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CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY, CLINICAL MANIFESTATIONS AND MANAGEMENT STRATEGIES

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of chemotherapy that damages peripheral nerves, causing sensory, motor, and autonomic abnormalities that significantly decrease the quality of life for cancer patients. Characterized by symptoms such as numbness and tingling, the incidence of CIPN can reach 68% in the first month post-therapy. The severity of this condition often forces a dose reduction or discontinuation of chemotherapy, which can compromise the effectiveness of cancer treatment. Based on this literature review of the last 10 years, CIPN is a significant clinical challenge. Therefore, comprehensive clinical guidelines for its diagnosis, symptom management, and prevention are needed to optimize cancer therapy outcomes.

Keywords: CIPN; chemotherapy; neuropathy; cancer therapy

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INTRODUCTION

Neuropathy is a condition that involves damage to the nervous system, and approximately 2.4 percent of the population is affected by peripheral neuropathy, with diverse pathological manifestations that require further evaluation and therapy (Hammi and Yeung, 2022). Peripheral neuropathy includes a variety of diseases involving nerve cells and nerve fibers, including cranial nerves, spinal nerve roots and ganglia, nerve trunks and divisions, along with the autonomic nervous system(Hammi and Yeung, 2022). Symptoms of peripheral neuropathy are numbness, paresthesia, pain, weakness, and loss of deep tendon

reflexes (Lehmann *et al.*, 2020; Hammi and Yeung, 2022). One of the causes of peripheral neuropathy is chemotherapy agents (Zhang, Chen and Huang, 2017; Hammi and Yeung, 2022). The effects of chemotherapy on the nervous system vary among the different classes of drugs and its single or cumulative doses (Zajaczkowską *et al.*, 2019). The condition where peripheral neuropathy appears after chemotherapy is called chemotherapy-induced peripheral neuropathy (CIPN) (Zhang, Chen and Huang, 2017; Zajaczkowską *et al.*, 2019).

The prevalence and incidence of Chemotherapy-Induced Peripheral Neuropathy (CIPN) are known to exhibit significant variation contingent upon several key factors. These include the specific chemotherapeutic agent utilized, the cumulative dose, the duration of treatment, and the assessment modality employed (Maihöfner et al., 2020).Following chemotherapy, acute CIPN symptoms may develop within hours or days, with approximately 68% of patients still reporting persistent neuropathy one month later. The prevalence of long-term symptoms, lasting five months or more, is estimated at 30% to 40%, and in some cases, these symptoms endure for years. The rising rates of cancer survivorship have led to a corresponding increase in CIPN prevalence, which significantly impacts patients' functional abilities and overall quality of life (Quintão *et al.*, 2019; Maihöfner *et al.*, 2020; Omran *et al.*, 2021).

Dose modifications, including reduction, delay, or cessation of chemotherapy, are the primary strategies for managing CIPN. However, this approach carries a substantial risk of compromising treatment efficacy and worsening patient outcomes. Specifically, reducing the dose of curative-intent adjuvant therapies in breast or colon cancer to mitigate CIPN can lead to inferior oncological results, affecting both disease control and survival rates. Evidence indicates that Chemotherapy-Induced Peripheral Neuropathy (CIPN) significantly compromises the quality of life (QoL) of cancer patients. For instance, among lung cancer patients undergoing platinum-based chemotherapy, CIPN can impair physical activity, reduce independence in activities of daily living (ADLs), and limit self-care capabilities. Furthermore, a positive correlation has been observed between the severity of CIPN and psychological distress; cancer survivors with more severe neuropathy report a higher incidence of anxiety and depression (Bonhof *et al.*, 2019; Hung *et al.*, 2021).

The underlying mechanism of Chemotherapy-Induced Peripheral Neuropathy (CIPN) is recognized as a complex and multifactorial process involving various components of the nervous system. While this complexity has been a focal point of numerous scientific studies and reviews, the exact pathogenesis induced by anticancer agents has not yet been definitively established Maihöfner *et al.*, 2020). Given the substantial clinical burden of Chemotherapy-Induced Peripheral Neuropathy (CIPN) on cancer patients, a comprehensive understanding of this condition is imperative. To this end, this review provides a consolidated overview of its core aspects. Specifically, this article will discuss the current knowledge of CIPN's pathophysiology, clinical manifestations, diagnostic approaches, and contemporary management strategies.

RESEARCH METHOD

The method used in this literature review is researching, reading, analyzing, and summarizing literature that is appropriate to the topic of the literature review. We searched the literature using Pubmed Central, Google Scholar, Cochrane, and Elsevier sites, and we selected the latest 10 years of publication.

