Ind. J. Pharm. Edu. Res, 2023; 57(2):342-353.
https://www.ijper.org

Review Article

Chemotherapy-Induced Peripheral Neuropathy

Ashish Jain, Hariprasad MG*, Mohammad Sharique, Moqbel Ali Moqbel Redhwan

Department of Pharmacology, KLE College of Pharmacy, Rajajinagar, Bengaluru, Karnataka, INDIA.

ABSTRACT

Chemotherapy-induced peripheral neuropathy is a frequent and dose-limiting complication of chemotherapeutic drugs such as platinum-based compounds, taxanes, vinca alkaloids, bortezomib, and thalidomide that damages peripheral nerves and has a severe influence on patients' well-being and sickness outcomes. Manifestations of CIPN include numbness, tingling, neuropathic pain, cramping, and trouble handling small objects and walking. Recent research in the CIPN pathogenesis has revealed new strategies and pathways for developing novel therapies that can be scrutinized clinically to improve the management of this devastating toxicity. Unfortunately, no single agent is completely protective against this adverse effect, and because no single treatment option works for everyone, duloxetine is the only treatment option that can be recommended. After a thorough review, alternative therapeutic options such as antidepressants, gabapentin, pregabalin, tricyclic and topical gels containing baclofen and ketamine can be considered. In addition, Vitamins, Omega-3 fatty acids, Calcium, Magnesium, Cannabinoids, Melittin, and other natural products, as well as non-drug methods such as exercise, may be used to reduce the adverse effects of CIPN treatment medications. This review focuses on the new strategies for the prophylactic and therapeutic approaches of CIPN, including pharmacological and non-pharmacological methods.

Keywords: Chemotherapy-induced peripheral neuropathy, Mechanism of CIPN, Prophylactic and Therapeutic approaches of CIPN.

Correspondence:
Dr. Hariprasad MG
Professor & Head, Department of Pharmacology, KLE College of Pharmacy
2nd Block, Rajajinagar, Bengaluru-560010, Karnataka, INDIA.
Email: hariprasadmg2004@yahoo.com

Received: 06-07-2022;
Revised: 09-11-2022;
Accepted: 06-02-2023.

INTRODUCTION

Chemotherapy-induced Peripheral Neuropathy (CIPN) is a common and often severe adverse effect of neurotoxic anticancer treatment that damages peripheral nerves and is linked to poor quality of life.[1] Symptom include numbness, tingling, neuropathic pain, cramping, gait, and difficulty handling objects, all common in CIPN. Toxic peripheral neuropathies are characterized by sensory loss in a stocking-glove pattern in long axons. The most common type of sensory axonal neuropathy is sensory axonal neuropathy. Neuropathic pain, a symptom of CIPN, is caused by changes in pathways of sensory areas in the spinal cord, thalamus, and brain areas, such as the somatosensory cortex and the insula. The symptoms of peripheral nerve injury may be exacerbated by these alterations in the central nervous system. The toxicity of CIPN is dose-limiting, and it can potentially increase mortality. Fifty percent of all CIPN patients may take more than six months to recover correctly after chemotherapy.[2]

ESPN's pathophysiology has been investigated for decades. However, it is still not fully understood that the damage to IENF (intraepidermal nerve fibers), oxidative stress, over-expression of inflammatory mediators like cytokine, abnormal spontaneous discharge, ion channel activation, and the neuro-immune system activation are all linked to the onset and progression of CIPN.[3]

According to a recent estimation, there are around 18.1 million new cancer cases annually.[4] Patients with CIPN are more likely to fall; thus, supportive care measures such as physical and occupational therapy, assistive equipment, and safety evaluations should be explored. In addition, it is critical to monitor CIPN during and after treatment.[1] The chemical employed, the cumulative dose, the number of cycles, the length of therapy, combination treatments, age, genetic characteristics, nerve injury, and persistent alcohol intake are all risk factors for CIPN.

Cancer patients' survival rates have grown dramatically as diagnostic and therapeutic technology has improved. In addition, the number of patients who require systemic chemotherapy has risen. As a result, the risk of acute and long-term adverse effects, like CIPN, develops.[5] Some chemotherapeutic drugs generate a variety of alterations in cellular structure and function, which result in toxic side effects that are cumulative, ongoing, and frequently permanent.[6] Chemotherapeutic agents, e.g., platinum compounds, vinca alkaloids, and taxanes, are all linked to an elevated risk of CIPN.[7]

DOI: 10.5530/ijper.57.2.44

According to certain studies, exercise has been proven to enhance sensory-motor capabilities and lessen CIPN symptoms in cancer patients with each exercise session by boosting the availability of mitochondrial glucose, blood, and oxygen.[8] Even some nutraceuticals like vitamin B complex, one of the agents being tested for the prevention of CIPN.[9]

Honey Bee Venom (HBV) is a honeybee substance with potential therapeutic usefulness for various disorders, including rheumatic and arthritic ailments. Melittin has many medicinal properties, including antiviral, antibacterial, antifungal, anti-parasitic, anti-neoplastic, and neuroprotective properties.[10] HBV acupuncture has shown a potent analgesic effect in tests employing various animal pain models. Studies have shown that HBV can help alleviate peripheral neuropathy produced by chemotherapeutic agents. Vitamins, Omega-3 fatty acids, Calcium, Magnesium, Cannabinoids, Melittin, and other natural items, as well as non-drug measures like exercise, may be used to minimize the adverse effects of CIPN therapy medicines.[11]

Mechanism of CIPN

The mechanism of CIPN is one of the most challenging tasks for various types of chemotherapeutics, and numerous theories and underlying mechanisms have been proposed. Axonal peripheral neuropathy is caused by neurotoxic drugs that damage microtubules and interfere with microtubule-based axonal transport, causing mitochondrial damage, Microglia, astrocytes activation, causing overexpression of pro-inflammatory mediators like cytokines, growth factors, and ion channels, or causing damage to DNA (Deoxyribonucleic acid). (Figure 1) The primary categories of chemotherapeutic agents that cause peripheral neuropathy include (platinum-based anti-neoplastic agents; oxaliplatin and cisplatin), (taxanes; paclitaxel and docetaxel), (vinca alkaloids; vincristine and vinblastine), (proteasome inhibitors; bortezomib), and (immunomodulatory medications; thalidomide). These classes have different anti-neoplastic actions and probably distinct mechanisms producing neuropathy. Most of the research has emphasized the role of taxanes and platinum compounds in chemotherapy.[12]

Administration of chemotherapeutic agents causes alteration in ion channel activity, DNA damage, formation of ROS, and an increase in inflammatory cytokines, leading to neuroinflammation and alteration in the excitability of peripheral neurons Table 1.

Taxanes

Taxanes are used to treat tumors of the prostate, breast, lungs, pancreas, and other types of solid tumors and act by preventing tubulin disintegration from the microtubule polymer.[13]

Paclitaxel binds to the pore of mitochondrial permeability transition, causes dysfunction of mitochondria, disrupts neuronal ATP (Adenosine triphosphate) generation leading to axonal microtubule network disruption, and it also increases ROS (Reactive Oxygen Species) production and oxidative stress in rat DRG (Dorsal Root Ganglia).[4] In experimental models, paclitaxel decreased the threshold level of excitability in DRG neurons while enhancing the expression of calcium ion channels (Cav) 3.2. Toll Like Receptor 4, TLR 4 is also upregulated, which causes an increase in intracellular calcium. Paclitaxel also promotes the production of Nav 1.7 (Voltage-Gated Sodium Channel) in DRG neurons culture resulting in an increased ectopic impulsive activity. Paclitaxel binds and activates TLR 4 on macrophages, initiating signaling pathways that result in the overexpression of genes and stimulation of Nuclear Factor kappa B (NF-kB) release, inflammatory mediators, and cytokines. The inflammatory mediators IL-6, IL-8, IL-10, activated Langerhans cells, and monocyte chemoattractant protein-1 (MCP-1) is elevated, resulting in increased production of a pro-inflammatory mediator like cytokine. Additionally, inflammatory and stress markers are overexpressed in neurolemmocytes and DRG neurons (Figure 2).[4]

According to the hypothesis, taxanes interact with TLR-4 on macrophages and stimulate TLR-4 expression, then activates macrophages, leading to NF-kB release and pro-inflammatory cascades. TLR4, MyD88, and Extracellular signal-regulated kinase (ERK1/2) expression are increased in IB4-/GCRP peripheral fibers and DRG neurons. After treatment with taxanes, the Cav 3. 2 and Nav 1.7 expression is increased, resulting in alterations in the peripheral neuron's excitability threshold. The sensitization and changes in the excitability of neurons result in ectopic impulsive activity and mechanical hypersensitivity, which leads to TIPN development.

