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Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer Patients: A Narrative Review

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ABSTRACT

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of paclitaxel- and taxanes-based chemotherapy, which is generally given to breast cancer and can lead to low quality of life along with neuropathy symptoms even after completion of the chemotherapy treatment.

Methods: In this paper, we present a narrative overview of CIPN, chemotherapy medication that causes neuropathy in breast cancer patients, treatment challenges for CIPN and pathological complications, current trends, and future research challenges, based on expert discussion and a current literature search.

Results: At present, there are no gold-standard treatment protocols available, which has made it more devastating for the patients suffering from breast cancer. The incidence rate of CIPN is 19% to 85% or above, and it can only decrease if treatment is available. Moreover, treatments are available, but only based on the symptoms.

Conclusion: Worldwide, cancer is the primary cause of millions of deaths annually. We still lack an appropriate treatment plan for the adverse effects that follow chemotherapy treatment, despite the fact that cancer treatment has advanced over the last decade. CIPN is one of the most frequent side effects, and the patients will experience symptoms of neuropathy after one or two chemotherapy cycles. Oncology nurses play a very critical role in managing CIPN symptoms but are sometimes overlooked during the assessment period. Managing neuropathic pain, maintaining safety protocol, improving physical function, and proper standardized nursing CIPN treatment protocol should be the primary goals for managing the CIPN.

INTRODUCTION

Cancer is one of the deadliest diseases in this human era. It has been the leading cause of millions of deaths each year globally. [1-2] Breast cancer is the most frequent cancer in women worldwide, making it a significant global public health concern. Breast cancer mainly consists of a group of biologically and molecularly hazardous diseases arising from the breast. The most important causative factor for breast malignancy is notable mutations in breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2). The

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beginning of breast cancer starts in the ducts, lobules, or the tissues in between.[3-5] With almost 2 million new cases in 2022, breast cancer is the most common cancer detected in women. Its incidence and death rate have increased in the last three decades due to the change in the profile of the risk factor. Approximately 80% of breast cancer women nowadays are older than 45 to 50 years old. The survival rate also depends on the stage and molecular types.[6]

There are several different types of breast cancer, yet the most prevalent are as follows: invasive (infiltrating) ductal carcinoma (IDC), which begins in the milk duct and spreads to nearby breast tissue; lobular breast cancer, which begins in milk-producing glands (lobules) and frequently spreads to nearby breast tissue; and ductal carcinoma in situ (DCIS), which begins in the milk duct and stays there.[5-6]

Breast cancer symptoms include changes in the dimension and shape of the breast, the presence of a tumor or lump, changes in the appearance or feel of the skin around the nipples or breast area, a hardened area beneath the skin, and a clear or blood-stained secretion from the nipple. Age, sex, genetics, family history, smoking, alcohol consumption, obesity, radiation exposure, and hormone replacement therapy are the key risk factors for breast cancer. The most significant complication of breast cancer is metastatic breast cancer, which means the cancer spreads to other areas of the body like the brain, bones, liver, and lungs, as well as peripheral neuropathy due to the complications of the treatment protocols, mainly chemotherapy.[7,5]

The main treatments available for breast cancer are surgical removal of the tumor, chemotherapy, radiation therapy, or combination therapy. The treatment is expensive and has many side effects (e.g., chemotherapy-induced nausea and vomiting, immuno- and myelosuppression, cardio-, hepato-, or nephrotoxicity, joint pain, numbness in the extremities, dizziness). Among them, chemotherapy-induced neurotoxicity is widely noticed globally and is very common in breast cancer patients. The duration of treatment may be limited by the serious impacts that chemotherapy may have on the central and peripheral neurological systems. There are numerous contemporary chemotherapeutic drugs that might cause CIPN, including taxane, paclitaxel, and platinum derivatives. This symptom can be seen within 72 hours of receiving the dosages. The prevalence of CIPN ranges from 19% to over 85%. It frequently occurs in the platinum class of chemotherapeutic medications (cisplatin, carboplatin, and oxaliplatin), comprising 10 to 80% thalidomide and its analogs and 70 to 100% taxanes (paclitaxel and docetaxel). A dosage of 20–60% increases or maximizes the chance of the chemotherapy's side effects when taken at maximum dosages and in single, large doses. Patients may have CIPN-related symptoms, such as pain or changes in bodily sensation, for months or years after finishing or stopping chemotherapy. Thus, even though the patient may recover from cancer, the anguish brought on by neurological issues brought on by chemotherapy will lower their quality of life.[8]

