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Chemotherapy Induced Peripheral Neuropathy; Mechanism and Treatment

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Abstract

The use of chemotherapeutic agents to treat cancersis associated with several adverse effects, one of the debilitating and often dose-limiting side effect is peripheral neuropathy, manifested with different clinical signs and symptoms. Most common being sensory neuropathy, followed by motor; presenting with loss of sensation, paraesthesia in the limbs, motor symptoms like weakness in the limbs, difficulty in walking, difficulty in carrying out fine motor movements; the effect on autonomic nerves have not been studied in detail. Numerous mechanisms are proposed by different researchers to explain the basis of neuropathy associated with the use of anti-cancer drugs. The chemotherapy induced peripheral neuropathy (CIPN) often requires dose-reduction and drug withdrawal, hampering the effectiveness of the drug and compromising survival outcomes. Various life modification strategies like mindfulness, exercise, occupational therapy etc. are being used to reduce the intensity of side effects and to tolerate the drugs better. In addition, various neuroprotective agents have been tried as adjunct therapy but according to published systematic reviews and meta-analysis, none of these agents have robustly proven their efficacy in treating CIPN. Anti-oxidants, anti-convulsants, anti-depressants, calcium and magnesium etc. are some of the drugs being used for reducing the intensity of CIPN. Out of these, topical pain relievers and duloxetine are considered as the first line of treatment for CIPN. Well planned clinical trials are required to establish the clinical utility of others.

The current review briefly focusses on the mechanisms involved in the genesis of CIPN and treatment strategies available for the same.

Keywords: Anti-Neoplastic Agents; Chemotherapy; Neuroprotective Agents; Peripheral Neuropathy.

Introduction

Chemotherapy induced peripheral neuropathy (CIPN) is a frequently observed and dose-limiting adverse effect of many chemotherapeutic (antineoplastic drugs) agents including taxanes (paclitaxel, nab-paclitaxel, ordocetaxel), platinum based drugs etc [1-5]. The incidence of CIPN ranges from 2% to 100% depending on the patient medical history and clinical condition and also on the chemotherapeutic agent being used [6]. This complication is one of the cause of significant disability in cancer patients leading to further deterioration of the quality of life. The anti-neoplastic drugs may affect the sensory and motor nerves and peripheral autonomic nerves to some extent. The involvement of autonomic nerves has not been studied extensively. The symptoms may vary from sensory loss (glove-and-stocking distribution), dysesthesia, and paraesthesia to shooting pain (features of nerve hyper excitability) and decreased muscle tone [7]. CIPN can be evaluated using a patient-based instrument, the Patient Neurotoxicity Questionnaire (PNQ) and a physician-based instrument, the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) in patients with cancer on chemotherapy [9,10]. Neurophysiological tests beneficial in diagnosis of CIPN include measurement of sensory and motor nerve conduction velocity (NCV), sensory nerve action potential (SNAP), and compound muscle action potential (CMAP) together with needle electromyography (EMG). EORTC QLQ-CIPN20 instrument, N06CA, developed by the European Organization for Research and Treatment of Cancer is a another widely used questionnaire for the assessment of CIPN [11]. In this review, we would briefly discuss the mechanism leading to the genesis

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of CIPN and current treatment strategies available for the same.

Chemotherapy Induced Peripheral Neuropathy

CIPN is a debilitating side effect associated with the use of various chemotherapeutic agents. The imperative antineoplastic agents responsible for CIPN are taxanes like paclitaxel (Taxol), docetaxel and newer cabazitaxel; platinum derivatives, such as cisplatin and carboplatin; vinca alkaloids and two old drugs with new applications- suramin and thalidomide etc [1-4].

Sensory neuropathies are more common chemotherapy-induced neuropathy. Early signs include tingling or numbness in the feet or fingers. Sensory symptoms including paresthesia; dysesthesia; tingling; itching; and burning, tight, stabbing, sharp (lightning like), or aching pain are often reported by patients [12]. Sensory loss in the feet and legs can cause sensory ataxia and gait disorders. Platinum compounds in addition alter smell and taste sensations; cause vestibular dysfunction and hearing loss. Motor neuropathy is manifested as absence of Ankle reflexes. Vinca alkaloids may cause distal weakness, including foot drop. Autonomic signs are rare but can be seen in vinca alkaloids, taxanes, and platinum compounds. Several drugs cause muscle cramps or weakness [13,14]. Raynaud's syndrome is observed in long-term survivors of testicular cancer [15].