ATP-Adenosine Triphosphate, Cav 3.2-Voltage Gated Calcium Channel 3.2, Nav 1.7–Voltage-Gated Sodium Channel 1.7, DRG-Dorsal Root Ganglia, TIPN-Taxane Induced Peripheral Neuropathy, TLR 4–Toll-Like Receptor 4, IL-Interleukin, MPTP-Methyl Phenyl Tetrahydropyridine, DAMP- Damage Associated Molecular Pattern.

Vinca alkaloids

Vinca alkaloids are widely utilized in treating lymphoma, neoplasm of the lung, and testis. Vincristine, a chemical constituent of vinca, and uses the most severe neuropathic pain than vinorelbine and vinblastine.[6] Vinca alkaloids disrupt microtubule polymerization and mitotic spindle and increase the microtubule's stability, reducing the cell's ability to modify the cytoskeleton shape, affecting axonal transport dynamically.[4]

Vincristine also affects mitochondrial function in DRG neurons by influencing downstream calcium and its affinity to NCS1 (Neuronal Calcium Sensor 1) and by acting the mitochondrial membrane. The changes in mitochondria's function result in increased ROS generation and disrupt neuronal excitability. Sensory fibers are more severely affected by Vincristine than

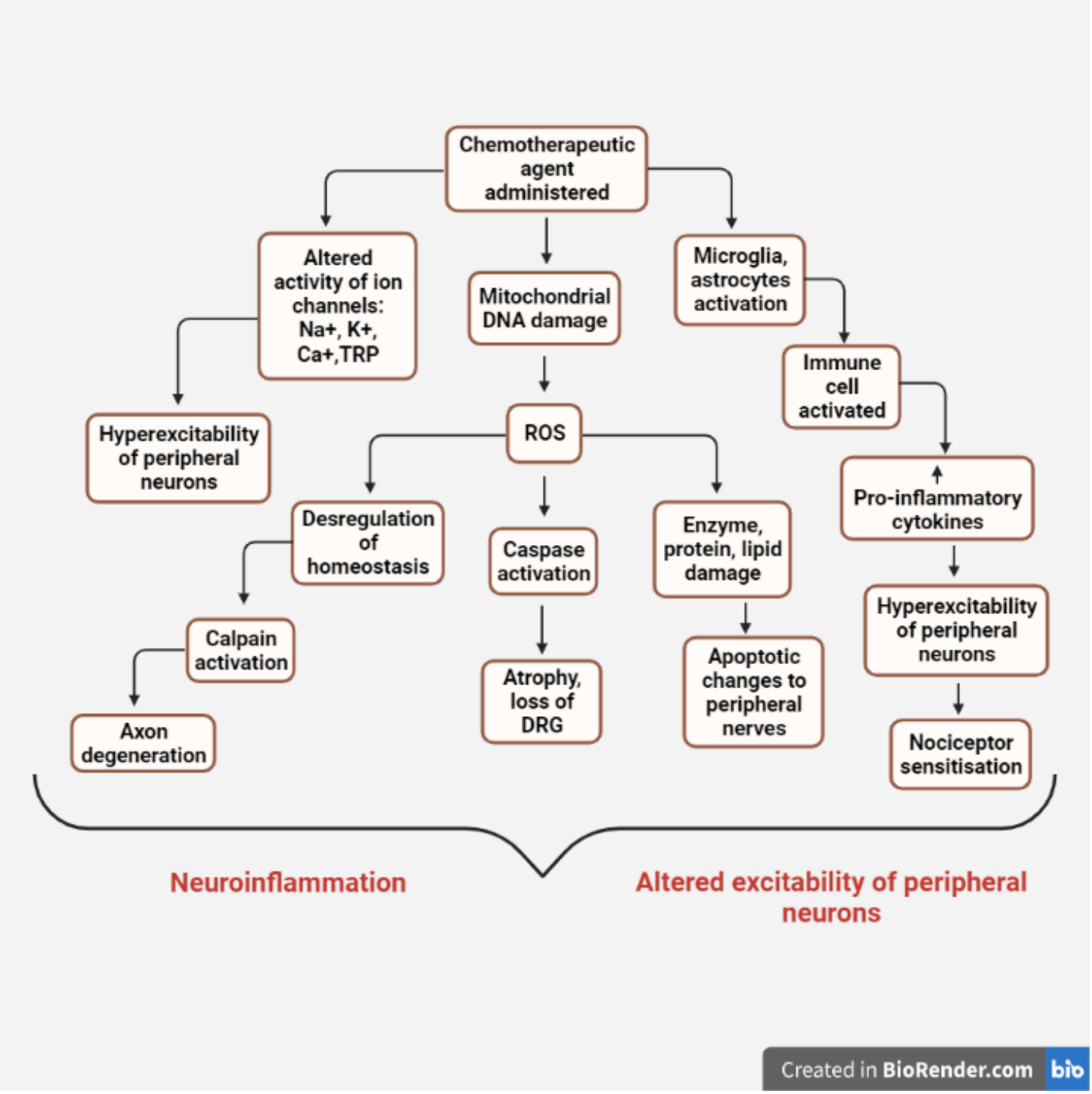

Figure 1: Mechanism of chemotherapy-induced peripheral neuropathy (CIPN).[12]

motor fibers. Vincristine also influences the cranial nerves, particularly the oculomotor nerve.[6]

Platinum-based compounds

For the last four decades, Platinum-based drugs such as cisplatin, oxaliplatin, and carboplatin have proven vital in treating breast, lung, ovarian, and colon cancers. Platinum compounds have chemotherapeutic effects and are alkylating agents. It exerts a few effects by adhering to cellular DNA and forming intra-strand cross-links. Apoptosis happens when DNA damage surpasses the cell's ability to repair it. The cell cycle is unaffected by platinum-based compounds.[6] The dorsal root ganglion is the primary anatomical structure destroyed by platinum compounds, resulting in intense neuropathic pain and peripheral nerve hyperexcitability, causing cold-induced allodynia, and muscle cramps (Figure 3).[4]

Oxaliplatin

There are two forms of oxaliplatin neurotoxicity: acute and chronic.[14] The most essential mechanism implicated in acute is

