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Chemotherapy-Induced Peripheral Neuropathy: Pathophysiology, Diagnosis, and Treatment

Ica Justitia[1], Putri Krishna Kumara Dewi[2], Yanuar Rahmat Fauzi[3], Ilsa Hunaifi[4]
[1] Meninting Public Health Center, West Lombok District Health Office, West Lombok, Indonesia
[2] Department of Biomedical Science, Faculty of Medicine, Universitas Pendidikan Ganesha, Bali, Indonesia
[3] Department of Medical Science, University of Miyazaki, Miyazaki, Japan
[4] Department of Neurology, Faculty of Medicine, Universitas Mataram, Mataram, Indonesia

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common and severe neurological side effect of many commonly used chemotherapy agents. It affects more than 60% of cancer patients. Approximately 30%–40% of patients have persistent symptoms five months or longer after stopping treatment. Even years after completing chemotherapy, some patients still experience CIPN symptoms. CIPN increases the annual cost of healthcare, leads to detrimental dose reduction and even cessation of treatment, and severely affects cancer survivors' quality of life. Chemotherapy induces neurotoxicity through a variety of mechanisms that lead to neuronal cell damage or cell death. This mechanism of neurotoxicity varies depending on the specific agent. CIPN is characterized predominantly by sensory axonal peripheral neuropathy. Motor and autonomic symptoms may appear, but less frequently. To diagnose CIPN, a thorough patient's history and neurological examination are required. The current approach to CIPN management focuses on managing the symptoms of neuropathic pain and reducing or stopping the chemotherapy agent when CIPN manifests. There is no proven or advised prophylaxis therapy for CIPN. The point of this review was to talk about how some commonly used chemotherapy agents (such as platinum-based compounds, taxanes, vinca alkaloids, bortezomib, and thalidomide) cause CIPN, how to diagnose it, and the newest treatments that are available.

Corresponding Author
Ilsa Hunaifi
Department of Neurology, Faculty of Medicine, Universitas Mataram, Mataram, Indonesia
email: ilsahunaifi@unram.ac.id

INTRODUCTION

Peripheral neuropathy is defined as damage to the peripheral nervous system. It can affect the cell body, the neuron, and the axon.[1] Several factors, including diabetes mellitus, vitamin deficiencies, nerve compression, alcohol use, infection, hereditary disease, toxin exposure, and drugs, such as chemotherapy agents, may cause peripheral neuropathy.[2] Chemotherapy agents can cause peripheral neuropathy, known as chemotherapy-induced peripheral neuropathy (CIPN). It's the most common and severe side effect of many chemotherapeutic agents, like platinum-based compounds, taxanes, vinca alkaloids, proteasome inhibitors, and thalidomide analogs.[3,4] These chemotherapeutic drugs serve as the first line of treatment for cancers of the breast, lungs, testicles, prostate, ovary, gastrointestinal tract, blood, or bone marrow.[5]

Complex factors and processes, which vary depending on the type of chemotherapy drugs used, influence the development of CIPN. Platinum compounds damage the DNA's structure. Taxanes and vinca alkaloids cause microtubule dysfunction. The proteasome inhibitor boratezomib appears to promote cell death and inhibit normal cell growth rates.[6]

Acute symptoms of CIPN may appear in the hours and days following the drug infusion. One month after finishing chemotherapy, approximately 68% of patients experience persistent neuropathy symptoms. About 30% to 40% of patients experience persistent symptoms five months after chemotherapy or longer. Even years after chemotherapy, some patients report CIPN symptoms.[5,7] Nowadays, as cancer survival rates increase, so does CIPN prevalence. CIPN makes it more likely for cancer patients to suffer from functional impairment and reduced quality of life.[8]

CIPN increases annual healthcare costs, leads to detrimental dose reduction and even cessation of treatment, and severely affects cancer survivors' quality of life.[3,9] Patients with painful CIPN face a significant financial burden compared to those without the condition, primarily due to the high costs of prescription analgesic drugs, a higher rate of hospitalization, emergency visits, and outpatient hospital visits.[10] On average, those with CIPN require 12 more outpatient visits, three more hospital days, and USD 17,000 more in medical expenses. CIPN can significantly hinder the physical, emotional, functional, social, economic, and occupational components of life.[5,10]

Some studies show how CIPN greatly affects the quality of life of cancer patients. In lung cancer patients receiving platinum-based chemotherapy, CIPN may limit the patients' physical activity, independence in daily living, and ability to take care of themselves.[11] Cancer survivors with higher CIPN levels than those with lower levels reported higher anxiety and depression symptoms.[12] Meanwhile, the treatment and prevention of CIPN are extremely challenging.

