Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Frequently Asked Questions

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What is CIPN?

CIPN is the abbreviation for chemotherapy-induced peripheral neuropathy, which is a progressive, enduring, and often irreversible condition featuring symptoms such as pain, numbness, tingling, and sensitivity to cold in the hands and feet. It is estimated that CIPN afflicts between 30% and 40% of patients undergoing chemotherapy.[1]

What is the cause of CIPN?

The classes of chemotherapy drugs that cause CIPN include platinum agents, such as oxaliplatin; taxanes, such as docetaxel; vinca alkaloids, such as vincristine; and proteasome inhibitors, such as bortezomib.[1]

The causes of CIPN are multifactorial. Pinpointing the exact underlying mechanisms of CIPN in patients with cancer is difficult because of the extensive comorbidities that exist in this patient group.[2]

Several factors influence the incidence of CIPN in patients receiving neurotoxic chemotherapy, including patient age, dose intensity, cumulative dose, duration of therapy, coadministration of other neurotoxic chemotherapy agents, preexisting conditions such as diabetes, and alcohol abuse.[3,4]

A number of molecular mechanisms have been implicated in the development of CIPN (**Figure 1**). These mechanisms target several different components of the peripheral nervous system.[5]

What increases the risk of developing CIPN?

Higher individual doses of a chemotherapy agent, combination chemotherapy regimens, or a longer course of chemotherapy may increase the risk of CIPN. The overall incidence of CIPN is estimated to be approximately 38% in patients treated with multiple chemotherapeutic agents.[1]

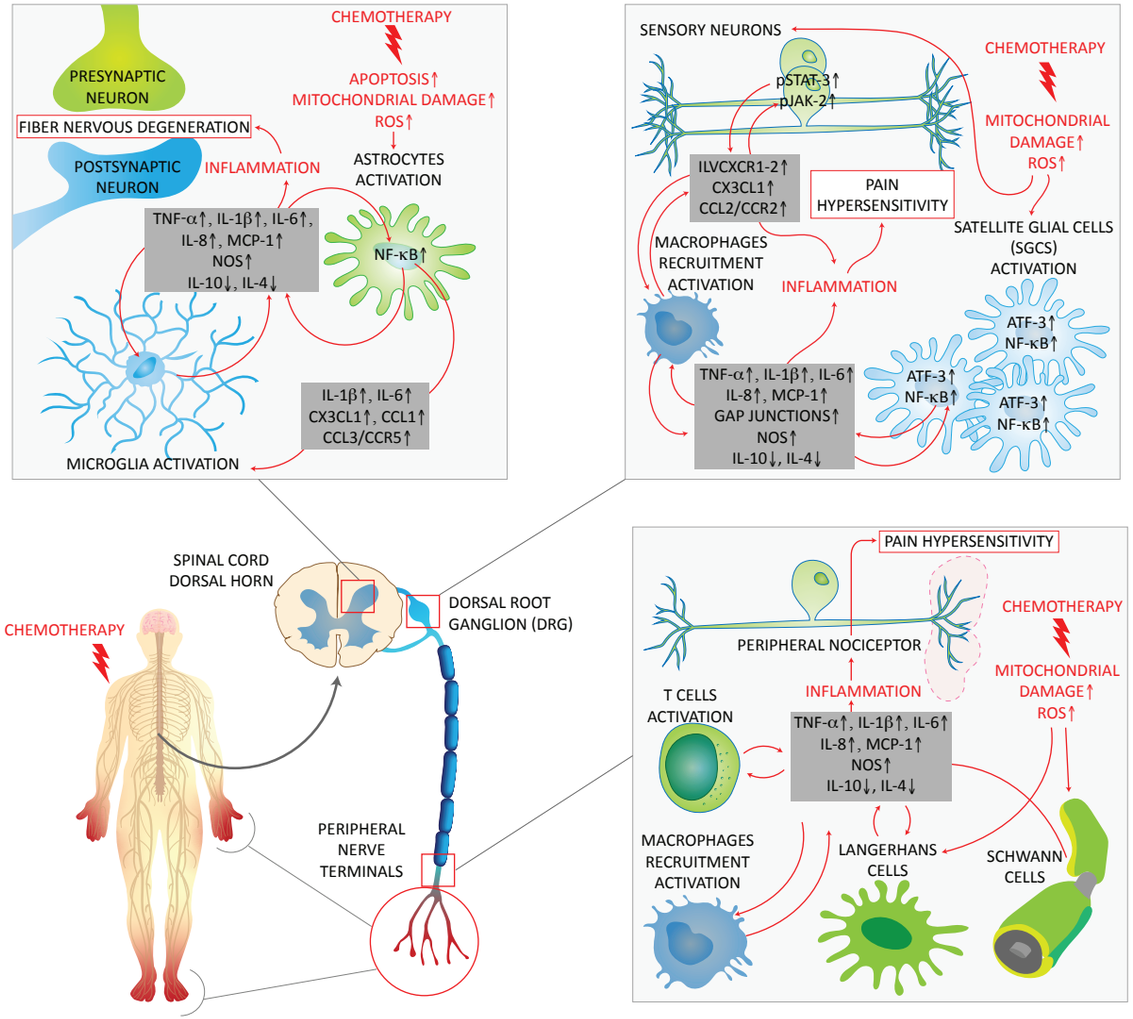
Patients who are older and those with a history of diabetes, smoking, vitamin deficiencies, reduced renal function, or peripheral neuropathy are at a greater risk of CIPN, as are patients with preexisting neuropathy.[3,4,6]