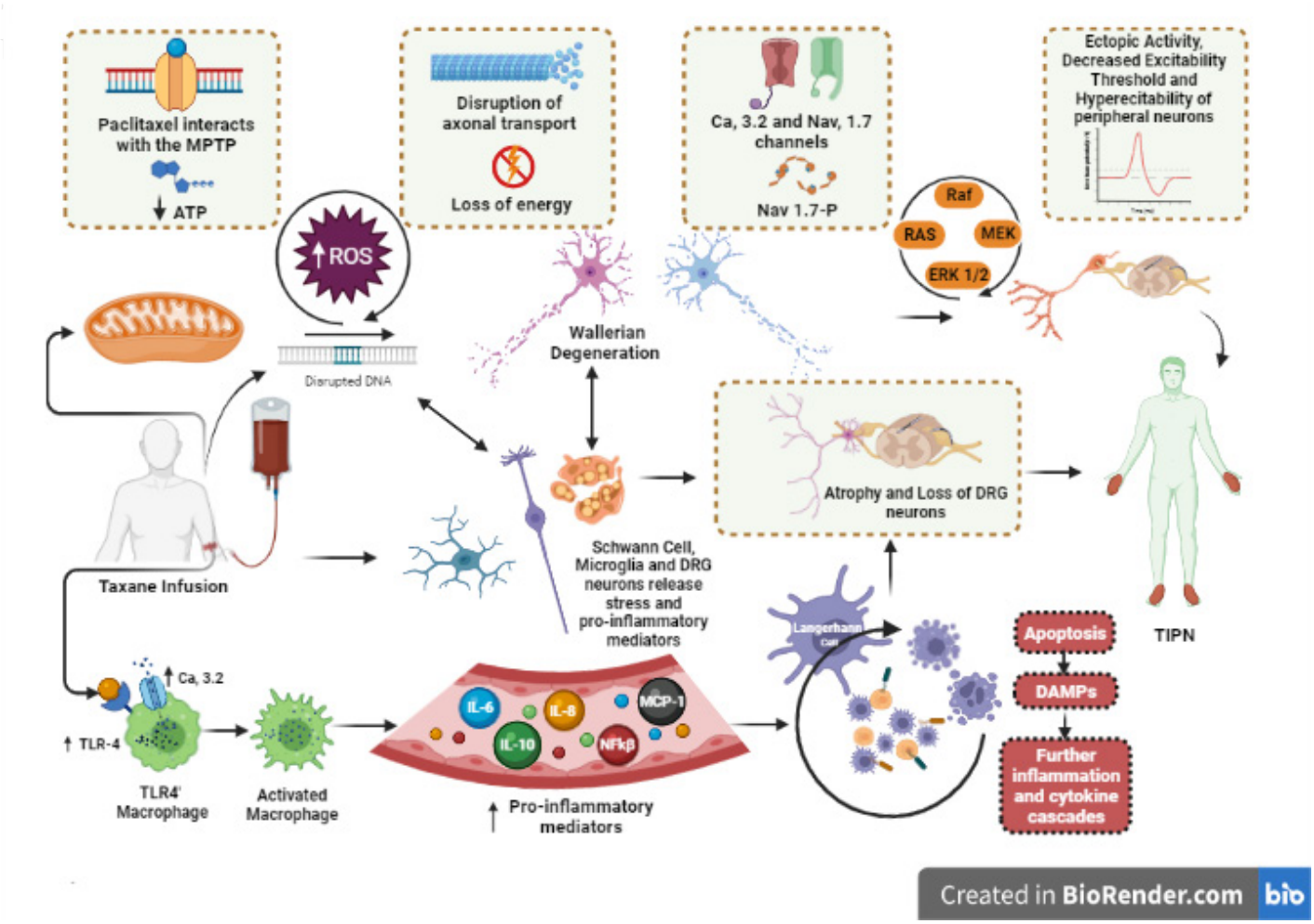

Figure 2: Mechanism of Taxane-Induced Peripheral Neuropathy.[4]

the alteration of voltage-gated Na^+, K^+, and Ca^{2+} channels, TRP (Transient Receptor Potential) channels, OCT2 (Organic Cation Transporter) protein, and glial cells are also involved in acute OIPN (Oxaliplatin Induced Peripheral Neuropathy). The fundamental mechanisms of chronic OIPN include nuclear DNA damage, mitochondrial damage, excessive oxidative stress, glial activation, and neuroinflammation. This article describes the progression of chronic OIPN and numerous possible mechanisms.[15]

Platinum-based chemotherapeutics are very toxic to the nervous system. These substances impact neuronal membrane excitability, disrupt neurotransmission by causing axonal transport malfunction, promote inflammation by releasing pro-inflammatory chemokines, and alter the expression of voltage-gated ion channels. DRG neurons are sensitive to neurotoxic drugs since the BBB does not protect them. Sensory neuron death is assumed to be the primary cause of long-term distal sensory loss and binding of platinum-based drugs to mitochondrial DNA.[6]

Oxidative stress disrupts the replication and transcription of DNA and mtDNA, which causes a reduction in energy level and stimulates neuronal cell death. Leukocytes are eventually activated and migrate to the DRG and peripheral nerves, causing neuroinflammation. Dysregulation of calcium, axonal energy loss, and disruption to neuronal organelleareis caused by damage to DRG and apoptosis due to ROS release and neuroinflammation. Oxaliplatin interacts with the NaV channel, VGKC, in sensory neurons, and TRPM, isoforms contribute to cold hyperalgesia and peripheral neuron hyperexcitability. mtDNA-Mitochondrial DNA, VGKC-Voltage Gated Potassium Channel, TRPM-Transient receptor potential melastatin, TNF-Tumor Necrosis Factor, NaV-Voltage gated Sodium channel, PIPN-Platinum Induced Peripheral Neuropathy.

Proteasome Inhibitors

Bortezomib, Carfilzomib, and Ixazomib are examples of proteasome inhibitors. Due to interference with mitochondrial and microtubule activity, these medications appear neurotoxic and produce a painful small fiber predominate axonal sensory neuropathy. Proteosome inhibitors promote microtubule polymerization and show impaired axonal transport and function in sensory neurons. However, newer proteasome inhibitors, such as carfilzomib and ixazomib, are found to have a decreased

prevalence of CIPN. Additional causes may include nuclear accumulations of ubiquitinated proteins and altered protein transcription in sensory ganglionic neurons.

Bortezomib

The first proteasome inhibitor to be authorized for human use was Boetezomib.[6] Bortezomib inhibits proteasomes, which are responsible for intracellular protein degradation, and has anti-neoplastic capabilities. Bortezomib induces a painful slight fiber predominance axonal sensory neuropathy.[16] Bortezomib produced neurotoxicity in PC12 (Pheochromocytoma 12) neuroblastoma cells by inducing apoptosis, which was relieved by antioxidants.[4] The cause of neuropathy in plasma cell myeloma patients appears to be HtrA2 (High-Temperature Requirement Protein A2), a stress-inducible mitochondrial protease that protects neurons from death.[6] Bortezomib treatment increases the production of the T-cell chemoattractant chemokine C–C motif ligand 21 and GATA3 protein, which involves the regulation of inflammatory pathways.[4]

Immunomodulatory Drugs: Thalidomide, Pomalidomide, and Lenalidomide

The drug thalidomide, used to treat multiple myeloma, induces peripheral neuropathy when used for a long time. Thalidomide's neurotoxicity was well-studied when it was first introduced as a sedative in the 1960s. Newer formulations, such as lenalidomide and pomalidomide, appear to be less harmful to the nervous system Figure 4.[16]

Immune checkpoint inhibitors

Immunological-mediated neuropathies have been linked to newer forms of immunological checkpoint inhibitors, which are increasingly being used to treat melanoma and other cancers. Tremelimumab and Ipilimumab target the human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), prompting cytotoxic T lymphocytes to kill cancer cells. Nivolumab and Pembrolizumab are two novel immune-stimulating monoclonal antibodies used to treat cancer (glioma, stage IV melanoma, adenocarcinoma, and squamous cell carcinoma) that act on PD-1 (Programmed Cell Death Protein-1) receptor, which involves in immune cell death. These immune checkpoint inhibitors have been related to various neurological side effects, including peripheral and central nervous system illnesses, some of which are fatal. Acute and chronic inflammatory demyelinating neuropathies or vasculitic neuropathies are common neuropathy. Even though they are uncommon, they can develop in up to 3% of patients. To address these side effects, immune-boosting chemotherapy is discontinued, and immunotherapy (steroids or IVIG) is initiated, which is successful in many patients.[16]

Prevention and treatment

Unfortunately, there are no therapies available to prevent CIPN. It's difficult to comprehend why medications designed to fight quickly proliferating cancer cells can damage non-dividing, post-mitotic neurons. The risk that any drug may reduce the chemotherapeutic efficacy complicates the development of CIPN-preventing medicines. Preventative measures must either distinguish neurotoxicity from cancer cytotoxicity or uncover cell features exclusive to neural cells (e.g., receptor sensitivity to neuronal growth factors). Despite extensive investigation, this mechanism-based approach has yet to provide a successful cure.[16] The prophylactic approaches, including neuroprotectants and nutraceuticals, have not shown consistent beneficial effects in preventing the development of CIPN evaluated in clinical trials. As a result, contemporary treatment techniques focus on changing the chemotherapy regimen, such as changing the dose, treatment cycles, timing, dosage form, and duration, as well as symptomatic care employing a variety of pharmaceutical treatments Figure 5.[13]

Serotonin-norepinephrine reuptake inhibitors, anticonvulsants, and analgesics are among the medications used to treat CIPN. Herbal supplements, Vitamins, diet adjustments, and exercise are all examples of non-pharmacological methods. Patient-doctor communication and patient education are also crucial for CIPN treatment.[6]

EMG-Electromyography, NCS-Nerve Conduction Study.