RESULTS AND DISCUSSION

Currently, cancer is the main cause of death worldwide. Chemotherapy agents are therapy that is often used in cancer. This therapy effectively fights the cancer cells because the chemotherapy agents directly target and eliminate the process of cancer cell proliferation. However, even though chemotherapy is considered an effective therapy to fight cancer, this therapy can still cause side effects when used due to the possibility of affecting normal body cells, causing signs and symptoms such as anemia, changes in appetite, nausea, vomiting, diarrhea, constipation, susceptibility to infection, fluid retention, fatigue, hair loss, infertility, neurological changes, pain and peripheral neuropathy (Zhang, Chen and Huang, 2017; Zajaczkowską *et al.*, 2019).

Peripheral neuropathy that occurs as a result of the use of chemotherapy agents is called chemotherapy-induced peripheral neuropathy (CIPN), which causes peripheral nerve damage and results in sensory, motor, and autonomic abnormalities, due to use of these chemotherapy agents (Zhang, Chen and Huang, 2017; Maihöfner *et al.*, 2020). CIPN is characterized by sensations of numbness, tingling, and burning in the hands and feet (Kim, 2020). CIPN as the name suggests, is a common complication due to the anti-cancer therapy, that can occur during and after the regimen of chemotherapy is finished (Colvin, 2019). The incidence of CIPN was found to be 68% in patients undergoing therapy with chemotherapy agents in the first month, 60% at three months, and 30% at six months post-chemotherapy (Kim, 2020). The presence of neuropathy as a side effect of chemotherapy agents will certainly affect patient's quality of life (Zhang, Chen and Huang, 2017). Moreover, CIPN that occurs in an acute onset with a severe manifestation can affect the dosage of chemotherapy agents or even stop the course of the therapy regimen, potentially increasing morbidity and mortality from cancer (Gewandter *et al.*, 2020; Kim, 2020).

Chemotherapy Agents associated with CIPN

CIPN is often caused by first-line chemotherapy agents, such as taxanes (paclitaxel, docetaxel), platinum agents (cisplatin, carboplatin, oxaliplatin), vinca alkaloids (particularly vincristine), epothilones (such as ixabepilone), proteasome inhibitors (such as bortezomib), and immunomodulating drugs (Brewer *et al.*, 2016; Ibrahim and Ehrlich, 2020; Kim, 2020).

The Mechanism of CIPN

Chemotherapy agents can cause changes in cell structure and function, leading to toxic effects that are progressive, continuous, and generally irreversible (Ibrahim and Ehrlich, 2020). CIPN can occur at any point after the initial treatment including weeks to months after treatment has ended (Brewer *et al.*, 2016).

Chemotherapy agents can cause injury to the nervous system and different compounds can give a different neuropathy effect. This toxicity can occur from a high single dose or after repeating doses (Zajaczkowską et al., 2019). Repeated treatments using taxanes, vinca alkaloids, platinum drugs, bortezomib, and thalidomide can increase the risk of causing CIPN. CIPN developed mainly through mitochondrial toxicity, oxidative stress, DNA damage, axonal transport disruption, and ion channel remodeling in peripheral nerves. Taxanes and vinca alkaloids work on making microtubules incapacitated. Microtubule dysfunction disrupts the axonal transport of cell products important in axon function and structure (Staff *et al.*, 2017; Desforges *et al.*, 2022).

One example of taxanes drugs is paclitaxel. Neuropathic pain caused by paclitaxel was known to be accompanied by a reduction in small fiber sensory axons. Many reports also describe the degeneration of fine-intradermal nociceptive fibers, axonal demyelination, and Meissner's corpuscles loss. Paclitaxel also induces mitochondrial damage indirectly by causing changes in mitochondrial membrane potential and subsequent calcium release. This damage induces the release of reactive oxygen species (ROS), resulting in intra-oxidative stress inside the axon. Paclitaxel can cause inflammation via numerous pro-inflammatory chemokines released from dorsal root ganglion (DRG) neurons or associated cells (Staff et al., 2020).

Vincristine is categorized as vinca alkaloid drug. Other than targeting microtubules, vincristine also induces the expression of integrins (immune markers) on endothelial cell surfaces. This action will allow macrophages to express CX3CR receptors to adhere to the endothelium and migrate towards nervous tissue. This process will produce ROS that will act as an immune-neural mediator and by that evoke pain. Mitochondria is the third mechanism for vincristine-induced peripheral neuropathy. By altering the movement of $Ca2^{+}$ across the mitochondrial membrane, mitochondrial function will differ and consequently increase neurotransmitter exocytosis and ROS release. These alterations will lead to the reduction of neuronal excitability and glial function, activating apoptosis (Triarico *et al.*, 2021).