Ghoreishi et al (2018) reported that age, body surface area, and hormone status (progesterone receptor–positive [PR+]) are risk factors for CIPN and should be considered before commencement of chemotherapy with paclitaxel in patients with breast cancer.[7] Older patients, those with greater body surface area, and patients with PR+ disease may need closer follow-up and more medical attention due to the greater incidence and severity of CIPN.

Some neurotoxic events are attributable to Cremophor EL®.[6] Because taxanes such as paclitaxel are poorly soluble in an aqueous medium but soluble in organic solvents, they are formulated in a vehicle that increases solubility, which is composed of a 1:1 blend of Cremophor EL and ethanol. This blend is diluted with normal saline or dextrose solution (5%) by 5- to 20-fold for intravenous administration. The neurotoxic events attributable to Cremophor EL include ganglionopathy, axonopathy, and demyelination. These events are most likely induced by peroxidation products of residual unsaturated fatty acids.[6]

In addition, clinical data suggest a direct and independent effect of paclitaxel in the development of peripheral neuropathy. Neurotoxicity represents the major remaining challenge for further improvement of paclitaxel administration, because neurotoxicity is due not only to the Cremophor EL in the intravenous formulation but also directly to the paclitaxel molecule itself.[8]

Figure 1. Mechanisms of CIPN[5]



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ATF, activating transcription factor; CCL, chemokine (C-C motif) ligand; CCR, chemokine receptor; CXCR, CXC chemokine receptor; CX3CL, C-X3-C motif ligand; IL, interleukin; MCP, monocyte chemoattractant protein; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOS, nitric oxide synthase; pJAK-2, phosphorylated form of Janus kinase 2; pSTAT-3, phosphorylated form of signal transducer and activator of transcription 3; ROS, reactive oxygen species; TNF, tumor necrosis factor.

How can the risk of CIPN be reduced?

Regular exercise, reducing alcohol use, and treating preexisting medical conditions (eg, vitamin B12 deficiency) may reduce the risk of CIPN.[9-11]

Can CIPN be prevented?

Some data support the benefit of calcium-magnesium in the prevention of oxaliplatin-induced neurotoxicity and suggest that treatment with calcium-magnesium does not interfere with oxaliplatin-based antitumor activity.

Omega-3 fatty acids may be an efficient neuroprotective agent for prophylaxis against CIPN. A study reported by Ghoreishi et al (2012) showed that 70% (21/30) of patients taking omega-3 fatty acid pearls (640 mg 3 times daily) during treatment with paclitaxel and for 1 month following the last dose did not develop CIPN, compared with 40.7% (11/27) in the placebo group. A significant difference was seen in CIPN incidence (odds ratio [OR] 0.3; 95% confidence interval [CI] 0.10-0.88; $P = 0.029$). There was a nonsignificant trend in differences of CIPN severity between the two study groups; however, the frequencies of CIPN in all scoring categories were higher in the placebo group.[12] There are data to suggest that vitamin E may potentially decrease the incidence and/or severity of CIPN.[11,13] Two small randomized trials suggest that glutathione is beneficial for the prevention of cisplatin- and oxaliplatin-induced peripheral neuropathies; another trial demonstrated that the addition of glutathione to cisplatin therapy reduced toxicity and allowed more cycles of treatment to be administered.[9]

What is the pathophysiology of CIPN?