For the treatment of CIPN, topical therapies are an appealing choice. In a clinical study, topical menthol showed better BPI scores and improved CIPN symptoms in some patients when the therapy given in combination with baclofen, amitriptyline, and ketamine.[17] Potent opioids offer some of the most significant "numbers needed to treat" (NNT 4.3, 95 percent confidence interval 3.4–5.8) for neuropathic pain. The use of transcutaneous electrical nerve stimulation showed significant improvement in CIPN symptoms. In a recent study, scrambler therapy was found to be more beneficial than sham treatment postulated as a potential treatment for CIPN.[12]

Prophylactic approaches for CIPN (Natural products) Vitamin E

Vitamin E is an antioxidant, lipid-soluble that may be found in almonds, green leaves, and vegetable oil. The Vitamin E molecule alpha-tocopherol has the most incredible action. The synthetic form of Vitamin E All-Rac-alpha-tocopheryl acetate is more used than the natural form alpha-tocopherolerol found in plants. Tocopherols are absorbed as free alcohols in the small intestine with or without lipid products and then metabolized in the liver.[18]

Vitamin E deficiency can cause symptoms of peripheral neuropathy in the central and peripheral nervous systems. As a

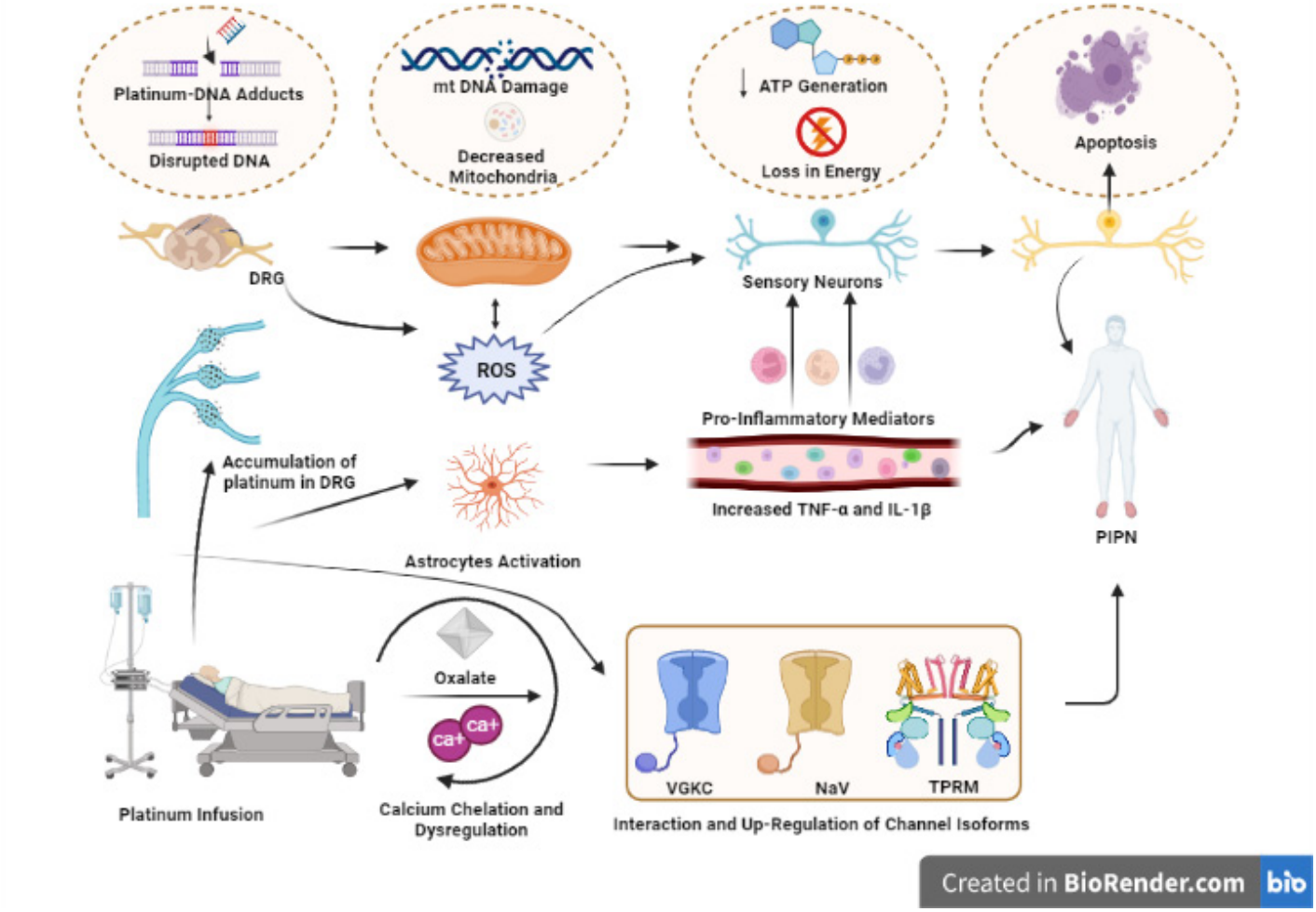

Figure 3: Mechanism of Platinum-based compound.[4]

result, many people feel that taking Vitamin E supplements can help avoid the development of CIPN.[19]

The study says prophylactic Vitamin E prevented peripheral neuropathy induced by cisplatin. During cisplatin chemotherapy, the treatment group was administered 300 mg of oral alpha-tocopherol twice daily and continued for three months, but the control group was not administered.[20] Neurotoxicity incidence was measured using the NDS (Neurological Disability Score) and NSS (Neurological Symptom Score) after cycles 3, 6, and 3 months of treatment. The incidence of neurotoxicity differed considerably across groups, with the relative risk of developing being much more significant in the control group than the treatment group, indicating that Vitamin E may protect against cisplatin neurotoxicity. The neuroprotective role of Vitamin E for Cisplatin-induced peripheral neuropathy was revealed in phase III clinical trial.[21] The clinical trial was conducted on 108 patients receiving cisplatin who were randomly administered with Vitamin E or a placebo. In the end, only 41 cases met the criteria for statistical analysis. Although the Vitamin E group showed less neuropathy than the placebo group, only 17 individuals were randomized to Vitamin E treatment in this experiment.[5] Long-term usage of Vitamin E supplements was linked to an increased risk of prostate cancer in a randomized clinical study of 35,533 males.[19]

Omega-3 fatty acids

Polyunsaturated omega-3 fatty acids are found in the phospholipid membrane of cells in the central and peripheral nervous systems. ALA (alpha-linolenic acid) is located in plant oils, whereas EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are found in fish oils.[19] Paclitaxel was given to 57 female breast cancer patients in a randomized, placebo-controlled clinical trial. Patients randomly received either omega-3 fatty acid or placebo, and the risk of CIPN symptoms was reduced by 70% in the group that received omega-3 fatty acid than the group that received placebo.[22]

Calcium and Magnesium

Calcium and magnesium salts have been utilized to prevent Oxaliplatin induced acute neuropathy. One hundred and one individuals were given Oxaliplatin at doses ranging from 85 to 130 mg/m^2. Sixty-three of them were also given calcium gluconate and magnesium chloride intravenously before and after Oxaliplatin delivery (treatment group), while the others

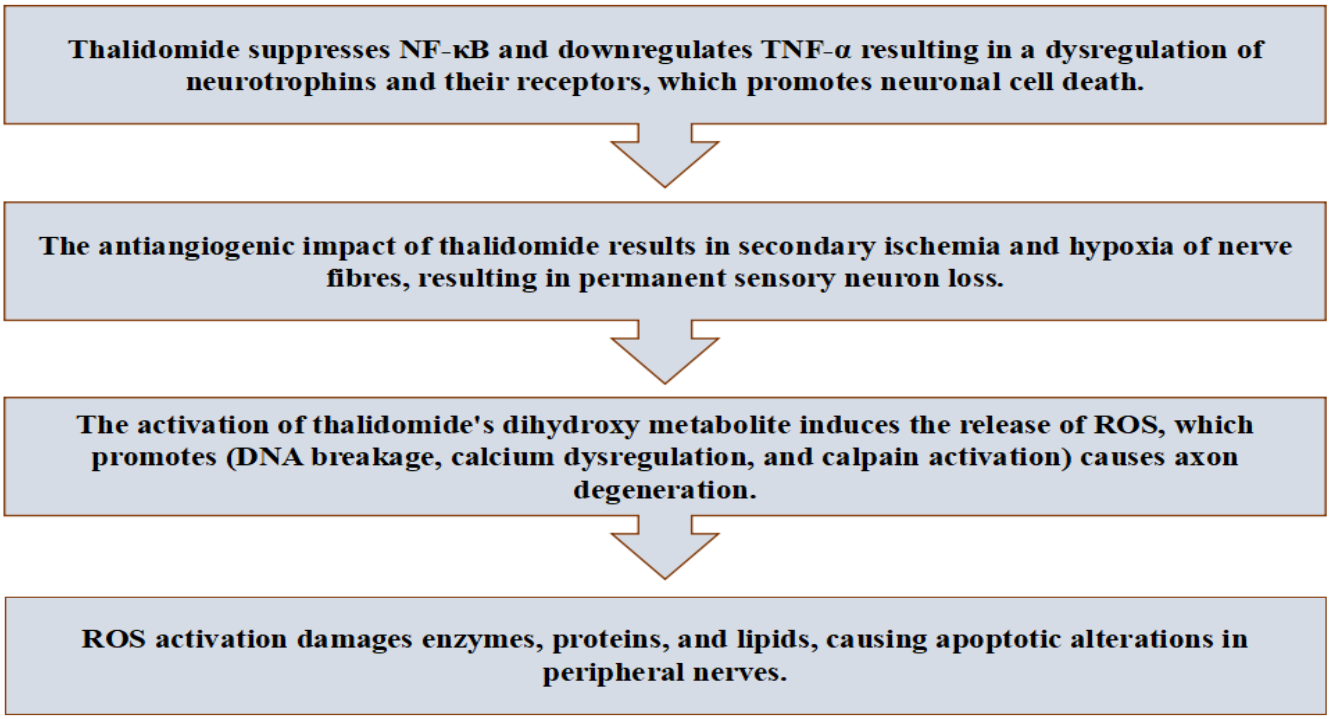

Figure 4: Mechanism of Thalidomide induced CIPN.[16]

