomfort being associated with other adverse effects of chemotherapy [23].

Mechanisms of CIPN

The mechanisms underlying chemotherapy-induced neurotoxicity are diverse and include damage to neuronal cell bodies in the dorsal root ganglion and axonal toxicity via transport deficits or energy failure. More recently, axonal membrane Na⁺ ion channel dysfunction has been identified and reported [24].

Clinical presentation of CIPN

Typically, the clinical presentation reflects an axonal peripheral neuropathy with glove-and-stocking distribution sensory loss, combined with features suggestive of nerve hyperexcitability including paresthesia, dysesthesia, and pain [24].

Clinical examination

Pain evaluation using Visual analogue scale [25], sensory examination, motor examination, reflex testing, structured questionnaires (patient-reported) and evaluation scales (clinician-rated), functional evaluation, quality of life assessment, anxiety and depression scales, and other psychosocial assessments [26]. Alterations in vision, hearing, deep tendon reflexes, vibratory sense, cutaneous sensation, balance, muscle strength, and orthostatic blood pressure were noted, but gait remained unchanged in CIPN [27].

Loss of balance and subsequent risk of falls increased with each cycle of chemotherapy and this risk was found to be drug-specific, with patients reporting muscle weakness and interference with walking or driving were at higher risk of falls [28].

Mild cognitive impairments such as short-term memory loss, and attention and concentration problems associated with chemotherapy or CIPN are termed collectively as 'chemobrain' or 'chemofog' [29].

Outcome measures

Self-reported questionnaires

Body structure and function: National Cancer Institute-Common Toxicity Criteria (NCI-CTC) [30],

the modified Inflammatory Neuropathy Cause and Treatment (INCAT) group sensory sumscore (mISS) [30], Chemotherapy-induced peripheral neuropathy assessment tool (CIPNAT) [31]; Patient neurotoxicity questionnaire (PNQ) [32]; Scale for chemotherapy-induced long-term neurotoxicity (SCIN) [33].

Activity limitation and participation restriction: Chemotherapy Induced Neurotoxicity Questionnaire (CINQ) [34], European Organization for Research and Treatment of Cancer (EORTC) Quality of life questionnaire (QLQ-C30) for Chemotherapy-induced peripheral neuropathy (CIPN20) [30,35], Functional Assessment of Cancer-Gynecologic Oncology Group, neurotoxicity (FACT/GOG-Ntx) [36] were recommended to be valid and reliable measures of quality of life in people with CIPN.

Evaluation scales: The Total Neuropathy Score (TNSc) [37] and its reduced version (TNSr) can be used for grading the severity of CIPN, and are reliable methods for assessing not only the severity but also the changes in CIPN [38,39]. Smith et al. [40] in their systematic review on use of Total Neuropathy Score in CIPN, found that the scale is cumbersome, and later Smith et al. [41] modified it into a shorter version with five components, and Gilchrist and Tanner [42] recently found the validity and reliability of pediatric modified total neuropathy score for use in children.

WHO scoring criteria [43], Eastern Co-operative Oncology Group [44], Ajani [45], and NCIC-CTC criteria [46] were commonly used in which the CIPN severity ranges from grade 0, meaning non-existent, to grade 4, meaning intolerable, unacceptable or life-threatening. Grade 3 toxicity is intended to lead to corrective measures, being the level of dose-limiting toxicity. Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire [47] was also reported to be useful. Minor modifications of these scales to suit symptoms and signs of specific cancer types had been suggested and such scales are Gynecologic Oncology Group (GOG) performance status scale, and the GOG toxicity criteria [48].

Investigations

Investigations comprise of laboratory investigations (blood tests) for screening other etiologies of peripheral neuropathy [49], nerve biopsy for neuropathological evaluation [50], nerve conduction studies for neurophysiological evaluation [50], and ultrasonography for neuromechanical evaluation [51].

The investigation procedures documented in CIPN population include; **Neurohistological assessment:** Electron microscopy and X-ray diffraction methods for ultrastructural evaluation of peripheral nerves [52]; **Nerve excitability assessment:** Nerve excitability equipments are sensitive biomarkers that utilize infusion techniques to evaluate patients at-risk for neurotoxicity prior to onset of chronic neuropathy, and they can reveal development of acute Na⁺ channelopathy in motor and sensory axons [53]; **Touch sensitivity assessment:** Boyette-Davis et al. [54] described the utility of a novel touch assessment methodology as Bumps detection test that can detect subclinical peripheral neuropathy in patients undergoing chemotherapy; and, **Vibration perception threshold testing:** The changes in hand/foot numbness/discomfort were significantly associated with change in vibration threshold, but not so with touch perception [55].