CIPN results from a number of cellular-level alterations, including electrical signaling enhancement through voltage-gated ion channels, increases or decreases in neurotransmission, and changes in specific receptor subtypes. Furthermore, CIPN involves impairments in cellular structures. Many of these impairments are related to the activation of various intracellular pathways.[14]

- The sodium voltage (Na_v) channels, which are some of the most abundant voltage-gated ion channels, are strongly implicated in the development and maintenance of CIPN with some agents.
- Potassium channels, specifically the potassium voltage 7 (Kv7) family, can contribute to neuropathic pain.[14]
- The voltage-gated calcium channels consist of a diverse family of subtypes, with several indicated as contributing to CIPN in animal models.[14]

Alterations in processes involved primarily in neurotransmitter signaling following chemotherapy treatment have been documented in numerous studies.[14]

- Glutamate transporters have been shown to be diminished following treatment with bortezomib, paclitaxel, and vincristine in spinal astrocytes in in vitro studies using rat tissue.
- There is evidence in animal models that 5-HT receptor changes are involved in CIPN.
- The transient receptor potential (TRP) channels, especially the TRP vanilloid (TRPV) family, have been widely studied with regard to the development of CIPN. Evidence collected from in vitro and in vivo studies in rats and mice supports the idea that TRPV1 is responsible for the heat-sensitive hyperalgesia and mechanical allodynia in sensory neurons induced by cisplatin, oxaliplatin, bortezomib, and paclitaxel.

Changes in neuronal and glial structures have been demonstrated following chemotherapy and have been shown to be related to the development of CIPN.[14]

CIPN is a complex condition that is best understood by incorporating mechanisms that extend beyond traditionally understood neuronal and neuronal/glial function. Cytokines and chemokines can have a profound impact on cells. The inflammatory response triggered by chemotherapeutic agents has been implicated as a cause of the nociceptive process in CIPN.[5]

- The importance of the chemokine (C-C motif) ligand 2 (CCL2)–chemokine receptor type 2 (CCR2) signaling pathway is well established in paclitaxel animal models of CIPN, whereby CCL2/CCR2-mediated signaling is linked to the recruitment and activation of monocytes and the development of pain hypersensitivity.[5]
- Paclitaxel is known to activate toll-like receptor-4 signaling in rodents that mimics molecular damage. This suggested mechanism induces increased expression of CCL2, thereby promoting macrophage infiltration of the dorsal root ganglion in CIPN.[5]

Are there genetic factors that influence CIPN development?

A recent meta-analysis of 93 studies identified consistent single-nucleotide polymorphism (SNP) changes related to some chemotherapeutic agents. For example, CIPN resulting from paclitaxel treatment was associated with *CYP2C8*3*, and vincristine-related CIPN risk was increased with *CYP3A5*3*. Both genes belong to the CYP450 family, which is involved with drug metabolism. However, currently it is unclear how these genes contribute to the development of CIPN.[14]

A genome-wide genotyping evaluation in women receiving single-agent paclitaxel as adjuvant therapy for breast cancer identified several novel genetic loci related to paclitaxel-induced sensory peripheral neuropathy. A common genetic variant in *FGD4*, a causal gene for the congenital peripheral neuropathy Charcot-Marie-Tooth disease, was associated with increased onset of neuropathy in both Europeans and African Americans. This variant was validated as a genetic predictor of paclitaxel-induced sensory peripheral neuropathy.[15]

Schneider et al reported a genome-wide association study (GWAS) in 3,431 patients from a phase 3 adjuvant breast cancer trial (ECOG-5103) to compare genotypes with taxane-associated CIPN.[16] These investigators also performed candidate validation of top SNPs for CIPN in another phase 3 adjuvant breast cancer trial (ECOG-1199).[17]

In an evaluation of the incidence of grade 3-4 CIPN in ECOG-5103, 120 SNPs had a *P*-value of $<10^{-4}$ associated with patients of European descent. In ECOG-1199, 30 candidate SNPs were subsequently tested, and SNP *rs3125923* was found to be significantly associated with grade 3-4 CIPN ($P = 1.7 \times 10^{-3}$; OR 1.8). Race was also a major predictor of CIPN; patients of African descent experienced an increased risk of grade 2-4 CIPN (hazard ratio [HR] 2.1; $P = 5.6 \times 10^{-16}$) and grade 3-4 CIPN (HR 2.6; $P = 1.1 \times 10^{-11}$) compared with others. A SNP in *FCAMR, rs1856746*, showed a trend toward an association with grade 2-4 CIPN in patients of African descent from the GWAS in ECOG-5103 (OR 5.5; $P = 1.6 \times 10^{-7}$).[16]

rs3125923 represents a SNP validated to predict grade 3-4 CIPN. Genetically determined race of African descent represents the most significant predictor of taxane-associated CIPN.[16]

What are the symptoms of CIPN?