Severity of CIPN depends on various factors; age and dose being the primary factor. In addition, cumulative dose, delivery method, prior and concomitant use of other anti-cancer drugs (synergistic neuro-toxicity), pre-existing neuropathy of any aetiology (hereditary or inflammatory) also add to the manifestations of CIPN [7,16,17]. In a study by Pereira S, no significant differences was reported in the variation of breast cancer patient-reported outcomes between the baseline and 1-year follow-up evaluations. Alcohol consumption and diabetes were shown not to be significantly associated with CIPN [10]. Chemotherapy induced sensory neuropathy in patients on Paclitexal, was reportedly increased during active treatment in terms of both the PNQ and NCI-CTC assessments. Contrary to this, increase in motor neuropathy symptoms were reported only by the PNQ [9].

Polymorphisms in several genes, for example the in the ones coding for voltage-gated sodium channel or genes affecting the activity of pivotal metal transporters, can also impact drug neurotoxicity [18].

Mechanism of CIPN

Various mechanisms have been proposed to explain the basis of CIPN, some are specific and others non-specific. Taxanes are the most common culprit leading to CIPN, manifested as symmetric, axonal sensory distal neuropathy, there is less of motor involvement. They primarily act by degenerating Schwann cells, neuronal body and also bring about changes in axonal transport and cytoplasmic flow in the affected neurons. Molecular mechanism bringing about degenerative changes in the peripheral nerves are DNA damage, alterations in cellular system repairs, mitochondria changes, oxidative stress [19] and various ion channelopathies [8]. Sensory symptoms have been implicated to structural deficits in dorsal root ganglia and sensory nerves [19,20].

Platinum derivatives, such as cisplatin and carboplatin, affect mainly the peripheral nerves and dorsal root ganglia neurons, possibly by progressive DNA-adduct accumulation and inhibition of DNA repair pathways. Oxaliplatin causes acute neurotoxicity by altering calcium sensitive voltage gated sodium channels [18].

Treatment of CIPN

Treatment options for CIPN include dose adjustments, drug withdrawal, altering the chemotherapy, and handling CIPN with adjunct therapy or any neuroprotective agents. Adoption of management strategies focussing on exercise, mindfulness, occupational therapy etc. is recommended [4,21,22].

Neuroprotective Agents

According to the systematic review and meta-analysis by Albers [23,24], the data on the benefits of neuroprotective agents are insufficient to conclude their protective role in chemotherapy induced neurotoxicity, as determined using quantitative, objective measures of neuropathy. Till date, numerous chemo protective agents viz. thiols, neurotrophic factors, anticonvulsants (oxcarbazepine), acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, antioxidants like glutathione, retinoic acid, and vitamin E have been proposed to be useful in preventing or limiting the neurotoxicity of chemotherapeutic drugs and have been tested in pre-clinical models and clinical trials [25].

In a pre-clinical study on Wistar rats, erythropoietin given systemically has shown a wide range of

neuroprotective actions against central and peripheral nervous system damage [26]. Adjunct therapy with topical agents, tricyclic antidepressants, and anticonvulsants, such as pregabalin and gabapentin, have also shown limited efficacy. Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI) was found to be more effective than placebo in treating oxaliplatin- or paclitaxel-induced CIPN, was well tolerated, and was proposed to be considered to be a first-line treatment option for CIPN [27,28].

Calcium and magnesium infusions have strongest preliminary data regarding their potential efficacy in preventing CIPN, venlafaxine, another SNPR is also effective in preventing CIPN but are not routinely used because of concerns related to decreased chemotherapy efficacy [28].

Though anti-convulsants and anti-depressants have been found to be useful in CIPN but none of the findings have been duplicated in an RCT with a large sample size [29].

In one of the study, patients with CIPN were treated with regulated dose of acetyl-L-carnitine for at least 10 days. Out of twenty-six patients evaluated after completion of 10 days of acetyl-L-carnitine therapy, at least one WHO grade improvement in the peripheral neuropathy severity was shown in 73% of the patients [30].

Literature search has revealed the effectiveness of vitamin E supplementation in decreasing the incidence and severity of peripheral neurotoxicity in patients receiving cisplatin chemotherapy [3,31].

Although several of these agents hold promise as possible neuroprotective factors, clinical data are still controversial and none have as yet robustly been proven effective against CIPN. Agents with the strongest supporting evidence for efficacy in the treatment of CIPN include topical pain relievers, such as baclofen/amitriptyline/ketamine gel, and serotonin and norepinephrine reuptakeinhibitors, such as venlafaxine and duloxetine. Cutaneous electrostimulation, a nonpharmacological therapy appears, from an early pilot trial, to be potentially effective in the treatment of CIPN [4]. Chu SH points towards the need and importance of conducting well-designed RCTs to generate evidence on CIPN symptom management [29].

Since data on the effect of chemotherapy on peripheral autonomic nervous system is scarce, we are working on a project designed to evaluate the autonomic activity in patients receiving chemotherapy.

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