Given the severe impact of CIPN on cancer patients, further investigation is necessary to understand this phenomenon fully. It is conducted by answering three main questions: What causes CIPN? How to diagnose CIPN? And what are the recent treatments for CIPN? Therefore, this article discussed the pathophysiology, clinical appearance, diagnosis approach, and recent treatment available for CIPN.

For this review, relevant articles were searched. The search was conducted for English-language articles that were published in the last ten years through the National Center for Biotechnology Information (NCBI)/PubMed database, the ResearchGate database, the American Society of Clinical Oncology Journal, and other relevant sources. Databases were searched using the combination of keywords "chemotherapy," "chemotherapy-induced," "peripheral neuropathy," "pathophysiology," "diagnosis," and "treatment". The exclusion criteria included articles that did not specifically address peripheral neuropathy caused by drugs and chemotherapy agents, as well as those with inconclusive and unclear recommendations. This review included articles that passed the screening and were available in free full-text format.

REVIEW

CIPN Pathophysiology

Chemotherapy-induced neuropathy can impact any neuron, especially the peripheral neurons, which are not shielded by specific structures like the blood-brain barrier. The effects of the chemotherapeutic agents on the peripheral nervous system depend on the characteristics of the drug, mechanism of action, and dosage. This neurotoxicity may occur directly through the drug's direct interaction with the neuron cell, or indirectly through glial damage, inflammation, and other mechanisms. As a result, patients receiving anti-cancer treatment may experience a wide range of CIPN symptoms.[13]

a. Platinum-based compounds

The drugs in this group are cisplatin (first generation), carboplatin (second generation), and oxaliplatin (third generation).[13] Platinum-based drugs are typically used to treat solid tumors of the ovary, uterus, lung, head and neck, bladder, and gut.[10] All platinum-based compounds bind specifically to guanosine and adenosine, making DNA crosslinks that

inhibit replication and transcription, leading to cell cycle arrest and programmed cell death. Neuronal DNA crosslinks are the primary mechanism for its neuropathic side effects. Platinum agents may also permanently attach to mitochondrial DNA (mtDNA). This triggers mitochondrial depletion. As a result, the number of mitochondria in neural cell bodies decreases, reactive oxygen species increase, and oxidative stress increases.[9,13,14] The main anatomical structure affected is the dorsal root ganglion (DRG), which manifests as sensory neuropathy. Due to its location outside of the central nervous system and lack of blood-brain barrier protection, the DRG is especially vulnerable to chemotherapeutic agents.[9]

Cisplatin induced more neuropathy than carboplatin and oxaliplatin. The administration of oxaliplatin did not have a positive effect on macrophage infiltration or accumulation. As a result, using a macrophage depletory did not improve the neuropathic symptoms.[13] Additionally, oxaliplatin binds with voltage-gated potassium channels (VGKC), which are expressed on peripheral motor neurons. This interaction is linked to the acute phase of oxaliplatin-induced neuropathy, when patients had symptoms resembling neuromyotonia, such as prolonged depolarization, enhanced neurotransmission, and hyperexcitability of the nerves.[13]

b. Anti-microtubule Agents

Taxanes

Paclitaxel, docetaxel, and cabaliztaxel are the drugs in this group. Taxanes are the first-line treatments for cancers of the breast, ovaries, lungs, pancreas, bladder, prostate, and other solid tumors.[13,15] Taxanes cause neuropathy in a dose-dependent manner. Taxanes target the microtubules. Microtubules are cytoskeletal proteins that play essential roles in cell functions such as cell shape regulation, mitosis, chromosome segregation, and retrograde and anterograde cellular transport. Microtubule function rides on a balance of permanent aggregation and disaggregation of the α- and β-tubulin subunits. Taxanes promote microtubule polymerization (inhibit tubulin disassembly) by binding β-tubulin subunits. This could alter mitotic spindles, inhibit regular mitosis, and cause apoptosis. Studies have shown that paclitaxel alters acetylated tubulin; however, tubulin expression quickly returns to normal levels following drug treatment cessation.[9,13]