were given vehicle (control group). Neuropathy affected 6% of patients in the treatment group and 56% in the control group.[15] Infusion of Calcium and Magnesium is one of the most promising techniques for CIPN prophylaxis. The activity of sodium channels is facilitated by increasing the concentration of extracellular calcium by i.v administration of Calcium and Magnesium, which blocks them. Before treatment, 551 participants in a significant phase III research with 720 patients with colorectal cancer got a Ca^{2+}/Mg^{2+} infusion (calcium glubionate and MgCl in 5% glucose solution). Ca/Mg infusion significantly reduced the incidence of oxaliplatin-induced neurotoxicity of all grades.[3]

Physiotherapy

Manual therapies, such as massage; neuro-developmental techniques, such as sensorimotor retraining; cardiopulmonary treatment, such as lifestyle modification and breathing exercises and most commonly, physiotherapy management strategies, use therapeutic exercises. Massage is said to be the most popular manual treatment approach for treating CIPN symptoms. The improved circulation linked with massage treatment improves the severity of CIPN symptoms and substantially improves quality of life.[18]

Yoga is a contemplative movement therapy that uses mind-body awareness to enhance physical conditioning, flexibility, and balance. According to several pilot and feasibility studies, yoga appears to enhance quality of life, anxiety, sadness, tiredness, and functional results in breast cancer patients and survivors who have had chemotherapy.[23]

Cross-sectional and randomized human studies reveal that exercise can help cure or prevent CIPN. Their findings show that individuals who are older, not fit aerobically, and overweight have more severe CIPN symptoms. Furthermore, for younger, fitter, and slimmer individuals, a higher dosage of exercise (3 hr per week of aerobic activity instead of 1.5 hr per week) may be more beneficial in treating CIPN symptoms.[2]

According to specific research, exercise can help cancer patients with CIPN symptoms by lowering them. Activity has been demonstrated to improve CIPN symptoms with each practice session[24] by increasing the level of mitochondrial glucose, blood, and oxygen. As a result, lowering neuropathic symptoms and improving the sensorimotor functioning in cancer patients with CIPN symptoms.[8]

Therapeutic approaches for CIPN

The majority of CIPN treatment focuses on symptomatic relief of neuropathic pain. Drugs that induce peripheral neuropathy elevates the symptoms like numbness and weakness, which may be particularly troublesome in older persons and contribute to foot ulcerations, gait instability, and falls. Other concomitant illnesses, particularly diabetes with strict glucose control, must be managed appropriately to prevent neuropathy development. Furthermore, moderate aerobic and resistance training

Table 1: Different categories of Chemotherapeutic agents with their doses causing Peripheral Neuropathy.[38]

Class of Drug	Examples	Threshold Dose	Sensory Neuropathy	Motor Neuropathy	Autonomic Neuropathy
Taxane	Paclitaxel	>300mg/m^2	Predominant sensory neuropathy	At higher doses, myalgia, and myopathy	Rare
	Docetaxel	>100 mg/m^2	Predominant sensory neuropathy	At higher doses, myopathy and myalgia	Rare
Platinum compound	Oxaliplatin	>550 mg/m^2	Acute and chronic sensory neuropathy	Acute cramps and fasciculations	Rare
Vinca alkaloid	Vincristine	>2-6 mg/m^2	Sensory neuropathy	Mild distal weakness and cramps	Yes
Immunomodulatory agent	Thalidomide	>20 g	Sensory neuropathy	Mild distal weakness and cramps	Rare
Proteasome inhibitor	Bortezomib	>16 mg/m^2	Painful, small-fiber sensory neuropathy	Rare	Yes

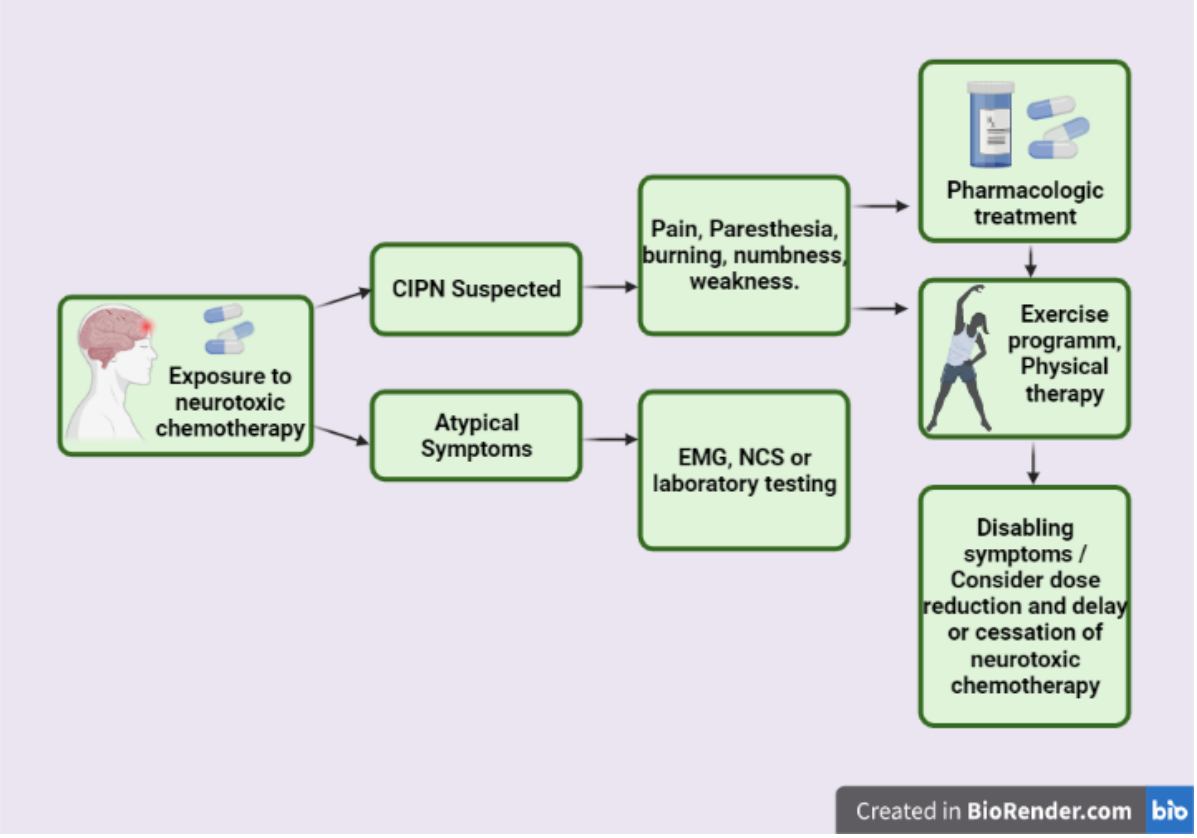

Figure 5: Overview of Pharmacological and non-pharmacological interventions for the prevention of CIPN.[6,13,17]
EMG-Electromyography, NCS-Nerve Conduction Study.