Platinum agents target DNA and induce neural toxicity through dorsal root ganglion (DRG). Platinum agents change the size of nucleolar in the sensory DRG cells (Desforges *et al.*, 2022). Cisplatin usually induces neuropathy when the dose reaches >350 mg/m^2. Neuropathy induced by cisplatin usually manifests at the lower and upper extremity as tingling, numbness, and mechanical and thermal hyperalgesia. With a higher cumulative dose, neuropathy may become chronic and irreversible (Starobova and Vetter, 2017; Desforges *et al.*, 2022)**.** Oxaliplatin can cause acute and chronic neuropathy. These two types of neuropathies induced by oxaliplatin work differently. The acute neuropathy mechanism involves changes in voltage-gated Na^{+} channels, K^{+} channels, Ca^{2+} channels, transient receptor potential channels, OCT2 protein, and glial cells. The chronic main mechanism were nuclear DNA damage, mitochondrial damage, overload oxidative stress, glia activation, and neuroinflammation (Kang *et al.*, 2021)

Bortezomib is a first-generation proteasome inhibitor and often used for the treatment of multiple myeloma. The mechanism of bortezomib is by acting on sphingolipid metabolism alteration in astrocytes which involved in pain modulation and perception. Other pathological aspect that was observed was mitochondrial and endoplasmic reticulum morphological alteration, oxidative stress, sensitization of transient receptor potential ankyrin 1 (TRPA1), and neuroinflammation. Bortezomib does not penetrate the blood-brain barrier but accumulates at DRG and causes neurotoxicity (Yamamoto and Egashira, 2021; Desforges *et al.*, 2022). Thalidomide is a glutamic acid derivative and is hypothesized to work on immunomodulation, angiogenesis inhibition, and cytokine alteration. Thalidomide works by downregulating TNF- α and NF-kB, resulting in neurotrophin dysregulation and subsequently accelerating neuronal cell death. Neurotoxicity caused by thalidomide increased when the accumulative dose reached 20 g (Zajaczkowską *et al.*, 2019; Desforges *et al.*, 2022).

Clinical Manifestations of CIPN

Clinical symptoms of CIPN generally appear with pure symptoms of sensory neuropathy which are symmetrical (numbness, loss of proprioception sense, tingling, pins, and needles sensation, hyperalgesia or allodynia) in the hands or feet in a stocking-glove distribution (Brewer *et al.*, 2016). Patients usually describe this neuropathy as burning, shooting, stabbing, electrical shocks, "like walking on glass", or "as if wearing gloves with bees inside" (Colvin, 2019). Pain can appear early in the treatment cycles, meanwhile, the numbness and tingling develop later and can last years after cessation of treatment. CIPN distribution in the form of "glove and stocking" is associated with anti-tumor agents that target longer axons located in the extremities (Ibrahim and Ehrlich, 2020).

CIPN can also present with damage to motor fibers, causing motor neuropathy, commonly due to paclitaxel and vincristine. Meanwhile, autonomic neuropathy is related to vinca alkaloids, causing orthostatic hypotension, severe constipation, and erectile dysfunction (Brewer *et al.*, 2016). In chronic conditions, some patients are found with unsteady gait, difficulty walking or feeling small objects, or difficulty buttoning clothes (Ibrahim and Ehrlich, 2020). Patients having a severe form of CIPN also show fatigue, pain, and gastrointestinal disorders. These persistent symptoms are associated with an increased risk of falling, disability, and psychosocial distress. CIPN symptoms are known to be dose-dependent and no biomarker is clinically valid for diagnosing and monitoring CIPN (Avallone *et al.*, 2022). CIPN can affect the autonomic nervous system leading to autonomic dysfunction which can manifest as orthostatic hypotension, cardiac dysthymia, sweat abnormality, incontinence, erectile dysfunction, or gastrointestinal symptoms. Histopathologic evaluation of nerve biopsies can be used for diagnosing and detecting changes in peripheral nerves. Early CIPN started from the distal nerve which makes the sural nerve the most appropriate location to take biopsy (Eldridge, Guo and Hamre, 2020).

Treatment of CIPN

Therapy for CIPN can be categorized into pharmacological and non-pharmacological. Non-pharmacological treatments are diet and exercise. There are different results regarding the benefits of diet. Studies using mouse models have shown that a fenofibrate-enriched diet can prevent the development of mechanical and cold hypersensitivity and also reduce sensory nerve action potential. Flavonoid is another substance that is considered beneficial due to its mechanisms. Magnesium and multivitamin were correlated with a lower risk of CIPN or less severe symptoms. Other studies found that patients consuming a higher intake of vegetables, fruits, and dietary fat have more neuropathy symptoms (Maihöfner *et al.*, 2020; Mezzanotte *et al.*, 2022). Acetyl-L-carnitine (ALC) has been shown to give neuroprotective, analgesic, and regeneration effects. With these benefits, ALC was proven not to disturb the activity of the antitumor drug. In taxane-induced neuropathy, ALC was shown to be ineffective and can exacerbate CIPN. Vitamin B group including B1, B2, B3, B5, B6, B12, folate, choline, and biotin helps in neurotransmitter and membrane synthesis. Prevention using vitamin B complex supplementation was shown to be ineffe