Mitochondrial damage has been also proposed as a mediator of paclitaxel-induced pain.[9,13] When paclitaxel interferes with the mitochondrial permeability transition pore, it causes mitochondrial dysfunction, reduces mitochondrial respiration, and interferes with the neurons' ATP production. Rats given taxane had higher levels of reactive oxygen species (ROS) and oxidative stress. They also exhibited reduced mitochondrial metabolic activity, membrane potential, and antioxidant bioavailability. Taxane, in addition, upregulates toll-like receptor (TLR) 4 and increases pro-inflammatory cytokine production.[10] In vitro studies showed that co-administration of paclitaxel and probiotics normalizes TRPV4 and acetylated α-tubulin expression. This study was supported by the discovery that probiotic-treated mice did not develop mechanical hypersensitivity during paclitaxel treatment.[13]

Vinca Alkaloids

The vinca alkaloids include vincristine, vinblastine, and vinorelbine.[13] Vinca alkaloids are used primarily in hematological malignancies as monotherapy or in combination with other drugs.[3,10] Vinca alkaloids cause sensory-motor neuropathy, with vincristine having the most severe neurotoxicity of all.[13] Similar to taxanes, vinca alkaloids also target microtubules. Rather than providing structural stability, they bind to the β-tubulin subunit and block microtubule formation (microtubule aggregation). They disrupt the microtubular α-tubulin polymerization process. As a result, the mitotic spindle cannot form.[9,13] According to recent preclinical data, SARM1 (sterile alpha and TIR motif containing 1), a protein that helps with Wallerian degeneration, seems to play a substantial role in degeneration of axon caused by vincristine.

c. Bortezomib

Bortezomib, a proteasome inhibitor, was newly discovered compared to the other chemotherapeutic drugs and has been applied to managing various hematologic malignancies.[13] Bortezomib kills cancer cells by inhibiting the 20S core proteasome, suppressing the unfolded protein response, accumulating ubiquitinated proteins, stabilizing tumor suppressor proteins like p21, p27, Bax, and p54, and increasing reactive oxygen species.[13] Bortezomib is also linked to the dysregulation of intracellular calcium, thus inducing apoptosis. Bortezomib has been demonstrated to change nerve action potentials and decrease nerve conduction velocities in the peripheral nerves. However, there is still no clear explanation for how precisely bortezomib causes peripheral neuropathy.[13,16]

d. Thalidomide

Thalidomide is used to treat several cancers, including multiple myeloma, glioblastoma, melanoma, renal cell carcinoma, breast and prostate cancer, as well as colorectal and lung carcinoma.[10] The exact mechanisms by which thalidomide fights cancer are unknown; it involves speeding up cell death by inhibiting NF-κB activation and TNF-α production. The mechanisms underlying thalidomide-induced chemotherapeutic effects have been proposed as the

mechanisms of thalidomide-induced neuropathy.[3,13]

e. 5-Fluorouracil (5-FU)

5-Fluorouracil has the ability to bind to DNA and change the nucleotide sequence. Increased dosages may cause RNA dysfunction, disrupt cellular protein synthesis, and trigger apoptosis, resulting in CIPN.[13]

f. Cyclophosphamide, Alkylating Agents

Cyclophosphamide's mechanism of action is similar to that of platinum compounds. Cyclophosphamide creates crosslinks between the two DNA strands at the guanine N-7 position. Thus, it prevents cell replication and repair, which ultimately results in cell death.[13]

Central Neurotoxicity

Some studies have revealed that the central nervous system plays a role in the pathophysiology of CIPN. The brain alterations observed in CIPN are more likely the result of neurotoxic chemotherapy's indirect effects on the brain. CIPN is associated with hyperactivity and hyperexcitability in various brain regions, as well as reduced GABAergic inhibition in the brain. Both alter the excitatory/inhibitory balance and produce a molecular milieu that encourages neuronal hyperactivity. However, this hypothesis still needs more attention and research.[5]