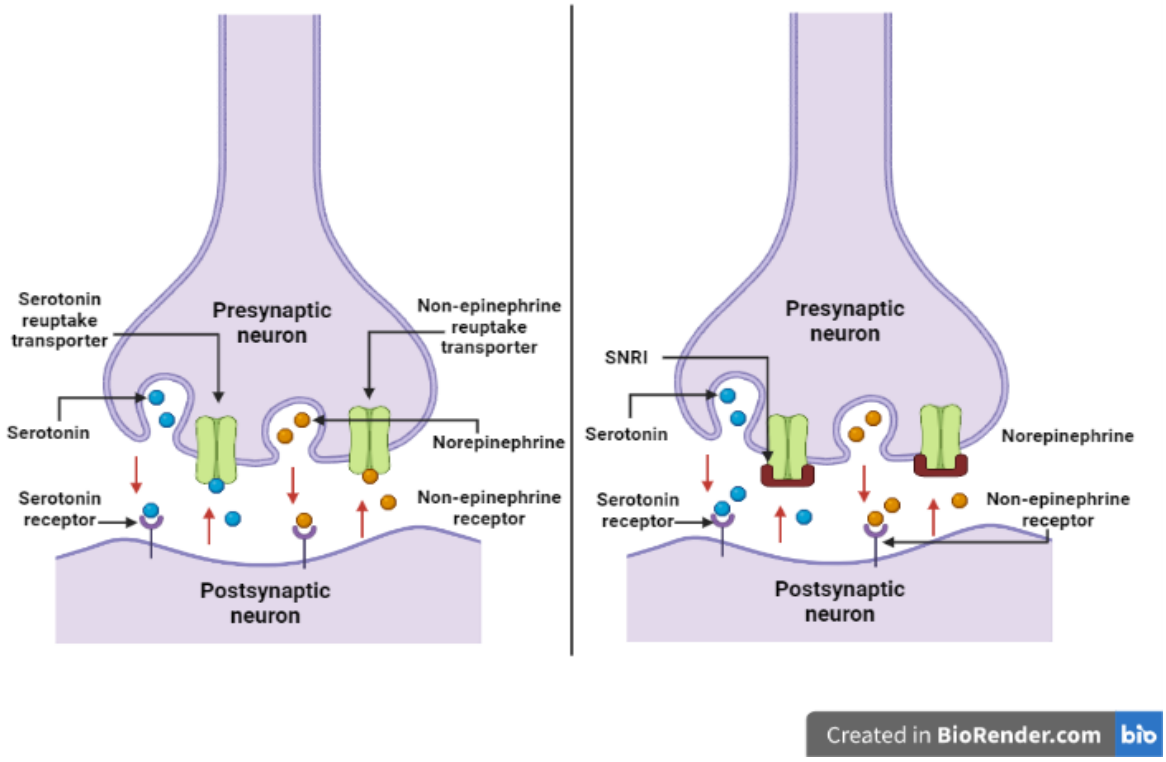

Figure 6: Mechanism of SNRI improves pain and peripheral neuropathy.[26-29]

regimes have been demonstrated to enhance postural control, independence, and quality of life in people with CIPN.[25]

Antidepressants, anticonvulsants, topical therapies, and integrative approaches have all been used in the CIPN treatment with little success. If a patient isn't a good candidate for systemic therapy, topical therapies can be used instead, as they have few to no systemic adverse effects. When compared to placebo, topical therapy with a combination of baclofen, amitriptyline, and ketamine has been proven to relieve neuropathic symptoms. In limited, non-randomized investigations, lidocaine gel or patches, capsaicin cream, or menthol lotion have been proven to give symptomatic relief of pain symptoms.[1]

Antidepressants

Because there are no pharmaceutical treatments for loss of tingling, sensation, or muscle weakness, therapy for chronic CIPN patients mainly focuses on neuropathic pain reduction or alleviation (so-called plus symptoms). Duloxetine, an SSRI (Selective serotonin reuptake inhibitor), exhibited moderate therapeutic improvements in individuals with neuropathic pain in a cross-over trial.[26]

Neurotransmitters like serotonin and norepinephrine are known to play a role in the descending inhibitory pain pathway, amplifying central sensitization's effects.[27] According to[28] SNRIs (Serotonin-norepinephrine reuptake inhibitors) block the reuptake of (Serotonin and norepinephrine) and increase synaptic concentration of these neurotransmitters, can block sodium channel currents and affect the descending inhibitory pain neural networks, preventing input to the spinal dorsal horn and thus decreases pain transmission (Figure 6).[29]The only randomized phase III intervention research in CIPN linked with a substantial decrease in neuropathic pain symptoms has been duloxetine, a SNRIs.[30]

In a phase III trial, on the other hand, 48 patients were randomly allocated with oxaliplatin-induced neurotoxicity to venlafaxine or placebo. The use of venlafaxine resulted in a significant increase in individuals experiencing complete remission from acute neurotoxicity (31 percent vs. 5 percent).[5]

In a study including 48 individuals with oxaliplatin-induced acute neurotoxicity, the neuroprotective benefits of venlafaxine were investigated. Patients were given either 50 mg of venlafaxine 1 hr before oxaliplatin infusion with venlafaxine extended release 37.5 mg twice daily from day 2-11 in this randomized, double-blind trial or placebo. In the venlafaxine group, 31.3 percent of patients reported complete alleviation of acute neurotoxicity, compared to 5.3 percent in the placebo group.[31]

Although the tricyclic antidepressant amitriptyline is the gold standard for neuropathic pain, individuals with benign prostatic hyperplasia or the elderly may have urinary retention or severe disorientation. Opioids, such as tramadol or lidocaine patches, were only moderately effective as second-line treatments for neuropathic pain.[32]

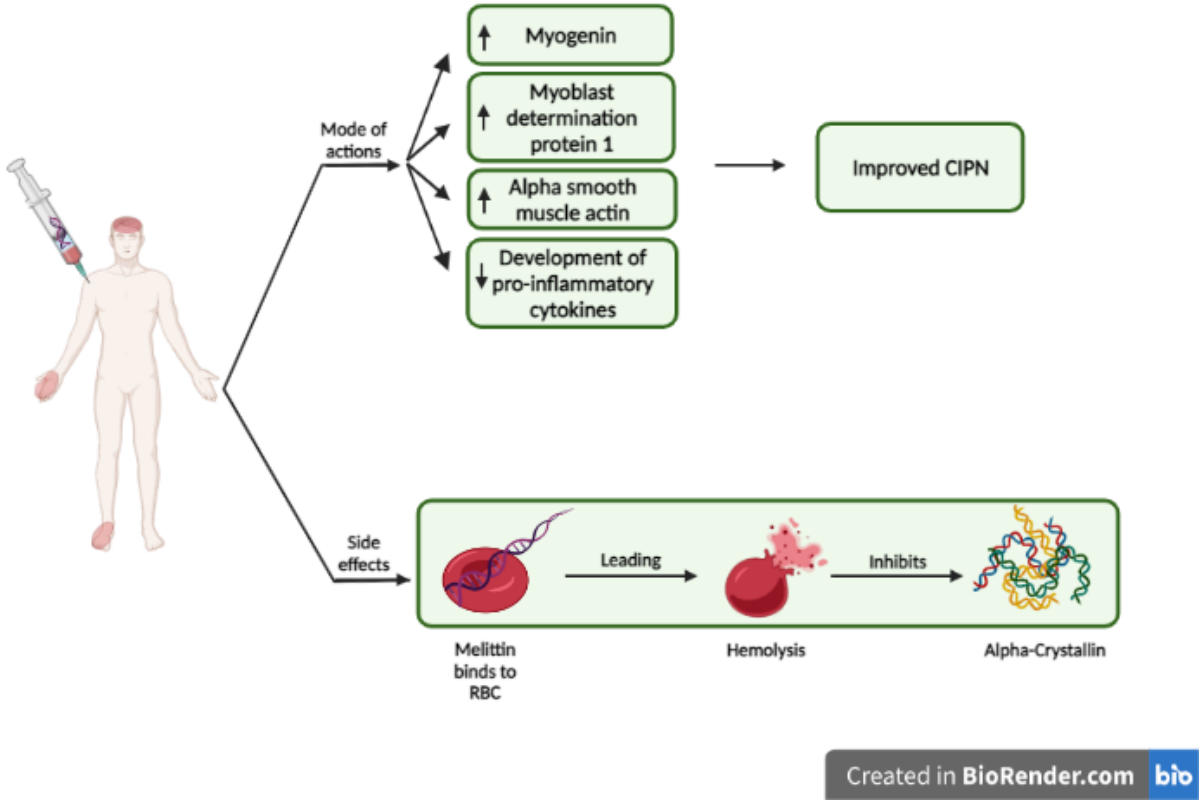

Figure 7: Mechanism of melittin on CIPN.[11]

By blocking the reabsorption of Serotonin and Nor-epinephrine into the presynaptic neuron, more Serotonin and Nor-epinephrine accumulates to bind post-synaptic neuronal receptors.