Clinical risk factors of CIPN

Due to the advancement of the cancer treatment, the survivability of breast cancer is increasing. However, severe CIPN can cause chemotherapy dose reduction and ultimately termination of the treatment, which can affect the overall health of the patient. Therefore, it is important to understand the risk factors before the start of chemotherapy. The main risk factor of CIPN is the chemotherapy drug itself. However, clinical and demographic factors, blood-related CIPN problems, serum micronutrients, Vitamin E, D and prealbumin are also problematic. [9] There is evidence of an indirect correlation between the pathophysiology of CIPN and thyroid dysfunction, metabolic disorders, and infectious diseases such as HIV, hepatitis B, or C. Other research indicates that patients with advanced cancer or those receiving cancer therapy, as well as those who are older, obese, or have a higher body mass index, and who experience sleep difficulties along with severe anxiety or depression, are at risk for CIPN. Genetic factors also play an important role as a risk factor for the patient. For older people, there is a 6% higher chance of developing the CIPN. [10]

Furthermore, altered neutrophil to lymphocyte ratio and pre-treatment anaemia have also been reported as risk factors for CIPN. However, different people may experience CIPN symptoms according to the type of cancer, the type of chemotherapy drugs, and the general condition of the patient. Therefore, nurses should be vigilant while doing the assessment during chemotherapy treatment. [11]

Causes of CIPN

CIPN will cause sensory neuropathy where motor and autonomic nervous systems will be affected. Generally, platinum drugs such as cis-diammine-dichloroplatinum (cisplatin) are known for peripheral neuropathy, which ultimately causes axonal degeneration due to the structural damage of the peripheral nerve. [12] In breast cancer patients CIPN can occur immediately after the administration of paclitaxel and oxaliplatin treatment, which is called a “coasting” phenomenon where the patient will start to experience tingling and burning sensations. However, taxane derivative drugs and vinca alkaloids like vincristine also play a role in developing CIPN.[13]

Additionally, the patients are more likely to develop CIPN in cases of diabetes mellitus, alcoholism, exposure to toxins, trauma or injury, the number of chemotherapy cycles, autoimmune diseases, thyroid issues, infectious diseases like lyme disease, hepatitis B, leprosy, and AIDS, as well as hereditary factors.[14] The toxicity may occur either after a single dose or multiple cycles where some patients will not experience neuropathic pain even after cessation of chemotherapy. This kind of variation will put the oncology team at risk during the treatment. So even after the successful treatment, some of the patients will suffer from neuropathic pain for many years. One of the severe complications of breast cancer treatment is breast-cancer related lymphedema (BCRL), where there is an obstruction of the lymphatic system, which can become life-threatening. Currently there is no cure for it. However, some studies suggest that axillary lymph node dissection (ALND), receiving ALND after mastectomy without radiation therapy (RT), obesity, or a higher body mass index can also increase the chances of developing BCRL. Therefore, it is important for the nurses to collect the proper history along with a standard assessment before starting chemotherapy for the breast cancer patient. [15-16]