Clinical Manifestation

In most patients, the clinical manifestations of CIPN are dose-dependent and appear after multiple rounds of neurotoxic chemotherapy. The onset of CIPN is a sign that the chemotherapy agent should be stopped or its dose reduced. This could make cancer treatment more difficult.[3] The CIPN primarily affects the sensory neuron because of the likely damage to the DRG.[3,5] Sensory symptoms typically start in the lower limbs and progress to the upper extremities, extending from toes and fingertips in a distal symmetric pattern resembling socks and gloves. The longest peripheral axons are particularly susceptible to toxic drugs. The majority of patients (± 68%) experience simultaneous upper and lower limb symptoms.[7] Neuropathic pain, sensory loss, and cold-induced pain in the mouth, throat, hands, and feet (cold allodynia) are the symptoms that can be found in patients. Sensory ataxia and loss of balance are sometimes present in patients. Symptoms of the motor (e.g., muscle cramps, paresis, diminished reflexes), autonomic (e.g., orthostatic hypotension, cardiovascular or urogenital dysfunction, gastroparesis), and cranial nerves can also arise, but are less common.[3,5,7] The clinical manifestations of each chemotherapy agent are reviewed below.

a. Platinum-based Compounds

Platinum-based agents have a significant impact on around seventy percent of patients, which is the highest prevalence rate for CIPN.[10] Every platinum compound in routine use causes long-term peripheral sensory damage. Carboplatin is thought to be less neurotoxic compared to cisplatin. Oxaliplatin-induced acute neuropathic pain frequently manifests as cold-induced allodynia, which is most severe in the hands, face, and mouth. One might experience excruciating pain from a cold drink or a cold wind on their face. The symptoms usually start during the second or third treatment cycle and continue for two to four days following the infusion.[3] The essential feature of CIPN in platinum-based compounds is the phenomenon known as "coasting." This is linked to the discovery that once therapy is stopped, CIPN from platinum-based agents, particularly cisplatin and oxaliplatin, may worsen for a few months. The symptoms may progress to chronic sensory neuropathy. The patient and the doctor find it distressing because they hope that when the chemotherapy is stopped, the patient's neuropathic symptoms will stabilize or improve.[3] Peripheral neuropathy caused by acute oxaliplatin use may necessitate a longer infusion time (~22%), dose reduction (15–43%), and the completion of treatment (6–21.4%).[10]

b. Taxanes

Taxanes are also frequently used and typically cause dose-dependent, painful, and length-dependent sensory neuropathy.[3] The incidence of taxane-induced neuropathy was around 30% when paclitaxel was used as a single agent in breast cancer. When combined with carboplatin at a lower dose to treat ovarian cancer, the incidence fell to 6%. However, adding platinum chemotherapy to paclitaxel has been shown to increase the incidence of neuropathy by up to 70%.[17] Taxane-induced neuropathy mostly impacts small-diameter sensory fibers, leading to changes in proprioception, paresthesias, dysesthesias, and numbness in a way that looks like stockings and gloves. Autonomic and motor dysfunction are less common.[13] The usual symptoms, including tingling, numbness, paresthesia, neuropathic pain, cold-induced dysaesthesia, and muscle cramps, will gradually improve with treatment cessation. However, 31-44% of patients treated with docetaxel and paclitaxel report symptoms that remain up to 6 years after chemotherapy cessation. Peripheral neuropathy is the most common non-hematological adverse event in taxanes.[10]

c. Vinca Alkaloids

Vinca alkaloid neuropathy develops in a dose-dependent way and typically causes length-dependent sensory neuropathy that is frequently accompanied by

some degree of motor impairment and infrequent involvement of the cranial nerve.[3,10] Vinca alkaloids-neuropathy symptoms usually appear in the distal lower extremities and develop proximally. The symptoms include reduced touch, vibration, and temperature sensation, as well as decreased deep tendon reflexes.[17] They may have late, residual, and long-term neuropathic side effects, especially in young adults and children.[3,10]

d. Thalidomide

Thalidomide causes mostly sensory neuropathy.[3] Thalidomide-induced neuropathy is identified by prominent paresthesia in the hands and feet, as well as numbness and mild motor dysfunction.[17]

e. Bortezomib

Bortezomib induces a painful, length-dependent transient distal axonopathy, as well as small-fiber predominant axonal sensory neuropathy. Bortezomib also induces mild motor weakness in the distal lower extremities. Recently, it has been discovered that subcutaneous administration of bortezomib reduces the risk and severity of neuropathy.[3]