Anticonvulsants

A cascade of molecular alterations at the peripheral nociceptor, the DRG, the dorsal horn of the spinal cord, and the brain cause peripheral hyperexcitability. Among the modifications, the modifications include sodium channel abnormalities, increased activity at glutamate receptor sites, alterations in aminobutyric acid (GABA-ergic) inhibition, and calcium influx into cells. The cellular alterations in certain kinds of epilepsy are similar to neuronal hyperexcitability and related molecular changes in neuropathic pain. As a result, anticonvulsant medications are now commonly used to treat neuropathic pain.[33]Pregabalin and gabapentin are structurally like gamma-aminobutyric acid and be effective in treating epilepsy and neuropathic pain. The primary issues include unsteadiness, dizziness, edema, somnolence, and lack of attention.[32]

Women between the ages of 18 and 65 with a satisfactory performance level had pathologically proven breast cancer and were candidates for paclitaxel as part of their adjuvant cytotoxic therapy were eligible. The findings supported gabapentin's potential as a CIPN preventative. Gabapentin has been shown to improve not just subjective but also objective outcomes. Gabapentin has been shown in an animal *in vivo* investigations to function on a theoretical basis for lowering nociception in neuropathic disorders.[34]

Cannabinoids

Clinical trials showed that cannabinoid-based drugs are not efficacious to treat the peripheral neuropathy, although there is little medical evidence that they are. A double-blind clinical trial on 16 patients found no evidence of cannabis having a significant advantage in the treatment of CIPN.[35] Cannabinoids are not indicated in neuropathic pain of any origin, according to a German Society for Neurology recommendation, because effectiveness is limited and the risk of adverse effects is high. Treatment with cannabis for pain management may be explored in unique circumstances and when other treatment options have failed.[7]

Cannabis sativa has long been used to alleviate neuropathic pain. Cannabinoids connect to cannabinoid receptors in cells and inhibit neurotransmitter release in the brain. They also have anti-inflammatory properties. Cannabinoids have been proven to have anti-cancer properties in animal models of cancer, and they are now being evaluated in phase I/II clinical studies as anti-tumor medicines.[36]

Topical therapy

The lidocaine patch of 700 mg was approved for the treatment of postherpetic neuralgia, although recommended for the treatment of other types of localized neuropathic pain, including CIPN. The capsaicin patch of 179 mg is licensed in Europe for the topical treatment of peripheral neuropathy as monotherapy or in combination with other pain-relieving products. In two open-label single-center trials (n = 18 and n = 16, respectively), the high-dose capsaicin patch proved effective in reducing pain in CIPN patients.[37]

(M Christian *et al.*) conducted a study on 51 patients, where topical treatment of CIPN with 1% menthol resulted in significant pain reduction as well as modest improvements in functioning and sensitivity. The patient group was, however, small, and the trial was not blinded.

In most cases, (menthol cream 1%) administered topically twice daily to sensitive regions for 4 to 6 weeks relieved neuropathic pain and reduced numbness caused by various chemotherapeutic drugs.[3]

Melittin as a potential drug for the CIPN

HBV is a colourless liquid, (pH 4.5–5.5) that is the honeybee's most beneficial product. Many ailments, notably rheumatic and arthritic ones, have been linked to its potential therapeutic efficacy. Melittin has a wide range of medicinal properties, including antiviral, antibacterial, anti-cancer, antifungal, antiparasitic, and neuroprotective properties.[10] HBV acupuncture has shown a substantial analgesic effect in trials utilizing several animal models of pain. Two research studies have revealed that HBV treatment can assist in alleviating peripheral neuropathy produced by chemotherapeutic agents. Melittin is safe to use in future patients. Prazosin (adrenergic receptor blocker, 30 g, i.t.) and idazoxan (adrenergic receptor blocker, 50 g, i.t.) prevented melittin analgesia on mechanical and cold allodynia when given 20 min before treatment. The spinal 1 and 2 adrenergic receptors may be involved in the melittin analgesic actions. BVA (Bee Venom Acupuncture) was demonstrated to improve the analgesic efficacy of clonidine injection Figure 7.[11]

Melittin improves peripheral neuropathy by elevating the expression of factors like alpha-smooth muscle actin, myoblast determination protein-1, and myogenin, and decreasing pro-inflammatory cytokines.

CONCLUSION

CIPN is a potentially life-threatening adverse effect of cancer therapy that is becoming increasingly important to the world's millions of cancer survivors. It's one of the most prevalent side effects that restricts use of anti-cancer drugs for longer periods of time or at higher doses. This restriction has affected patient's survival and morbidity. A variety of compounds have been produced to prevent or cure CIPN based on its pathogenesis. No single agent has been proven to be protective against this side effect; similarly, no single treatment option works for everyone; hence, duloxetine is the only therapy option that can be advised. However, following a comprehensive review, alternative therapy options such as tricyclic antidepressants, gabapentin, pregabalin, and topical gels containing baclofen and ketamine can be considered. Vitamins, Omega-3 fatty acids, Calcium, Magnesium, Cannabinoids, Melittin, and other natural items, as well as non-drug measures like exercise, may be used to minimize the adverse effects of CIPN therapy medicines. As a result, using natural products and physiotherapy during chemotherapy is seen as a cost-effective choice for the patient and safe, with the potential to avoid the development of CIPN.

ACKNOWLEDGEMENT

The authors thank KLE University, Belagavi, Karnataka, and special thanks to Dr. Hariprasad M.G., Head, Department of Pharmacology, KLE College of Pharmacy, Bengaluru, for guidance and support.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ALA: α-linolenic acid; **BIPN:** Bortezomib Induced Peripheral Neuropathy; **BVA:** Bee Venom Acupuncture; **CCL21:** C–C motif ligand 21; **CIPN:** Chemotherapy-Induced Peripheral Neuropathy; **CTLA-4:** Cytotoxic T-Lymphocyte-Associated Antigen 4; **ERK 1/2:** Extracellular-signal-regulated kinase 1/2; **HBV:** Honey Bee Venom; **HtrA2:** High Temperature Requirement Protein A2; **IENF:** Intraepidermal Nerve Fibres; **IVIG:** Intravenous Immunoglobulin; **MCP-1:** monocyte chemoattractant protein-1; **MyD88:** Myeloid differentiation primary response 88; **MPTP:** Methyl Phenyl Tetra hydro Pyridine; **NF-kB:** Nuclear Factor kappa B; **OCT2:** Organic Cation Transporter; **OIPN:** Oxaliplatin Induced Peripheral Neuropathy; **PC12:** Pheochromocytoma 12; **PD-1:** Programmed Cell Death Protein - 1; **TIPN:** Taxane Induced Peripheral Neuropathy; **TLR 4:** Toll Like Receptor 4; **TRPM:** Transient receptor potential melastatin; **VGKC:** Voltage Gated Potassium Channel.

SUMMARY

Chemotherapy-induced peripheral neuropathy is a common and dose-restrictive side effect of chemotherapeutic medications that results in neuropathic pain and limits the use of anti-cancer medications for longer periods of time or at higher doses.

Recent research in the CIPN pathogenesis has revealed new strategies and pathways for the development of novel therapies that can be scrutinize clinically to improve the management of this toxicity.

Thorough review revealed that, alternative therapy options such as tricyclic antidepressants, topical gels containing baclofen and ketamine, natural products including Vitamins, Omega-3 fatty acids, Calcium and Magnesium as well as non-drug measures like exercise, may be utilized to reduce the adverse effects of CIPN therapy medicines.

This review was done to explore and gather the new strategies for the prophylactic and therapeutic approaches of CIPN. This article may help readers to understand the mechanism of CIPN, its prevention and treatment.