Prevention

Erythropoietin (EPO), a well-established hematopoietic factor, is a very effective and widely used treatment for anemia in cancer patients undergoing chemotherapy. It also possesses generalized neuroprotective and neurotrophic properties [56] and thus is useful as a preventive agent for CIPN. Vitamin-E [57], Cytokines and growth factors [58] were also reported to be effective preventive agents.

Patient education

Self-management strategies such as emphasis on movements to reduce symptoms, attitude awareness, logistics to simplify demands, and environmental change which when implemented through exercise, mindfulness, occupational therapy and environmental planning provide a valuable therapeutic option [59]. Pa-

tients not only found difficulty in describing neuropathic symptoms but also experienced interference with many aspects of daily life both social and recreational [60], and hence adequate and appropriate education is indicated.

Medical management

Medical management includes aetiopathogenetic, neurotrophic, neuroprotective, symptomatic and palliative drugs, of which symptomatic management is the best approach by starting with Non-steroidal anti-inflammatory drugs, and following up with opioid therapy [61].

Medical management of neuropathic pain includes a range of drug options [62]. Topical agents such as baclofen/amitriptyline/ketamine gel [63], and oral drugs like serotonin and norepinephrine reuptake inhibitor drugs, venlafaxine and duloxetine are useful pharmacological options [64]. The neuroprotective strategies including use of calcium/magnesium infusion, amifostine, oral glutathione, oral glutamine, acetyl-L-carnitine and erythropoietin are promising methods [19].

Acetyl-L-Carnitine [65], Alpha-lipoic acid [66], Amifostine [67], cholest-4-en-3-one, oxime (TRO19622) [68], Cannabinoid type-1 receptor [69], Gabapentin [70], Glutamine [71], Lamotrigine [72], recombinant human leukemia inhibitory factor (rhuLIF, AM424, emfilermin) [73], Neurosteroids [74], Palmitoylethanolamide [75] and Retinoic acid [76] were studied individually for their efficacy in randomized clinical trials.

Surgical management

Surgical treatments for neuropathic pain involve interventional pain medicine techniques such as injections of Botulinum toxin and phenol blocks, nerve decompression surgeries and neuroablative methods [77]. Radiofrequency ablation of dorsal root ganglia [78], nerve decompression surgery [79] have been previously reported for their efficacy.

Alternative therapies

Complementary and alternative medicine approach-

es such as massage, acupuncture and other forms of treatment like reflexology-based methods may be attempted.

Treatments such as Acupuncture [80-82]; Sweet bee venom pharmacopuncture [83,84]; Kampo diagnosis and therapy [85] were documented in the literature.

Physical therapy

Popular methods of pain relief in PT include electrical and thermal modalities [86,87], exercises [88-90] and manual therapy [91]. Physiotherapy treatment methods for neuropathic pain were studied by Kumar et al. [91] and included treatments such as TENS, hot/cold application, flexibility and strengthening exercises, and manual physical therapy methods such as nerve massage and nerve slider techniques (for those who present with positive nerve palpation and neurodynamic tests).

The Oncology section of American Physical Therapy Association had released the CIPN fact sheet [92] which describes the types of chemotherapy agents associated with peripheral neuropathy, with implications for assessment (measures to quantify severity of CIPN), and planning for management using International classification of functioning, disability and health into addressing impairments (body structure/ function problems) and addressing functional mobility/disability problems (activities/participation problems).

Exercise therapy: Exercise plays a major adjunctive role and the important role of physical activity in prevention and treatment of disuse-associated musculoskeletal complications such as chronic pain, muscle weakness, joint stiffness and functional disability is well known. Exercise effects of pain relief through descending pain control pathway and endogenous peptides was also well documented.

Albrecht and Taylor [93] said, "Exercise in a variety of intensities and forms, including yoga, walking, biking, and swimming, has many health benefits for people, including those diagnosed with cancer. Research has shown that, for people with cancer (including advanced-stage cancer), exercise can decrease anxiety, stress, and depression while improving levels of pain, fatigue, shortness of breath, constipation, and insom-

nia".

Many randomized controlled trials [94] had reported efficacy of supervised aerobic exercise training in cancer patients undergoing chemotherapy with or without radiation therapy [95] administered either individually [96] or along a multimodal approach [97]. Courneya et al. [98] listed exercise-related predictors as demographic, medical, behavioral, fitness, psychosocial, and motivational variables. Patient preference, demographic variables, and medical variables moderated the effects of exercise training in breast cancer patients who were receiving chemotherapy [99]. Adherence to supervised exercise training was predicted by unique aspects of the location/center, disease stage, aerobic fitness, and depression but not motivational variables [100]. The authors found that both resistance training and aerobic training given alone or in combination was associated with beneficial patient-reported outcomes [101]. The therapeutic benefits include improvements in self-esteem, physical fitness, body composition, and chemotherapy completion rate without causing lymphedema or significant adverse events [102]. The patient-reported barriers to exercise training were found to be both cancer-related and its treatment-related [103].