Diagnosis Approach to Chemotherapy-Induced Peripheral Neuropathy (CIPN)

There is no definitive test to diagnose CIPN, but the condition can be identified based on the patient's history, symptoms, neurological examination, and chemotherapy type and dose.[5] When assessing a cancer patient who develops neuropathy, it is important to look at the drugs given, the cumulative dosage, the patient's clinical features, and the progression of their neuropathic symptoms to determine whether or not they have CIPN.[3] Firstly, *has the patient undergone any neurotoxic chemotherapy?* Platinum compounds, taxanes, vinca alkaloids, bortezomib, and thalidomide have a significant chance of causing CIPN. In contrast to cyclophosphamide and methotrexate, the probability is low. Second, *it is essential to consider the route of drug administration.* Bortezomib's neurotoxicity is reduced when administered subcutaneously. Administering methotrexate intravenously will result in neurotoxicity. Third, *has the patient received the dosage for CIPN*? Most CIPN occurs dose-dependently.[3] Table 1 lists the most commonly used drugs and estimates the cumulative dose linked to CIPN.

Documenting neurotoxic complaints and quality of life can be used to help support the diagnosis. Some questionnaires like the EORTC QLQ-CIPN 20 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN-twenty-item scale) or NCI-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events) can be used to collect this information. The QLQ-CIPN 20 is a questionnaire consisting of 20 items that assess sensory, motor, and autonomic symptoms and function. Each item is rated on an ordinal scale from 1 to 4 (1, not at all; 4, very much). The NCI-CTCAE rates both motor and sensory neuropathy according to four levels of neurotoxicity: asymptomatic (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4).[7,10] Nerve conduction studies and electromyography can be used to support the clinical diagnosis of CIPN.[7]

It is crucial to exclude other possible causes of neuropathy, such as metabolic and paraneoplastic before diagnosing cancer patients with CIPN.[3] Diabetes, alcoholism, hypothyroidism, anemia, renal insufficiency, and radiculopathy are risk factors that increase patients' risk of developing CIPN.[7,14] Identifying these risk factors is also important for the patient's diagnosis and treatment.

Table 1. Chemotherapeutic agents and their cumulative dose, symptoms, and signs. [7,9,10]

Chemotherapeutic agents		Cumulative dose	Symptoms/Signs	Progression
Drug	Class			
Oxaliplatin (acute)	Platinum	≥ 85 mg/m^2	Sensory: cold-induced allodynia, throat discomfort, tingling, numbness, pain in the hands and feet, fasciculation.	Acute: may lead to dose reduction or treatment cessation. Does not resolve between cycles.
Oxaliplatin (chronic)	Platinum	≥ 510 mg/m^2	Sensory: distal and symmetrical loss of sensation in the hands and feet, along with pain. Symptoms become more predominant in the feet after ±18 months. Motor: muscle cramps, fasciculations.	Coasting phenomenon

