

Chemotherapy Induced Peripheral Neuropathy- A Mini Review

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Abstract

With the growing population of cancer survivors, the concept of quality of life (QOL) has become important. Chemotherapy-induced peripheral neuropathy (CIPN) is one such common, ailing chronic condition characterized by tingling sensation, pain and sometimes decreased function of hands and foot, which hampers the QOL of patients post chemotherapy treatment. A PubMed search for 'chemotherapy-induced peripheral neuropathy' was done. Despite the volume of recent publications, there are limited preventive or therapeutic strategies for CIPN supported by high-level evidence. Recently the effect of alternative non-pharmacological therapeutic approaches and predictive biomarkers have been explored. As CIPN still affects a majority of patients, there is a need for critical analysis of the literature. The present study aimed to review the literature on chemotherapy-induced peripheral neuropathy and its treatment or other possible interventions.

Keywords: Chemotherapy-induced peripheral neuropathy (CIPN), quality of life (QOL), biomarker.

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INTRODUCTION

Presently, cancer is one of the leading causes of mortality and morbidity worldwide. The incidence of malignancy is on the rise, both due to increased life expectancy as well as advancement in modern medical science and it is quick to leave behind other non-communicable disease and itself grab the top spot leading to maximum mortality. As per WHO estimates, cancer is the most common cause of death in 91 out of 172 countries. Also, GLOBOCAN 2018 reports 18.1 million new cases and 9.6 million cancer related deaths worldwide with half the load in Asia [1]. Due to the better and more sensitive diagnostic tools, a large proportion of cancer patients are being detected in early stage increasing the number of cancer survivors by 35% from 13.7 million in 2012 to 18 million by 2022 [2].

Chemotherapeutic drugs quite efficiently arrest the progress of malignancy, thereby increasing survival but due to this, their side effects are also being greatly observed in the patients which may range from hair loss, haematological toxicity, nausea, vomiting, diarrhoea, constipation, skin rash to neurological side effects etc. Chemotherapy induced peripheral neuropathy (CIPN) is the most common neurological syndrome secondary to administration of chemotherapy affecting approximately 68.1% within the first month of chemotherapy, 60.0% at 3 months and 30.0% at 6 months or more [3]. Most common type is the sensory

neuropathy and it has a significant negative impact on the quality of life often leading to treatment breaks and high rates of relapse. CIPN is usually related to the drugs used, cumulative dose or dose intensity, duration of treatment, or nerve damage caused by cancer itself or any pre-existing conditions, eg: diabetes or alcoholism.

In the view of its clinical importance, this review article aims to emphasize upon the etiopathogenesis, assessment, management as well as the newer treatment and predictive markers of CIPN.

Pathogenesis

There are multiple factors involved in the pathogenesis of neuronal disruption by chemotherapeutic agents. To list the most important factors:

- Microtubule disruption: Aggregation and bundling of microtubules not only changes the cell shape and hampers cellular stability but also responsible for impaired axonal transport of synaptic vesicles (ion channels and neurotransmitters).
- Mitochondrial damage (related to chronic CIPN): Formation of mitochondrial DNA adducts that can't be repaired leading to oxidative stress.
- Production of Reactive Oxygen Species (ROS): Increase superoxide anion production,

induces lipid peroxidation, protein and DNA oxidation causing structural changes of peripheral nerves, increases apoptosis through mitochondrial pathway.

- Altered activity of ion channels: Membrane excitability and neurotransmitter release altered due to damaged sodium channels (NaV), potassium channels (KV) and transient receptor potential (TRP) channels.
- Myelin sheath damage (by ROS).
- DNA damage.
- Immunological processes and neuroinflammation: Monocytes and

macrophages infiltrate the neurons resulting in production of several cytokines (TNF α , IL1 β , IL6), chemokines (CX3, CL1, CCL2, CCL3, CCL4, CCL5 and CXCL8) and bradykinin, prostaglandins and nitric oxide.

However, the greatest hindrance to most of the agents causing CIPN is the blood–brain barrier, so they target mainly the DRG and the afferent and efferent axons, because of lack of an effective blood–brain barrier. Below is a brief review of the mechanism of CIPN by different chemotherapeutic drugs [4-6].