Dimeo et al. [104] found that aerobic exercise training resulted in a significantly higher maximal physical performance at discharge in the 33 cancer patients who received high-dose chemotherapy, with significant reductions in duration of neutropenia and thrombopenia, severity of diarrhea, severity of pain, and duration of hospitalization. Dimeo et al. [105] also found that aerobic exercise reduced fatigue and improved psychological distress among patients with cancer undergoing chemotherapy.

Physical activity: Physical activity in itself was shown to be beneficial for managing people with all types of cancer [106-108], and its therapeutic efficacy was reported among cancer patients of all ages [109] undergoing surgery, chemotherapy or radiotherapy [110] for improving biological and psychosocial [111] functions.

Oechsle et al. [112], Dahele et al. [113] and Stephenson et al. [114] found significant association between increase in physical activity and enhanced quality of life

in cancer patients who underwent palliative chemotherapy.

Midgaard et al. [115] in their quasi-experimental study on 6-week, supervised exercise program (muscle strength, cardiovascular fitness, relaxation, body awareness, and massage) in a heterogeneous group of 61 cancer patients found a significant post-program reduction in physical activity from 6 to 10 weeks and from 6 to 18 weeks with more than half patients reporting higher physical activity post-program.

ACS thus recommended physical activity both during and after cancer treatment [116] and hence released the guide for informed choices [117,118].

Manual therapy: The understanding behind the role of manual therapy in the treatment of pain is not new [119]. Manual physical therapy was shown to be useful for treating chronic musculoskeletal pain conditions [120,121], ranging from low back and neck pain to fibromyalgia and chronic fatigue syndrome, with documented mechanism-based efficacy [122].

Neurodynamics is the concept based on a close interaction of mechanics and physiology of the nervous system which is to be considered while assessing and treating patients via nervous system mobilization and manual therapy [123]. Neurodynamic testing had been validated for its use in detecting peripheral neuropathic pain [124], and it was Boyd et al. [125] demonstrated diminished mechanosensitivity of lower extremity peripheral nerves in individuals with peripheral neuropathy. Neurodynamic mobilization was shown to improve intraneurial fluid dispersion of tibial nerve in a cadaveric study and was suggested to be indicated for peripheral neuropathic pain syndromes [126].

Studies on manual therapy for peripheral neuropathic pain and neurological function: Kumar et al. [127] in their systematic review of neurodynamic mobilization for neuropathic pain included 22 clinical trials and concluded its efficacy on pain, neurological function and disability in many heterogeneous types of neuropathic pain.

Abnormal quantitative sensory testing was indica-

tive of nerve fiber dysfunction in peripheral neuropathy. Kumar et al. [128] found that tibial nerve massage produced significant positive effects of changes in vibration and thermal perception thresholds in asymptomatic subjects, and another pilot study [129] showed significant immediate effects of an impairment-based neurodynamic intervention comprising of nerve sliders and nerve massage on sensory perception thresholds, neuropathic pain and range of motion.

Cunningham et al. [130] described the use of manual therapy (therapeutic massage techniques of effleurage and petrissage) on a patient with grade-2 CIPN undergoing prior treatment with docetaxel and cisplatin for stage III esophageal adenocarcinoma, and the authors found that manual therapy was associated with almost complete resolution of the tingling and numbness and pain, with concurrent increase in superficial temperature.

He et al. [131,132] reported the short-term efficacy of a newly emerging treatment such as sciatic nerve press technique for patients with all etiologies of chronic pain including cancer pain, and is a simple and safe-to-use 2-minute technique for obtaining powerful relief of symptoms. However, this technique is yet to be evaluated for CIPN, or in palliative care settings.

Electrotherapy: Smith et al. [133] evaluated the efficacy of a patient-specific cutaneous electrostimulation device (MC5-A Calmare therapy device) on 16 patients with CIPN who were treated one-hour daily over 10 days, and found dramatic reductions in refractory pain, without any reported adverse events.

Discussion and Conclusion

This paper aimed at providing a focused update on assessment and treatment of CIPN from a physical therapy perspective, and the findings from existing evidence are insufficient, and they indicate the underreporting and underappreciation of CIPN [134] among other related professional disciplines such as physical therapy which is comprehensively associated with pain management teams in palliative care.