Cisplatin	Platinum	≥ 300 - 350 mg/m^2 ≥ 600 mg/m^2 ≥ 780 mg/m^2	Cisplatin implicated in ototoxicity. Sensory: cold-induced dysesthesias. Motor: muscle cramps, neuromyotonic, muscle weakness, fine motor impairment. There is a decrease of loss of deep tendon reflexes. Autonomic: orthostatic hypertension	A proportion of participants recovered, although not back to pre-chemotherapy baseline
Carboplatin	Platinum	≥ 400 mg/m^2	Sensory: distal and symmetrical loss of sensation in the hand and feet. Motor: large fiber involvement, ataxia; reduction or loss of deep tendon reflexes.	Acute: may lead to dose reduction or stopping treatment. Can progress to chronic Coasting effect.
Paclitaxel	Taxanes	≥ 100 mg/m^2	Sensory and motor neuropathy, predominantly sensory Mononeuropathies Paclitaxel acute pain syndrome: aching pain, arthralgia, myalgia, and muscle cramps in the lower extremities.	The severity of acute symptoms may lead to dose reduction or treatment discontinuation, and it is predictive of chronic and higher-grade neuropathy. Acute pain may not resolve between cycles.
Docetaxel	Taxanes	≥ 300 mg/m^2	Sensory and motor neuropathy, predominantly sensory Acute, length-dependent distal sensory neuropathy characterized by numbness and tingling, pain in a stocking-and-glove distribution Frequently neuropathic pain in the hands and feet Motor: reduction and /or loss of deep tendon reflexes, possible proprioceptive loss leading to unsteady gait, facial nerve palsy Rare autonomic: orthostatic hypotension paralytic ileus, arrhythmia, optic neuropathy	Recovery or improvement, once treatment is stopped in the majority of patients, although rarely back to normal pre-chemotherapy baseline. Some patients continue to persist with low-grade symptoms.
Vincristine Vinblastine Vinorelbine	Vinca alkaloids	≥ 4 mg/m^2	Predominantly sensorimotor: distal and symmetrical loss of sensation in the hands and feet characterized by numbness and tingling, pain; taste impairment, loss of sensory discrimination Motor: distal symmetric weakness in lower legs, walking difficulties, muscle cramps, foot drop, impaired fine motor skills, decrease of deep tendon reflexes Autonomic: orthostatic	Acute: may lead to dose reduction or stopping treatment. Progression to chronic has established genetic risk factors. Children and adolescents tolerate higher cumulative doses than adults.

			hypotension, paralytic ileus, constipation, urogenital dysfunction.	
Thalidomide	Immuno-modulator	≥ 50 mg/day	Sensory: distal and symmetrical loss of sensation in the hands and feet, characterized by hyperesthesia, hypoesthesia, and paraesthesia. The hands and feet experience numbness, tingling, burning pain, sensitivity to touch, and heat. Motor: distal weakness, tremor, muscle cramps, reduction and/or loss of deep tendon reflexes, loss of proprioception, gait ataxia.	Acute can progress to chronic. Long-term neurotoxic sequelae are uncommon. Treatment duration may be more neurotoxic than dose.
Bortezomib	Protease Inhibitor	≥ 1 mg/m^2	Sensory: distal symmetrical, length-dependent axonal sensorimotor neuropathy, mild to moderate sensory loss, and mid- to severe neuropathic pain in glove-and-stocking distribution; burning sensations, tingling, hyperesthesia, hypoesthesia, and weakness in the distal extremities, which may progress proximally. Motor: mild to moderate motor weakness in the distal lower extremities. Autonomic (rare): orthostatic hypotension.	It can progress from acute to chronic, although a majority of participants improve or completely resolve peripheral neuropathy.

Treatment of CIPN

The current approach to managing CIPN focuses on assessing patient symptoms, managing neuropathic pain symptoms, and reducing or stopping the chemotherapy agent when CIPN manifests. The appropriateness of dose delaying, dose reduction, or stopping chemotherapy (or substituting with other chemotherapy agents that do not cause CIPN) should be thoroughly assessed by clinicians in the treatment of cancer patients who experience CIPN. They should also engage in discussions with patients and use multidisciplinary approaches.[3,6,18] Systemic medications should be gradually increased from a low starting dose to a dose that offers the best effectiveness and the fewest side effects.[7]

Duloxetine was proven to be effective in CIPN with established neuropathic pain.[3,6,18] Clinical doses of duloxetine commonly range from 60 to 120 mg daily.[16] Duloxetine's side effects are usually light and include nausea, poor appetite, constipation, and drowsiness. Patients who have a creatinine clearance of less than 30 ml/min should avoid using duloxetine.[19] Duloxetine had the most impact on managing CIPN caused by platinum compound agents.[6] There are also some potential unproven interventions available, such as tricyclic antidepressants, antiepileptic drugs, opioids, topical preparations (e.g., lidocaine patch, capsaicin patch, gel formulation), exercise, acupuncture, and scrambler therapy (peripheral nerve stimulation).[5,7]