Neurotoxic chemotherapeutic agents may cause structural damage to peripheral nerves, resulting in aberrant somatosensory processing of the peripheral and/or central nervous system.[18]

A common clinical course begins with paresthesia (tingling, “pins and needles”) and dysesthesia (pain, burning, itching), commonly located in the toes and fingers. These symptoms then spread to affect both lower and upper extremities in a characteristic “glove and stocking” distribution.[18]

When do symptoms occur?

The onset of CIPN is usually delayed and appears to depend on the total cumulative dose of chemotherapy. Symptoms commonly occur in weeks to months after the administration of chemotherapy. However, symptoms can also occur in hours to days and can worsen with additional cycles of chemotherapy. Two drugs that are exceptions, paclitaxel and oxaliplatin, may cause an acute neuropathy that emerges either during or shortly after infusion.[19]

In severe cases, these symptoms can progress to a loss of sensory perception. Motor symptoms occur less frequently than sensory symptoms and generally present as distal weakness, gait and balance disturbances, and impaired movements. These symptoms have a marked impact on quality of life and safety; for example, patients with cancer who develop CIPN are three times more likely to experience a fall compared with those without CIPN.[4]

How long do symptoms persist?

In a study by Park et al, 108 patients receiving oxaliplatin therapy for colorectal cancer were followed for more than 2 years (median follow-up 25 months).[20] Most patients (95.8%) being treated with oxaliplatin reported acute neuropathic symptoms, including cold-triggered paresthesia and dysesthesia, muscle fasciculations, and cramps. The investigators noted that 30.4% of patients experienced an oxaliplatin dose reduction because of the severity of persisting neuropathic symptoms and 33.3% of patients stopped oxaliplatin treatment prematurely because of neurotoxicity.

Similar to other platinum-based chemotherapies, patients treated with oxaliplatin may develop worsening neuropathic symptoms after treatment has stopped. This is called the “coasting” phenomenon. Overall, 25% of patients reported worsening of neuropathic symptoms following completion of oxaliplatin treatment. During treatment, 29.2% of patients experienced mild neurotoxicity (grade 1), 41.6% experienced moderate neurotoxicity (grade 2), and 29.2% experienced severe neurotoxicity (grade 3).

At the time of follow-up (29 ±4 months post-oxaliplatin), 79.2% of patients reported persistent neuropathic symptoms. Residual sensory neuropathic symptoms in the upper limbs were reported by 45.8% of patients; 79.2% of patients reported residual symptoms in the lower limbs, primarily numbness in the extremities. All symptomatic patients reported numbness as the primary symptom.[20]

Can CIPN be treated, and if so, how?

There are presently no effective treatment options for CIPN, and its exact pathophysiology remains unclear. CIPN is most commonly considered neuropathic pain due to axonopathy by dying back axonal degeneration. Unfortunately, most of the pharmacologic treatments for neuropathic pain (eg, tricyclic antidepressants, antiepileptic drugs, and adjuvant analgesics) are minimally effective in CIPN, and while some have shown some activity in reducing neuropathic pain, many have unacceptable side effects.[21]

To date only duloxetine is recommended by the American Society of Clinical Oncology (ASCO) for the treatment of CIPN, on the basis of a modest positive result in a single randomized controlled trial.[21]

Although not a treatment for CIPN, newer formulations of paclitaxel that do not contain Cremophor EL are being investigated and have been shown to result in a lower incidence of CIPN.

In order to develop effective treatments for CIPN, a better understanding of its pathophysiologic mechanisms is needed. It is still unclear why some agents that benefit diabetic peripheral neuropathic pain are not effective for treating CIPN.[21]

What factors may contribute to the incidence or severity of CIPN, and what evidence is there to support prevention and management of CIPN?