REFERENCES

1. Wasilewski A, Mohile N. Meet the expert: How I treat chemotherapy-induced peripheral neuropathy. J Geriatr Oncol. 2021;12(1):1-5. doi: 10.1016/j.jgo.2020.06.008, PMID 32561202.
2. Kleckner IR, Kamen C, Gewandter JS, Mohile NA, Heckler CE, Culakova E, *et al*. Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: A multicenter, randomized controlled trial. Support Care Cancer. 2018;26(4):1019-28. doi: 10.1007/s00520-017-4013-0, PMID 29243164.
3. Hu LY, Mi WL, Wu GC, Wang YQ, Mao-Ying QL. Prevention and treatment for chemotherapy-induced peripheral neuropathy: Therapies based on CIPN mechanisms. Curr Neuropharmacol. 2019;17(2):184-96. doi: 10.2174/1570159X15666170915143217, PMID 28925884.
4. Burgess J, Ferdousi M, Gosal D, Boon C, Matsumoto K, Marshall A, *et al*. Chemotherapy-induced peripheral neuropathy: Epidemiology, pathomechanisms and treatment. Oncol Ther. 2021;9(2):385-450. doi: 10.1007/s40487-021-00168-y, PMID 34655433.
5. Bakogeorgos M, Georgoulias V. Risk-reduction and treatment of chemotherapy induced peripheral neuropathy. Expert Rev Anticancer Ther. 2017;17(11):1045-60. doi: 10.1080/14737140.2017.1374856, PMID 28868935.
6. Ibrahim EY, Ehrlich BE. Prevention of chemotherapy-induced peripheral neuropathy: A review of recent findings. Crit Rev Oncol Hematol. 2019;145:1-23.
7. Maihöfner C, Diel I, Tesch H, Quandel T, Baron R. Chemotherapy-induced Peripheral Neuropathy (CIPN): Current therapies and topical treatment option with high-concentration capsaicin. Support Care Cancer. 2021;29(8):4223-38. doi: 10.1007/s00520-021-06042-x, PMID 33624117.
8. Lin WL, Wang RH, Chou FH, Feng IJ, Fang CJ, Wang HH. The effects of exercise on chemotherapy-induced peripheral neuropathy symptoms in cancer patients: A systematic review and meta-analysis. Support Care Cancer. 2021;29(9):5303-11. doi: 10.1007/s00520-021-06082-3, PMID 33660078.
9. Schloss J, Colosimo M, Vitetta L. Herbal medicines and chemotherapy induced peripheral neuropathy (CIPN): A critical literature review. Crit Rev Food Sci Nutr. 2017;57(6):1107-18. doi: 10.1080/10408398.2014.889081, PMID 25849070.
10. Yang EJ, Kim SH, Yang SC, Lee SM, Choi SM. Melittin restores proteasome function in an animal model of ALS. J Neuroinflammation. 2011;69(8):1-9.
11. Tender T, Rahangdale RR, Balireddy S, Nampoothiri M, Sharma KK, Raghu Chandrashekar HR. Melittin, a honeybee venom derived peptide for the treatment of chemotherapy induced peripheral neuropathy. Med Oncol. 2021;38(5):52. doi: 10.1007/s12032-021-01496-9, PMID 33796975.
12. Gordon-Williams R, Farquhar-Smith P. Recent advances in understanding chemotherapy-induced peripheral neuropathy [version 1; peer review: 2 approved]. F1000Research. 2020;9:1-13. doi: 10.12688/f1000research.21625.1, PMID 32201575.
13. Starobova H, Vetter I. Pathophysiology of chemotherapy-induced peripheral neuropathy. Front Mol Neurosci. 2017;10:174. doi: 10.3389/fnmol.2017.00174, PMID 28620280.
14. Sałat K. Chemotherapy induced peripheral neuropathy-part 2: Focus on the prevention of oxaliplatin induced neurotoxicity. Pharmacol Rep. 2020;72(3):508-27. doi: 10.1007/s43440-020-00106-1, PMID 32347537.
15. Kang L, Tian Y, Xu S, Chen H. Oxaliplatin induced peripheral neuropathy: Clinical features, mechanisms, prevention and treatment. J Neurol. 2021;268(9):3269-82. doi: 10.1007/s00415-020-09942-w, PMID 32474658.
16. Staff NP, Fehrenbacher JC, Caillaud M, Damaj MI, Segal RA, Rieger S. Pathogenesis of paclitaxel-induced peripheral neuropathy: A current review of *in vitro* and *in vivo* findings using rodent and human model systems. Exp Neurol. 2017;81(6):772-81.
17. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, *et al*. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162-73. doi: 10.1016/S1474-4422(14)70251-0, PMID 25575710.
18. Brami C, Bao T, Deng G. Natural products and complementary therapies for chemotherapy-induced peripheral neuropathy: A systematic review. Crit Rev Oncol Hematol. 2016;98:325-34. doi: 10.1016/j.critrevonc.2015.11.014, PMID 26652982.
19. Samuels N, Ben-Arye E. Integrative approaches to chemotherapy-induced peripheral neuropathy. Curr Oncol Rep. 2020;22(3):23. doi: 10.1007/s11912-020-0891-2, PMID 32048067.
20. Argyriou AA, Chroni E, Koutras A, Iconomou G, Papapetropoulos S, Polychronopoulos P, *et al*. Preventing paclitaxel-induced peripheral neuropathy: A phase II trial of vitamin E supplementation. J Pain Symptom Manage. 2006;32(3):237-44. doi: 10.1016/j.jpainsymman.2006.03.013, PMID 16939848.
21. Pace A, Giannarelli D, Galiè E, Savarese A, Carpano S, Della Giulia MD, *et al*. Vitamin E neuroprotection for cisplatin neuropathy: A randomized, placebo-controlled trial. Neurology. 2010;74(9):762-6. doi: 10.1212/WNL.0b013e3181d5279e, PMID 20194916.
22. Ghoreishi Z, Esfahani A, Djazayeri A, Djalali M, Golestan B, Ayromlou H, *et al*. Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: A randomized double-blind placebo controlled trial. Biomed Cent Cancer. 2012;12(355):1-8.
23. Bao T, Zhi I, Baser R, Hooper M, Chen C, Piulson L, *et al*. Yoga for chemotherapy-induced peripheral neuropathy and fall risk: A randomized controlled trial. JNCI Cancer Spectr. 2020;4(6):pkaa048. doi: 10.1093/jncics/pkaa048, PMID 33225208.
24. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011;11(9):607-15. doi: 10.1038/nri3041, PMID 21818123.
25. Duregon F, Vendramin B, Bullo V, Gobbo S, Cugusi L, Di Blasio AD, *et al*. Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. Crit Rev Oncol Hematol. 2018;121:90-100. doi: 10.1016/j.critrevonc.2017.11.002, PMID 29198853.
26. Jordan B, Jahn F, Sauer S, Jordan K. Prevention and management of chemotherapy-induced polyneuropathy. Breast Care (Basel). 2019;14(2):79-84. doi: 10.1159/000499599, PMID 31798378.
27. Song SY, Ko YB, Kim H, Lee GW, Yang JB, Chang HK, *et al*. Effect of serotonin-norepinephrine reuptake inhibitors for patients with chemotherapy-induced painful peripheral neuropathy: A meta-analysis. Medicine. 2020;99(1):e18653. doi: 10.1097/MD.0000000000018653, PMID 31895829.
28. Hu S, Huang KM, Adams EJ, Loprinzi CL, Lustberg MB. Recent developments of novel pharmacologic therapeutics for prevention of chemotherapy-induced peripheral neuropathy. Clin Cancer Res. 2019;25(21):6295-301. doi: 10.1158/1078-0432.CCR-18-2152, PMID 31123053.
29. Li Y, Lustberg MB, Hu S. Emerging. Pharmacological and non-pharmacological therapeutics for prevention and treatment of chemotherapy-induced peripheral neuropathy. Cancers. 2021;13(4):1-15. doi: 10.3390/cancers13040766, PMID 33673136.
30. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, *et al*. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. JAMA. 2013;309(13):1359-67. doi: 10.1001/jama.2013.2813, PMID 23549581.
31. Kachrani R, Santana A, Rogala B, Pawasauskas J. Chemotherapy-induced peripheral neuropathy: Causative agents, preventative strategies, and treatment approaches. J Pain Palliat Care Pharmacother. 2020;34(3):141-52. doi: 10.1080/15360288.2020.1734144, PMID 32118502.
32. Tsai CH, Lin YH, Li YS, Ho TL, Hoai TLH, Liu YH. Integrated medicine for chemotherapy-induced peripheral neuropathy. Int J Mol Sci. 2021;22(17):1-17. doi: 10.3390/ijms22179257, PMID 34502166.
33. Jensen TS. Anticonvulsants in neuropathic pain: Rationale and clinical evidence. Eur J Pain. 2002;6;Suppl A:61-8. doi: 10.1053/eujp.2001.0324, PMID 11888243.
34. Aghili M, Zare M, Mousavi N, Ghalehtaki R, Sotoudeh S, Kalaghchi B, *et al*. Efficacy of gabapentin for the prevention of paclitaxel induced peripheral neuropathy: A randomized placebo controlled clinical trial. Breast J. 2019;00:1-6.
35. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage. 2014;47(1):166-73. doi: 10.1016/j.jpainsymman.2013.02.018, PMID 23742737.
36. Lee G, Kim SK. Therapeutic effects of phytochemicals and medicinal herbs on chemotherapy-induced peripheral neuropathy. Molecules. 2016;21(9):1-17. doi: 10.3390/molecules21091252, PMID 27657026.

Cite this article: Jain A, Hariprasad MG, Sharique M. Chemotherapy-Induced Peripheral Neuropathy. Indian J of Pharmaceutical Education and Research. 2023;57(2):342-53.