A study with nortriptyline (tricyclic antidepressants) in patients (n = 51) with cis-platinum-induced peripheral neuropathy showed a minor and unclear benefit. Nevertheless, tricyclic antidepressant medicines make sense to try since the limited alternatives for CIPN treatment, but they are not advised for frequent prescriptions. In a randomized cancer study, pregabalin outperformed amitriptyline, gabapentin, and placebo in treating neuropathic pain and related adverse effects. However, in a double-blind placebo-controlled trial that only treated CIPN symptoms in patients who received vinca alkaloid, platinum-based, or taxane agents, there was no benefit from the use of gabapentin or pregabalin. Opioids are used as a third-line option. Lidocaine patches could be a second-line treatment. In Europe, the capsaicin patch is approved for topical treatment of CIPN peripheral

neuropathic pain. Gel formulations with 1.5% ketamine, 3% amitriptyline, and 0.8% baclofen were mildly beneficial for CIPN patients.[7,19] Further investigations are needed, however, to verify the effectiveness and assess the treatment risks associated with the use of these topical agents.

A safer and more efficient treatment strategy could require combination therapy for neuropathic pain. For example, morphine plus gabapentin significantly decreased neuropathic pain compared to either medication alone in a randomized controlled trial. However, more clinical trials are needed to examine combination therapy specifically for CIPN.[7]

In addition to pharmacological therapy, certain non-pharmacological approaches have been reported to be useful in the treatment of CIPN. Exercise, in general, is a promising supportive treatment for patients with CIPN. In a scoping review of randomized controlled trials, Jones *et al.* found that sensorimotor training and whole-body fibration are effective in reducing pain, sensory, and motor symptoms, whereas yoga is both safe and effective in reducing CIPN pain and improving quality of life.[20]

Two trials in the systematic review of acupuncture for CIPN treatment found that acupuncture improved self-reported CIPN measures. A recent systematic review of 19 RCTs involving 1174 patients revealed that acupuncture significantly reduced pain and surprisingly improved nerve conduction velocity.[10] Patients experience less pain, numbness, and tingling after a six-week acupuncture course.[21]

Scrambler therapy is intended to substitute endogenous pain signals. Two-stage phase II randomized trials evaluating scrambler therapy showed scrambler therapy seemed to effectively treat painful CIPN. More studies in this field are required.[18,19] Several new treatments are being investigated to find a better way to treat or prevent CIPN. Some of these are axonal degeneration, botulinum toxin injection, mitochondrial enzymes, immunomodulation, neuronal transporter inhibition, and targeting endonuclease function.[19]

Prevention of CIPN

There is still no proven or advised prophylaxis therapy for CIPN.[3,7,18] Vitamin A, antioxidants (e.g., vitamin E, glutathione), and omega-3 were not suggested since there were no advantages for CIPN prevention.[10,16] According to a recent American Society of Clinical Oncology (ASCO) guideline, clinicians should discourage the use of acetyl-l-carnitine (strong recommendation) for CIPN prevention and make no recommendations for acupuncture, cryotherapy, compression therapy, exercise therapy, or ganglioside-monosialic acid for CIPN prevention.[18] Developing CIPN-preventing agents is challenging because any medication may also reduce the effectiveness of the chemotherapeutic treatment.[3]

CONCLUSION

Chemotherapeutic drugs can induce neurotoxicity and neuron cell death, thus causing peripheral neuropathy. The CIPN is characterized predominantly by sensory symptoms. Motor and autonomic symptoms are less frequent. The current approach to managing CIPN is focused on evaluating and managing the symptoms of neuropathic pain. Only duloxetine was found helpful in managing the CIPN pain. Some other pharmacological and non-pharmacological therapeutic options hypothesized to reduce CIPN symptoms may still require further study. There is no proven or specifically advised prophylaxis option for CIPN.

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Author Contribution
IJ and IH contributed to the concept and initial draft. PKKD and YRF contributed to the final draft and editing. All authors participated in revising the manuscript. All authors approved the submitted version.

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