Table-1: Mechanism of CIPN

Drug	Name	Cumulative Dose	Mechanism	Special Points
Platinum compounds	Cisplatin	Usually above 400 mg/m ²	Affects Dorsal Root Ganglion, damages vasa nervorum, neuronal inflammation	Always incomplete neurological recovery
	Carboplatin	>1600 mg/m ²		Reduced when given with pegfilgrastim or trastuzumab
	Oxaliplatin	540–850 mg/m ²	Calcium chelation by oxalate, increased apoptosis, ROS increased	Complete resolution in 6 months in 40%
Vinca alkaloids	Vincristine	>4 mg/m ²	Axonal transport damage by blocking polymerization into microtubules Metaphase arrest Neurofilaments accumulate in dorsal sensory ganglion	Complete recovery within 3 months after stopping
Taxanes	Paclitaxel	Single dose: 250 mg/m ² Cumulative dose: 480 mg/m ²	Neurofilament accumulated causing axonal transport disruption, altered excitability of neurons, damages Ca ²⁺ homeostasis	Delayed recovery
	Docetaxel	≥360 mg/m ²		
Immune modulators	Thalidomide Lenalidomide	>20 g	Decreases TNF α and expression of cell surface adhesion molecules required for leucocyte migration	
Proteasome inhibitor	Bortezomib	>30 mg/m ²	Increases TNF- α and IL-1 β Increases sphingomyelin metabolism Increased ROS production	Quick recovery (within 18 months)
Epothilones	Ixabepilone		Destabilizes type III beta tubulin	

Clinical Signs and Symptoms

Symptoms associated with CIPN are primarily sensory, though motor and autonomic symptoms are also reported. It predominantly affects small diameter nerve fibres leading to burning pain, hyperesthesia, loss of pain and temperature sensations. On the other hand, damage to large diameter nerve fibres cause loss of vibration sense, proprioception, and decreased nerve conduction velocity. Most commonly patients present with sensory disturbances like numbness, pain, paraesthesia, hypoaesthesia, and dysaesthesia. According to the International Association for the Study of Pain (IASP), neuropathic pain is defined as “pain caused by injury or disease of the somatosensory system”. Neuropathic pain is described mainly in the extremities, particularly fingertips and toes and is associated with damage of all three fibre types—A β , A δ , and C primary afferent fibres. Affected areas demonstrate an increase in sharpness-detection threshold (hyperalgesia) and lower skin temperature when compared with the unaffected areas. Neuropathy may simultaneously affect both the upper and lower extremities as also the cranial nerves. Symptoms usually develop late, weeks to months after

chemotherapy completion and their severity is directly proportional to the cumulative dosage.

Motor deficits are less common and is seen in patients suffering from severe sensory disturbances but pure motor neuropathy is extremely rare. Even, deep tendon reflexes, two-point discrimination, and temperature sensation may be affected. Motor symptoms are not usually reported but elicited mainly on clinical examination. Autonomic dysfunction presents as orthostatic hypotension, cardiovascular, erectile dysfunction, or gastrointestinal disturbances.

However, the prevalence of CIPN is drug-dependent, rates varying from 19% to 85%. It is highest with platinum-based drugs (70–100%) followed by taxanes (11–87%), thalidomide and its analogues (20–60%), and ixabepilone (60–65%) [7]. These toxicities are reported both after a high single dose or after cumulative exposure and tend to resolve at the completion of therapy. Mostly, these neuropathies improve when the offending drugs are withdrawn (e.g. bortezomib, thalidomide), except for cisplatin and oxaliplatin where CIPN continue to progress even after

the drug has been stopped. Chronic CIPN associated with cisplatin has been observed in 5–20% of patients even 12 months after cessation of therapy.

Some special symptoms associated with the chemotherapeutic agents are as follows:

- Cisplatin: dorsal column myelopathy and bilateral jaw pain.
- Oxaliplatin: Cold-induced neuropathy, pharyngo-laryngeal dysesthesia, coasting (progression of sensory loss even after completion of chemotherapy which may present as late as 3–6 months).
- Vincristine: Earliest sign is the blunting of deep tendon reflexes (hyporeflexia), especially the ankle reflex.
- Paclitaxel: Mechanical allodynia, cold allodynia, persistent burning pain, tingling, and numbness. Light touch and vibration are the most commonly affected sensations.
- Bortezomib: Pain symptoms typically manifest before the fifth cycle of treatment.
- Thalidomide: glove and stocking distribution, even may induce motor impairment and gastrointestinal and cardiovascular autonomic symptoms.