Pathophysiological mechanisms

The chemotherapeutic drugs primarily target the peripheral nerve system, especially the dorsal root ganglion cell bodies and axons, resulting in axonal damage, mitochondrial damage, and an oxidative stage that is likely linked to inflammation. The surrounding satellites of the dorsal root ganglion show some kind of pathological change, including alterations in the level of the multiple ion channels. Each chemotherapeutic drug shows a different mechanism according to its anti-mitotic effect. The nervous system gets harmed due to the pathological effects of the chemotherapeutic drugs, which in turn develop CIPN. Many factors are responsible for the progress of CIPN in the body. The etiological factors include microtubule disturbances, oxidative stress, mitochondrial injury, and alterations in the function of the ion channel. Due to this, it can harm the myelin sheath and DNA. Microtubule disruption is a further instance of neurotoxicity. Taxane-derived agents are widely used chemotherapy drugs among breast cancer patients. The exact pathophysiology is not well understood. However, the inhibition of tubulin depolymerization and the consequent microtubule dysfunction is the widely accepted mechanism related to taxane-related peripheral neuropathy.[17] Taxanes bind to B tubular components of microtubule dynamics; this mechanism has been linked to the disruption of axonal transport. Furthermore, it has been noted that taxane treatments, both in vitro and in vivo, enhance microtubule bundling in axons, altering the mechanical properties of peripheral neurons. Moreover, damage to the mitochondria and disturbance of mitochondrial activity could play a significant role in the onset and development of CIPN. Paclitaxel-based chemotherapy is one of the major contributing factors for CIPN. Some research shows that Paclitaxel neurotoxicity is generally caused by microtubule hyperstabilization rather than an off-target effect. Generally, the distal axon is primarily vulnerable to paclitaxel, where it acts directly on the axon which ultimately causes degenerative effects. Chemotherapies, including thalidomide, have the potential to harm the peripheral vasculature due to an energy deficit, which, through antiangiogenic effects that cause axonal degeneration, lowers the blood flow to peripheral nerves. Direct axonal poisoning at the distal terminals is another target of neurotoxicity that can result in neurotoxicity and Wallerian degeneration, similar to what happens after thalidomide, vincristine, and paclitaxel treatment. However, when the peripheral nervous system's regular functions and energy supply mechanisms are interfered with, common degenerative pathways may be set off, regardless of the possibility of varied methods. There is still disagreement over the molecular pathways leading to CIPN, despite the fact that it is well known that anticancer medications may act on a variety of subcellular targets of peripheral sensory nerves and that multiple chemotherapeutic agents may share the mechanisms of CIPN regardless of their anti-tumor properties.[6,8,18]

Signs and symptoms

Thirty to forty percent of individuals may experience CIPN during and after the treatment, which can result in tingling and numbness in the hands and feet. Just after the therapy is completed, many people experience side effects within 15 to 20 minutes. For the majority of individuals, the symptoms will go away or improve in six to twelve months, but in certain situations, nerve damage is irreversible. Usually starting during or following treatment, these symptoms could get worse over time. CIPN can cause a range of other symptoms, including pain in the hands and feet, tingling or burning sensations in the hands and feet, shooting or electrical sensations in the hand, feet, or leg, ringing in the ears, difficulty picking up objects, difficulty with tasks that require close contact, such as buttoning a shirt, very cold or hot hands or feet, loss of balance, painful or difficulty in urination, constipation, and weight loss.[4,19]

Clinical assessment and diagnosis

As there is still no proper diagnosis or management for the patients, physicians are facing an abundance of challenges in their day-to-day lives. Despite issues with preventative management, it is important to screen for CIPN during the course of treatment. Diagnosing symptoms and functional impairment should be part of the assessment process.

The acquisition of medical history, physical examination, and laboratory studies—such as skin biopsies to assess cutaneous nerve innervations, nerve and muscle biopsies for histopathological examination, and electromyography with nerve conduction studies (NCS) are the primary methods used in the diagnosis of chemotherapy-induced neuropathy. NCS can help distinguish between demyelination and axonopathy pathologies, which is useful in assessing CIPN because almost all cases are related to axonopathy. A reduced amplitude of the sensory nerve action potential will be seen in the NCS.[20-21] Some of the grading scales also help in diagnosing peripheral neuropathy, which are the Eastern Clinical Oncology Group (ECOG), the National Cancer Information Center-common toxicity criteria (NCIC-CTC), the World Health Organization (WHO), and the Common Terminology Criteria for Adverse Events (CTCAE).[22] There are some self-reporting tools that are used to assess the functional capacity of the patient. These include chemotherapy-induced peripheral neuropathy assessment tool (CIPNAT), functional assessment of cancer therapy/gynecology oncology group neurotoxicity (FACT/GOG-Ntx), modified total neuropathy score (mTNS), European Organisation for Research and Treatment in Cancer Quality of Life quest-CIPN (EORTC QLQ-CIPN), total neuropathy score reduced (TNSr), and total neuropathy score clinical version (TNSc).[23-24]