Assessment tools for CIPN require revision since

most scores mix impairment, disability and quality of life measures, which could lead to misinterpretation of the results and unpredictable under- or overestimation of the effect [135]. The most widely used tools such as National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale is open for misdiagnosis due to co-existing symptoms of fatigue, depression and cachexia [136].

Diagnosis and interpretation of symptoms in patients with CIPN should be done with care since Wolf et al. [137] found that severe sensory neuropathy symptoms (numbness, tingling) commonly exist without severe neuropathic pain symptoms (shooting/burning pain). A combination of pharmacological and non-pharmacological therapeutic strategies along a multidisciplinary biopsychosocial approach is indicated to combat the clinical challenge of CIPN [138].

Mechanism-based therapies were more successful than symptom-based or syndrome-based treatments, and Manual therapy was shown to have mechanism-specific effects [122] in painful conditions. Manual therapy techniques are simple-to-use, cost-effective, safe and technically sound, although the knowledge base behind the use of these techniques is relatively lesser [139]. Manual therapy addresses connective tissue impairments [140] effectively when applied along a clinical reasoning model [141], to specifically address the ensuing source of impairments and symptoms. A proposed clinical reasoning-based treatment decision making algorithm for using physical therapy management of people with CIPN is provided in Figure 1, which is explained as follows;

Patients with CIPN present with two types of symptoms- constant and intermittent. Constant symptoms are usually severe in intensity, and are associated with sleep disturbances and hence patients are likely to be in a stressful state [142]. Relaxation techniques such as deep breathing exercises, Jacobson progressive relaxation, Mitchell's relaxation method, music therapy were shown to be beneficial for chronic pain [143]. Once patient is relaxed, it is imperative that they can understand the whats and hows of their chronic painful state and its management options, for an effective educational intervention [144]. Non-responders to both the above techniques need referral to psychologist or

psychiatrist for initiating advanced psychological interventions [145-147].

Sciatic nerve press technique is a non-specific pain-relieving technique and hence it is useful to apply it as a first-level manual technique [131,132]. One symptoms become intermittent and well-tolerated, it is advisable to use manual therapy since the symptom behavior is understood to be mechanical. Intermittent symptoms in CIPN, which is dependent upon positions indicate vascular influence and hence soft tissue massage and mobilization will be useful [148,149].

Following treatments with nerve massage and nerve sliders for patients who show favorable response, it is indicated to begin exercise training (initially aerobic and later resistance) and then progress into functional restoration [150]. Activity pacing is a method of self-management which was shown to be an effective pain-relieving functional coping strategy for chronic pain [151,152].

Physical activity was shown to be beneficial both for prevention and treatment of cancer patients with or without chemotherapy, and chronic neuropathic pain both cancer-related and otherwise. Hence extrapolation of existing evidence for physical activity into CIPN is appropriate along an evidence-informed approach. Physical activity habits prior to cancer diagnosis and information about the benefits of physical activity appear to be important factors for higher levels of physical activity during and after chemotherapy [153].

The use of this proposed algorithm for physical therapy management of CIPN is advisable provided that an 'out of the box' [154] self-reflective evidence-informed critical thinking process is applied along a collaborative multidisciplinary [155] biopsychosocial [156] approach.

Visvosky [157] opined on the need for future research on physical activity, "Physical activity interventions with larger sample sizes and of longer duration are necessary to achieve long-term health outcomes. Physical activity interventions that include the older or more obese women with breast cancer are also needed, as this population may be most at risk of functional decline and the development of chronic illness. However, the role of physical activity during dose-dense chemother-

Figure 1: Clinical reasoning-based algorithm for physical therapy decision-making in symptomatic management of people with chemotherapy-induced peripheral neuropathy.

apy protocols has not been established". There is also need for healthcare professionals to measure the effectiveness of interventions such as exercise, patient education and self-care strategies in patients with CIPN, and to develop and/or participate in well-designed clinical trials on prevention and management of symptoms [158].

Cavaletti and Marmioli [159] opined, "No drugs capable of preventing the occurrence of CIPN or ameliorating its long-term course are available, and chemotherapy schedule modification is often required to limit its severity, which could potentially prevent patients from receiving the most effective treatment for cancer. Moreover, symptomatic therapy is often largely ineffective in reducing CIPN symptoms". The authors also emphasized a mechanistic approach to clinical management and thus Mechanism-based classification (MBC) and physical therapy management of patients with CIPN would be the future interest for clinicians and researchers in palliative care settings [160].

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