As in other studies, Mongiovi et al found that reporting of worse neuropathy was associated with increasing age, being overweight or obese, a change in weight from baseline, and being postmenopausal.[10]

The 2014 ASCO Clinical Practice Guideline Committee evaluated the evidence supporting prevention and management of CIPN and determined that there are no established agents recommended for the prevention of CIPN in cancer patients undergoing treatment with neurotoxic agents. This is based on the paucity of high-quality, consistent evidence and a balance of benefits versus harms.[1]

Although the data on venlafaxine support its potential utility, the evidence was not strong enough to recommend the use of venlafaxine in clinical practice. No recommendations can be made on the use of N-acetylcysteine, carbamazepine, glutamate, glutathione for patients receiving cisplatin- or oxaliplatin-based chemotherapy, goshajinkigan (GJG), omega-3 fatty acids, or oxcarbazepine for the prevention of CIPN.[1]

Acetyl-L-carnitine may worsen CIPN when given during chemotherapy.[9]

Given the limited options available for this prominent clinical problem, the ASCO committee felt that duloxetine may be used. Because of the demonstrated efficacy of tricyclic antidepressants in other neuropathic pain conditions, it is reasonable to try a tricyclic antidepressant (eg, nortriptyline or desipramine) in patients suffering from CIPN. Data are limited regarding the efficacy of gabapentin, but the committee felt that this agent may be used in selected patients with CIPN pain given the established efficacy of gabapentin and pregabalin for other forms of neuropathic pain.[1]

A topical gel treatment containing baclofen (10 mg), amitriptyline HCl (40 mg), and ketamine (20 mg) did decrease CIPN symptoms in a single trial to date and may be tried in selected patients with CIPN pain, following a discussion about the limited scientific evidence for use of the gel in CIPN, potential harms, benefits, cost, and patient preferences.[1]

Are there any racial or ethnic differences in the incidence or severity of CIPN?

Schneider et al reported that race is a major predictor of CIPN. Patients of African descent experienced an increased risk of grade 2-4 CIPN (HR 2.1; $P = 5.6 \times 10^{-16}$) and grade 3-4 CIPN (HR 2.6; $P = 1.1 \times 10^{-11}$) compared with others.[16]

What is the impact of CIPN on quality of life?

Neuropathy symptoms can last for months and even years after the end of chemotherapy, and a lack of supportive care is associated with depression, sleep disorders, and a decrease in health-related quality of life (HRQoL). Findings from a study by Tofthagen et al suggest that oxaliplatin-induced peripheral neuropathy remains a significant problem for survivors of colorectal cancer and is associated with increased depressive symptoms, reduced sleep quality, and reduced HRQoL.[22]

What is the economic impact of CIPN?

Few data exist regarding the health outcomes of patients with CIPN, the effects of CIPN on chemotherapy treatment, and the associated costs. Berger et al suggest that neuropathies in general can lead to adverse outcomes and higher costs, and that patients with neuropathies had healthcare costs triple those of controls. However, the study did not examine the costs associated with chemotherapy-related neuropathies specifically.[23]

Calhoun et al conducted a pilot study on the medical and work-loss costs associated with chemotherapy-induced toxicities in women with ovarian cancer.[24] Using survey data from 42 patients with chemotherapy-induced neurotoxicities, the study found the medical costs directly attributable to CIPN were $688 per episode but that indirect costs (patient and caregiver work-loss and paid caregiver costs) were higher than $4,220 per episode. This pilot study had limitations in that it relied on patient recall of medical services used over 3month intervals, and the sample was limited to women with ovarian cancer and did not consider other cancer types.[24]

A study by Pike et al assessed health outcomes as well as the healthcare (medical and drug) and work-loss cost burden of patients with CIPN (cases) in four tumor types (breast, ovarian, head/neck, and non-small cell lung cancer) from a third-party payor/employer perspective.[25] The study compared the healthcare costs of CIPN cases with those of matched controls who had the same cancer but no CIPN, work-loss costs in patients with and without CIPN, and the healthcare costs of CIPN cases and non-CIPN controls with comorbid diabetes. By examining these four tumor types, the study captured the use of the chemotherapeutic agents most commonly associated with CIPN.

Average healthcare costs were $17,344 higher for CIPN cases than for their non-CIPN controls; outpatient costs were the highest-cost component (CIPN cases had excess outpatient costs of $8,092). On average, each CIPN case had 12 more outpatient visits than controls, and spent more days in the hospital. Work-loss burden was higher for CIPN cases but not statistically different from that of controls.[25]

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Notes

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