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Chemotherapy Induced Peripheral Neuropathy in breast cancer Patients

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Abstract

Peripheral neuropathy induced by chemotherapy is considered the most common neurological disorder associated with chemotherapy. Different sites are involved in the mechanism of chemotherapy induced peripheral neuropathy and considered multifactorial. 68% of cases develop CIPN during the first month following the start of chemotherapy, 60% of cases develop CIPN within 3 months after chemotherapy and only 30% after 6 months. CIPN is caused by chemotherapeutic agents which include taxanes, platinum analogs, and vinca alkaloids. The clinical presentation of CIPN includes multiple symptoms that may cause functioning impairment and may require reduction of the dose of chemotherapy. CIPN considered a common sequel of different agents of chemotherapy and may last from months to years after chemotherapy completion. CIPN can be diagnosed by a detailed history and clinical examination. Clinical examination of a patient with CIPN can be done by the use of nerve conduction studies. Antidepressant includes tricyclic antidepressants and serotonin-noradrenaline reuptake inhibitors are common drugs used for CIPN. Patients may require reductions, substitutions, or stopping of chemotherapeutic agents according to the severity of symptoms.

Keywords: chemotherapy, peripheral Neuropathy, breast cancer, nerve conduction studies

Introduction:

Breast cancer in women is considered the second most common cancer in the world with, more than 2 million newly diagnosed cases in 2020. Recently, the incidence rates of breast cancer have been increased due to improvement in assessment of risk factors, registration of cases, and early detection of cancer. The survival rate is according to stage and molecular subtype [1].

Chemotherapy is classified into neoadjuvant and adjuvant chemotherapy and used in most cases of breast cancer. Choose the most appropriate one as regards the chara-cteristics of cancer. The best for locally advanced and inflammatory breast can-cers is the neoadjuvant chemotherapy, especially in large breast tumors to allow breast conserving surgery. Also, used in small tumors with worse prog-nostic subtypes such as HER2 and triple-negative breast cancers, which can be administered intravenously or orally[2] CIPN is considered frequent neurological disorder of oral and intra-venous chemotherapy occur in patients with breast cancer. Most common che-motherapeutic agents that cause CIPN include taxanes, platinum analogs, and vinca

alkaloids. Common presentations are, tingling, numbness, burning pain, and impaired sensory functions in both upper and lower limbs. Onset of pain symptoms can be acute (within hours) or chronic (after several doses of chemotherapy) [3].CIPN presents with multiple symptoms and may lead to long-term functional impairment that requires a reduction of the dose of a chemotherapeutic agent. Although 30–40% of patients have chronic symptoms, CIPN may improve after the stoppage of the chemotherapeutic agent [4].Clinical practice guidelines found that there are no agents that are highly recommended to prevent or treat CIPN [5]. Common drugs used for CIPN are serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, and pregabalin.Many clinical trials have been conducted to investigate the effectiveness of approved drugs against CIPN [6]. Most of these drugs have poor efficacy, except for duloxetine [7].

Prevalence of CIPN

The prevalence of CIPN is usually affected by the type of chemotherapy, dose, and treatment duration [8]. 68% of cases develop CIPN one month following the start of chemotherapy, 60% of cases develop CIPN within 3 months after chemotherapy, and only 30% of cases six months following treatment. [9].Symptoms of neuropathy usually last for 6 months or more even, after the stoppage of chemotherapy [10].42% of patients developed symptoms of CIPN within 2 years after use of docetaxel treatment[11].

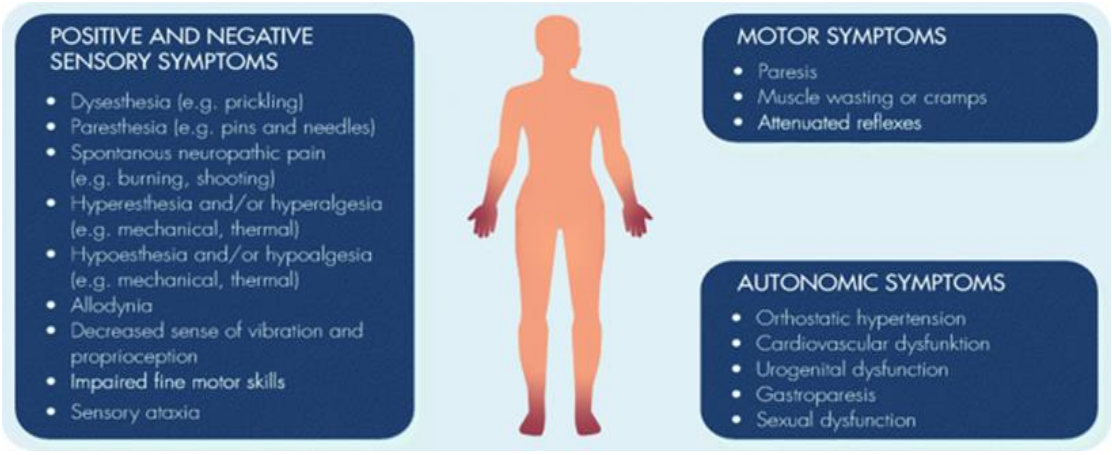
Mechanisms of CIPN:

The mechanism of the pathogenesis of CIPN is multifactorial. Chemotherapy develops toxic effects on several sites of nervous system which include myelin sheaths, axonal components and dorsal root ganglion especially sensory affected [15] cells. Pathways are started by triggering of degeneration followed by pro-inflammatory cytokine release and alteration of excitability of neurons followed by loss of epidermal fiber [12].The effects of oxaliplatin and cisplatin have effects similar to those of other platinum-containing compounds that disturb the proliferation of cancer cells by the formation of deoxyribonucleic acid (DNA)-platinum compounds. The platinum complex is formed of two chloride atoms which will be hydrolyzed after entrance to the cell and then transformed into a strong electrophile. Adenine and guanine bases of DNA are then cross linked by activated cisplatin, which will disturb messenger ribonucleic acid (mRNA) transcription and division of the cell [13].

Clinical features of CIPN:

Sensory neuropathy is the most predominant presentation of CIPN that may be associated with motor or autonomic symptom. Sensory neuropathy can accompanied by positive and negative symptoms. CIPN is predominantly sensory neuropathy in the form of sensory abnormalities in the stocking/glove distribution. Mild motor symptoms may occur but are less common. Rarely, autonomic impairment may be developed**.** The sensory abnormalities usually start in the lower extremities and then the upper extremities, but in 68% of the patients, they start in the upper and lower limbs simultaneously [14]. Paclitaxel and vincristine most frequently develop motor types of neuropathy. Impairment of the autonomic nervous system is a common adverse effect of use vinca alkaloids agent and presented by gastrointestinal, genitourinary and cardiovascular disturbance.

(Fig 1).Clinical presentation of CIPN as regards the type of peripheral nerves



Diagnostics

A baseline neurological examination should be done before the start of any neurotoxic agent for each patient with cancer to detect patients with a high risk of peripheral neuropathy [17]. History taking and clinical assessment are recommended when peripheral neuropathy is suspected. Clinical assessment of CIPN can be done by nerve conduction studies [18].Clinically-assessed neuropathy scores have been used to confirm diagnosis, which include the Total Neuropathy Score. This questionnaire used for assessment of symptoms includes the QLQ-CIPN20, which forms an ordinal 1–4 scale that measure 20 items (1, not at all; 4, very much) [19]. TNS can assess the severity and is considered a reliable tool [20].Other versions, which include the TNS-reduced scale and theTNS-clinical scale can evaluate patients with neuropathy [21]. Pain screening can be done by Pain DETECT, which is specifically used for the detection of pain in clinical [22].

Treatment of CIPN:

Clinical studies consider antidepressants, anticonvulsants, minerals, and vitamins as efficient compounds in the prevention of neuropathy induced by chemotherapy [23]. Some studies suggest that cooling of extremities can be used as a method to reduce the severity of symptoms, especially in patients receiving taxanes [24].Regular exercises include mobility recommended before initiation of neurotoxic agent therapies as physical exercise may minimize symptoms of neuropathy [25]. Non-pharmacological and pharmacological treatments are recommended by guidelines for manifest CIPN. The best treatment choice for pain includes gabapentin and antidepressants (SSRIs and tricyclic antidepressants). Existing guidelines recommend only duloxetine to treat neuropathy induced by chemotherapeutic agents [26].

Conclusion

CIPN represents a common neurological disorder in cancer patients. Chemotherapy-induced peripheral neuropathy is a common toxicity caused by cytotoxic agents, including platinums, taxanes, and vinca alkaloids. These agents result in pathologic insults to neurons that may last for several years after the stoppage of cytotoxic agent. Common presentations are tingling, numbness, burning pain, and impaired sensory functions in both hands and/or feet. Neurologic tests, including nerve conduction studies can be used for diagnosis. Chemotherapy-induced peripheral neuropathy can markedly impair functioning and the outcome of cancer. Limitation of the dose of a chemotherapeutic agent may be required in patients with CIPN.

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