Determining the extent of a patient's physical limits in their activities of daily living is an extremely challenging task. Asking the patient or a family member about their performance in daily activities, such as being unable to button shirts, walking unsteadily, falling while walking, or having trouble writing, will help us confirm whether the patient has physical limitations that affect their ability to carry out daily tasks. If such things are observed, doctors need to check, modify, and stop the chemotherapy and plan for further treatment.[25-26]

Prevention and management

Pharmacological approach and ongoing clinical trials

Although there is no CIPN treatment available right now that can heal nerve damage, a combination of alternative treatments, painkillers, vitamins, and supplements may help alleviate the symptoms. The patients who are all going through painful cancer treatment are generally prescribed duloxetine tablets for the reduction of pain, numbness, and tingling symptoms.[10,1] Pharmacological trials have been conducted involving the inclusion of acetyl-L-carnitine, acetyl cystine, alpha lipoic acid, amifostine, amitripiline, calcium/magnesium, carbamazepine, diethyldithiocarbamate, glutathione, omega-3 fatty acids, vitamin B, and vitamin E. However, none of the above trials have shown effective results. Recently, based on the clinical evidence, the use of a calcium-magnesium infusion has been proposed as a possible treatment for CIPN in oxaliplatin-treated patients, but it is yet uncertain whether to utilize it for acute or chronic CIPN.[27]

Methanol, baclofen, amitriptyline, and ketamine used locally have demonstrated significant effects on reducing neuropathic pain and improving quality of life. The symptoms of neuropathic pain can be lessened by applying a topical capsaicin 8% patch. Some ongoing clinical trials show the combination of calcium and magnesium can help patients with breast cancer reduce peripheral neuropathy.[28] However, we may need to wait for the result.

Non-pharmacological treatments

The adverse effects of chemotherapy and other pharmacological treatments on breast cancer patients are devastating. Once the medical treatment is over, healthcare workers seem to overlook the peripheral neuropathy problems. While no proper pharmacological management is available, non-pharmacological treatments have shown effectiveness in improving CIPN symptoms. The most important thing in non-pharmacological management is health education, and very good communication among the people plays an important role in the management of the CIPN. The use of vitamins, exercise, and cold applications plays a vital role in non-pharmacological treatment. There are many other therapies that have shown great productivity in treating the symptoms of CIPN including neuromodulation, transcutaneous electrical nerve impulses, and scramble therapy. However, they need clinical trials on a large-scale population.[14,19,25] A study was conducted where cryotherapy with frozen socks was given for the treatment of the CIPN in the patient, and improvement was seen in the result, but still, the proof is insufficient. Sensorimotor training near about 3 weeks could be beneficial for improving CIPN. Endurance exercises, adaptive coping, acupuncture, pain inhibiting neuromuscular release, transcutaneous electrical nerve stimulation, reflexology, and photo biomodulation have shown promising results in

improving blood flow, activating pain inhibiting receptors and also stimulating neurogenesis.[29]

Furthermore, mindfulness therapies, neurofeedback, and regular range of motion exercises can play a vital role in the strengthening of the muscles and the improvement of nerve functioning.[30,25,26] Recent research suggests that Buerger-Allen exercise (BAE) shows a promising improvement in CIPN symptoms among breast cancer patients.[31] But we do not have proper evidence about the efficacy of the exercise yet. Hopefully, in the coming days, we may see some promising non-pharmacological treatment for CIPN.

Initial screening and nursing intervention for CIPN

Chemotherapy-induced peripheral neuropathy (CIPN) is a neurotoxic disorder that can occur by the use of agents such as taxanes and vinca alkaloids and also can cluster with other treatment-related side-effects.[32] To ensure the best possible care for the breast cancer patients, nurses should be at the forefront of the CIPN education and the overall patient assessment.[33]