Diagnosis

Under ideal conditions, CIPN can be diagnosed by taking a detailed history and performing a complete neurological examination. The most sensitive clinical signs are impaired vibration sense,

proprioception and two-point discrimination. On conducting quantitative sensory testing (QST), it is seen that there is an increase in touch threshold, abnormal cold as well as pain threshold and decrease in detection of sharpness. But grading of CIPN accurately is difficult since it is subjective, depends on perception of patients and thus QST may help to play in identify early CIPN.

Diagnosis of CIPN is difficult because nerve conduction tests and electromyography which are used routinely for diagnosis of neuropathy are insensitive during early stages although the patients are symptomatic. Reliable data on conduction of small fibres are not obtained from the nerve conduction velocity (NCV) because they measure velocity and amplitude in the large diameter fast conducting nerve fibres. Another drawback of NCV is that it demonstrates the status of surviving fibres only without any details of the fibres affected. However, the gold standard for CIPN diagnosis is electroneuromyography (ENMG). This can detect the neuropathological involvement by depicting the behaviour changes of nerves, specially myelinated nerve fibres. Most common pattern of involvement seen in ENMG is absent or decreased amplitude of sensory potential, particularly in the sural nerve.

Grading

Clinical oncologists use various grading scales to determine the severity of neuropathy, most commonly used is the NCI-CTC toxicity grading.

Table-2: Grading Of CIPN

Scale	Grade 0	Grade I	Grade II	Grade III	Grade IV
WHO [8]	None	Paraesthesia, decreased tendon reflexes, or both	Severe paraesthesia, mild weakness, or both	Intolerable paraesthesia, marked weakness, or both	Paralysis
ECOG [9]	None	Decreased tendon reflexes, mild paraesthesia, mild constipation	Absent tendon reflexes, severe constipation, mild weakness	Disabling sensory loss, severe peripheral neuropathic pain, obstipation, severe weakness, bladder dysfunction	Respiratory dysfunction, secondary to weakness, obstipation requiring surgery, paralysis confining the patient to bed/wheelchair
NCI-CTC: sensory neuropathy [10]	None	Loss of deep tendon reflexes or paraesthesia (including tingling) but not interfering with function	Objective sensory loss or paraesthesia (including tingling) interfering with function, but not interfering with activities of daily living	Sensory loss or paraesthesia interfering with activities of daily living	Permanent sensory loss that interferes with function
NCI-CTC: motor neuropathy [10]	None	Subjective weakness but no objective findings	Mild objective weakness interfering with function, but not interfering with activities of daily living	Objective weakness interfering with activities of daily living	Paralysis
Ajani sensory neuropathy [11]	None	Paraesthesia, decreased deep tendon reflexes	Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional abnormality	Severe paraesthesia, moderate objective abnormality, severe functional abnormality	Complete sensory loss, loss of function
Ajani motor neuropathy (11)		Mild or transient muscle weakness	Persistent moderate weakness but ambulatory	Unable to ambulate	Complete paralysis

Management and Prevention

Various agents have been tried to prevent CIPN which include vitamin E, aminophosphatine, glutathione, adrenocorticotrophic hormone analogues (ACTH) and diethylcitocarbamate but till date none of their roles have been established. A meta-analysis including three retrospective and four prospective trials showed calcium and magnesium infusion was associated with a lower incidence of grade III acute neurotoxicity (OR=0.26, $p=0.0002$). Similarly, cumulative and late toxicity was also reported to be less in the group receiving infusions of calcium and magnesium (OR=0.42, $p=0.0001$ and OR=0.60, $p=0.02$ respectively). No differences were observed in progression-free survival, overall survival or response rate, thus proving that the efficacy of chemotherapy is not affected by administration of calcium and magnesium [12]. However, these results were refuted by N08CB trial where the investigators reported no advantage with administration of ions, similar rates of cumulative neurotoxicity, acute neurotoxicity and chemotherapy discontinuation in all the study arms [13].