ctive but still showed some effect on reducing sensory peripheral neuropathy. Meanwhile, CIPN patients with comorbid of vitamin B12 deficiency showed a beneficial result from taking vitamin B complex supplementation. Another vitamin that shows a

possible benefit in improving CIPN symptoms is vitamin E. Some studies show that taking vitamin E supplementation can reduce the incidence of CIPN and also ameliorate the neuropathy symptoms. Supplementation using vitamin E has its downside. A long-time vitamin E supplementation was known to increase the risk of prostate cancer, therefore this therapy might outweigh the beneficial effect gained (Szklener *et al.*, 2022). Exercise is another non-pharmacological treatment for CIPN. Several studies shows that exercising can reduce the progression and stabilize the symptoms of CIPN. Exercising using multiple types of training shows a better result than conventional physical therapy. Types of training programs used in those studies are progressive walking, resistance, endurance, sensorimotor, strength, and balance training. These training durations are ranging from 6 to 8 weeks of a supervised training program (Brett Whalen *et al.*, 2022). A meta-analysis by Guo et al shows that the exercise intervention group has improved quality of life, physical function, and a reduction in neuropathic pain (Guo *et al.*, 2023)

Pharmacological therapy for CIPN is important to treat the severity of symptoms which also affect the patient's quality of life. There are a few types of drug classes such as serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, gabapentinoids, opioid analgesics, and some additional agents (Burgess *et al.*, 2021; Mezzanotte *et al.*, 2022). In a newer study, gabapentin and pregabalin were found to significantly reduce pain compared to the placebo group. The visual analog scale was reduced from 8,3 + 1,43 to 1,8 + 2,51 in the gabapentin group and 8.2 + 1,62 to 0,8 + 0,96 in the pregabalin group. The adverse effects of these medications were sedation, drowsiness, diplopia, and blurring of vision. Lamotrigine was also used in treating CIPN but one study found that no pain, depression, or quality of life improvement was seen in patients with CIPN. Duloxetine is one of the most commonly used drugs in treating CIPN. This drug is still effective and well-tolerated. The effective dose is between 20 to 60 mg/day. Duloxetine is well-tolerated up to 4-6 weeks of treatment and monitoring of adverse effects should be done continuously. Common adverse effects of duloxetine are nausea, insomnia, drowsiness, constipation, dizziness, and fatigue (Wang, Chen and Jiang, 2022). Topical medication can be used as an alternative. A study by Genevois et al shows an effective treatment for neuropathic pain using 10% topical amitriptyline. Amitriptyline was administered for 1 month in severe CIPN patients (Genevois *et al.*, 2021). Capsaicin can be used as another alternative. Topical capsaicin 8% for 30 minutes was found to reduce pain significantly and may induce nerve fiber regeneration and restoration (Anand *et al.*, 2019).

Other therapeutic method is acupuncture. Acupuncture is an intervention using metallic needles that is inserted into the body's anatomical locations to stimulate the central and peripheral nervous system. In a randomized controlled trial by Lu et al, acupuncture was given for 8 weeks and another 8 weeks for follow-up in 40 breast cancer patients. This study shows a significant reduction in pain intensity, pain interference, and improvement in quality of life (Lu *et al.*, 2020). The mechanism of acupuncture in the management of CIPN is not yet clear. This treatment can increase blood perfusion in the fingertips and then improve the circulation to nourish neurons and helps in repairing neural lesion. Acupuncture has been proposed to activate GABAergic, serotoninergic, and adrenergic neurotransmission and deactivate hypersensitization of sensory neurons by modulating neurotrophins and nerve growth factors (Huang *et al.*, 2023).

Cryotherapy can be used for the management of CIPN. Frozen socks or gloves can be used for skin cooling. This cooling was found to preserve motor nerve amplitude.

Compression therapy can be an alternative to cryotherapy. This therapy uses the same mechanism by reducing the blood flow in cold tissue as the fingertips of the compressed hand had a significantly lower temperature (Jordan *et al.*, 2019)

CONCLUSION

CIPN represents a major concern in cancer therapy because it can affect the dosage of chemotherapy agents or even stop the course of the therapy regimen, related to its nerve-damaging adverse effect of anticancer drugs used in chemotherapy. CIPN still needs clinical guidance for diagnosis, treatment or symptom management, and prevention.

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