Initial screening and neuropathic pain

Numbness, burning sensation, and tingling are the early symptoms of the CIPN, and in breast cancer, the side effects may occur as early as 72 hours after receiving chemotherapy. Patients are sometimes reluctant to open up about the CIPN problems due to many reasons, such as fear of discontinuation from chemotherapy, not wanting to burden the clinicians, and the idea of perceiving CIPN as a normal side-effect after chemotherapy treatment. The majority of breast cancer patients will experience pain due to the progression of the disease. Therefore, they are often not able to differentiate between physical and neuropathic pain. Hence, patients will deny having the pain of peripheral areas when asked.[34] As nurses are the important aspect of the overall treatment of the breast cancer patient, it is important for the nurses to ask every patient who is receiving chemotherapy at every hospital visit regarding new numbness, tingling sensation, or discomfort in upper or lower limbs. If the symptoms are confirmed by the patient the next step is to ask the patient three questions regarding (1) neuropathic pain, (2) upper extremity loss of sensation, and (3) lower extremity loss of sensation, and the responses will determine the next course of treatment plan and additional assessment. Neuropathic pain is an additional symptom that needs to be thoroughly assessed. Generally, neuropathic pain is often described as shooting, stabbing and burning pain. However, patients may also experience lancinating pain, allodynia, muscle cramps, hyperalgesia, and loss of proprioception during the course of treatment. The healthcare team often underestimates these symptoms, so every patient who reports numbness or loss of sensation in the upper or lower extremities should be assessed for neuropathic pain. Moreover, a well-known pain assessment scale such as PQRST [35] can also be used in a clinical area to gather information about the patient's pain.[36-37]

Patient education

Patients must receive daily health education that includes symptom identification and lifestyle modification. A health education program can also be implemented in the hospital for the cancer patients receiving chemotherapy to make them understand the early symptoms of CIPN. Some of the teaching includes:

1. Teach the patient and the family members regarding the early symptoms and late symptoms of CIPN along with having a safe environment at home.
2. It is important for the patient to avoid any injury, so differentiate between neuropathic pain and other injury-related pain.
3. The patient should use a lukewarm temperature 120^0 or below if any sensational changes are suspected in the peripheral body areas.
4. The room should be properly illuminated mainly the bathroom and entrance areas along with non-skid floors and tubs.
5. The patient should not walk on the bare foot. They should always walk with footwear and use socks, which will help maintain the body temperature.
6. In cases of postural hypertension, the patient should avoid sudden rising from the bed. They must slowly get up from bed and sit in the bed for around three minutes and then get up. Also, the patients must know the symptoms of constipation, urinary retention, head spinning, etc for seeking early treatment.
7. The patient should daily check for any injury and changes in the skin colour.
8. Teach the patient for light exercises such as range of motion exercises (ROM) and walking, which will improve mood and blood circulation.
9. In case of any history of substance use, patients must stop the consumption and should increase taking green leafy vegetables and fruits that have thick skin and lots of fluids.
10. Patients should always protect their extremities such as fingers, feet and toes by wearing gloves and socks to prevent thermal injury.
11. In case of overthinking or stress, the patient must talk to the loved one, therapist, or need to try doing new activities or exploring new places, or can develop new hobbies which can help them

overcome stress. Also, they must avoid playing extreme sports to avoid injury.
12. In case of working in the garden, it is recommended to wear rubber shoes.
13. Patients should use the finger shield while chopping the vegetables.
14. Keep walkways clear and free from any sharp objects.[8,34]

CONCLUSION

For breast cancer patients, CIPN is the common side effect, and hence, proper awareness needs to be spread among the patients so that they can prevent themselves from this CIPN by decreasing the symptoms priorly. As specialized nurses are the ones who give care to cancer patients, they play a very vital role in the early identification of CIPN symptoms in breast cancer patients. Though proper treatment is not available for all patients, healthcare professionals can decrease the symptoms if informed priorly. Education for the patient is also needed about the CIPN. Therefore, in this narrative review, we tried to identify the overall dimensions of the CIPN in breast cancer patients. However, due to a lack of evidence-based conclusions from previous studies, we are unable to recommend a specific treatment to prevent CIPN in breast cancer. Therefore, we recommend nurse researchers develop and try new treatments or clinical trials to improve CIPN symptoms based on clear theoretical and evidence-based research.

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CONFLICT OF INTEREST

The author reports no conflicts of interest in this research work.

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The corresponding author can be contacted directly for access to the data.

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