Tricyclic anti-depressants have been used to treat CIPN because they interact with the serotonin and norepinephrine neurotransmitter system. CALBG 170601 trial was the first large phase III double blinded placebo-controlled study which evaluated the efficacy of duloxetine (serotonin–norepinephrine re-uptake inhibitor) in CIPN induced by oxaliplatin or taxanes [14]. The regimen followed was one tablet (30mg) per day during first week followed by 2 tablets (60mg) per day for four weeks. As compared to placebo arm, the relative risk of pain reduction by 30% was 1.96 and by 50% was 2.43 with duloxetine. Those patients treated with oxaliplatin had greater advantage than those treated with taxanes. Also, significant improvement in quality of life was observed with duloxetine. Another drug which has shown some benefit in treatment of chronic neurotoxicity induced by oxaliplatin and paclitaxel is venlafaxine. Two other small trials investigated the role of amitriptyline (maximum dose of 50 mg/day) and nortriptyline (maximum dose of 100 mg/day) in management of CIPN but both trials failed to depict any significant improvement in symptomatic relief or quality of life [15, 16].

Another randomized placebo-controlled study NCCTG N06CA has evaluated the role of baclofen (10mg), amitriptyline (40mg) and ketamine (20mg) in a lecithin in organogel (BAK-OLP) versus placebo (OLP) for the treatment of CIPN. This topical application resulted in little though statistically significant improvement of both sensory and motor symptoms ($p=0.021$) when compared to placebo group in the absence of undesirable local toxic effects or systemic toxicity [17].

In CIPN, there is neuronal hyperexcitability due to alteration of various ion channels as also occurs in painful peripheral neuropathy. Anti-epileptic drugs act by decreasing their excitability. Both gabapentin and pregabalin up-regulates $\alpha 2 \delta 1$ subunit of voltage dependent calcium channels reducing the neuronal excitability. Two trials to evaluate the effect of anticonvulsants on CIPN management were unable to demonstrate any benefit of either gabapentin (target dose 2700 mg/day) or lamotrigine (target dose of 300mg/day) [18, 19] on pain relief (calculated both on ECOG neuropathy and numerical rating scale). Ethosuximide (300 mg/kg), selective T-type calcium channel blocker, has shown almost complete reversal of paclitaxel-induced mechanical allodynia/hyperalgesia as also vincristine and paclitaxel-induced cold allodynia [20].

Role of Alternative Medicine

Since no curative pharmacological management is available, so patients also seek alternative medicine help for pain relief. A pilot trial conducted in Korea on breast cancer patients suffering from paclitaxel induced peripheral neuropathy reported significant pain improvement with acupuncture administered 3 times a week for 4 consecutive weeks, 25 ± 5 minutes at each session and the effect lasted for at least 4 weeks [21]. Physical rehabilitation may be useful to prevent muscle wasting and to assist mobilization. Nowadays, neuromodulation therapy is used for management of resistant cases of neuropathic pain. Also, spinal cord stimulation and DRG stimulation may have some role in the management of resistant CIPN patients though at present, no evidence supports its use.

Role of Predictive Biomarkers

Predictive biomarkers can foresee the risk of patient developing the said condition in response to a particular course of treatment. Diaz *et al* have extensively studied the predictive genetic models to detect CIPN and concluded ARHGEF10 rs9657362, CYP2C8 rs11572080/rs10509681 and FGD4 rs10771973 to be associated with the same [22]. All of them affect drug metabolism by complex pathways when mutated by single nucleotide polymorphism. A systematic review and meta-analysis by Marta Seretny *et al.*, reported CIPN was associated with polymorphisms involving voltage-gated sodium channels, proteins related to Schwann cell function, cell surface receptors for collagen, receptors involved in neuronal apoptosis, development of neuronal crest cell and an enzyme involved in metabolism of pyruvic acid.

CONCLUSION

CIPN is one of the severe side effects related to management of malignancy that negatively affects therapeutic efficacy. Although modern chemotherapeutic agents are being modified such that

they have minimal side-effects, still platinum based compounds, taxanes and vincristine are widely used in the management of common cancers which are notorious for causing CIPN. Improved preventive, diagnostic and management strategies are warranted to reduce the incidence, prevalence and severity of CIPN. Also, more research works are needed in this field to simplify the complex pathogenesis and for development of targeted therapy including gene therapy, if needed. Though, alternate medicine and predictive biomarkers have a potential role to play, confirmatory findings are warranted.

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