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TAXANES INDUCED PERIPHERAL NEUROPATHY IN BREAST CANCER PATIENTS

[1]MILIN THOMAS, [2] Dr.K SREEJITH, [3]MUHAMMAD FAIROOS A,[4] VISMAYA MV,[5]SHABEEBA O P

[1]MPHARM STUDENT, [2]ASSISTANT PROFESSOR , [3]MPHARM STUDENT,[4]MPHARM STUDENT,[5]MPHARM STUDENT

KERALA UNIVERSITY OF HEALTH SCIENCES

Abstract: Taxanes induced peripheral neuropathy (TIPN)is a common side effect of taxane-based chemotherapy, characterized by damage to the peripheral nerves, leading to sensory, motor, and autonomic dysfunction. Up to 80% of breast cancer patients receiving taxane-based chemotherapy may experience TIPN. Risk factors include Dose and duration of taxane therapy, age, pre-existing neuropathy, and genetic predisposition. This review aims to enhance the current understanding of TIPN ,its pathophysiology, risk factors ,management and impact on the quality of life of breast cancer patients

Index Terms - Breast cancer, Taxanes, Peripheral neuropathy

INTRODUCTION

Breast cancer and taxanes

Cancer continues to be a major health challenge, despite significant progress in understanding the disease. Among women, breast cancer is the most common cancer, second only to skin cancer. Globally, breast cancer is the leading cancer in women, with 2.3 million new cases reported in 2020, making up nearly 12% of all cancer diagnoses. Worryingly, the global incidence of breast cancer is expected to rise, with projections indicating almost 2 million cases by 2030[1]. However, there is no universal treatment approach, as treatment plans are tailored to individual patients, considering factors like hormone receptor and HER2 status. To enhance treatment effectiveness, researchers are exploring new strategies, such as personalized medicine and novel drug developments. Natural compounds, particularly plant-derived secondary metabolites like taxanes, are vital in cancer therapy. Taxanes, found in yew trees, are a group of diterpenoid compounds. Paclitaxel, the most commonly used taxane, was first isolated from the western yew tree in the 1960s and approved for clinical use in 1994 for ovarian cancer. Docetaxel was synthesized from the European yew tree (Taxus baccata) in the 1980s. Paclitaxel and docetaxel are the most widely used taxanes, though other drugs and formulations, such as cabazitaxel and nab-paclitaxel, have also been developed[2]. Taxane-based treatments are highly effective and frequently used in the adjuvant treatment of breast cancer.

Mechanism of action of taxanes

Microtubules are dynamic structures made of tubulin proteins that are essential for maintaining cell shape, organizing intracellular transport, and regulating cell division. Taxanes disrupt microtubule function by stabilizing them, preventing their normal dynamic behavior[3]. This interference blocks cancer cells from growing and dividing, causing them to undergo cell death. As a result, cancer cells are unable to complete mitosis, leading to cell cycle arrest and apoptosis.

Taxanes have been shown to trigger several forms of cell death in cancer cells, including:

Apoptosis (programmed cell death): Taxanes activate key caspases, such as caspase-3, -8, and -9, which break down cellular proteins and structures, leading to cell destruction.

Necroptosis: Taxanes can induce necroptosis, a regulated form of necrosis, marked by cell swelling, membrane rupture, and the release of cellular contents[4].

Cell membrane damage: Taxanes can directly damage the cell membrane, altering its permeability and leading to cell death.

TAXANES INDUCED PERIPHERAL NEUROPATHY(TIPN)

Taxane-induced neurotoxicity is a significant and debilitating side effect of taxane-based chemotherapy, particularly with paclitaxel. It can lead to considerable distress and negatively affect patients' quality of life. The clinical symptoms include painful peripheral neuropathy, such as burning sensations, numbness, and tingling in the hands and feet, as well as central neurotoxicity, which may present as cognitive impairment and encephalopathy. The incidence is high, with 60-90% of patients experiencing mild to moderate neuropathy, and up to 30% experiencing severe neuropathy. This can result in reduced daily functioning, cognitive impairments, and an increased risk of falls and injuries. Effective management requires a holistic approach, including dose adjustments guided by therapeutic drug monitoring, symptom management through both pharmacological and non-pharmacological interventions, and collaborative care involving oncologists, neurologists, physical therapists, and mental health professionals. By recognizing the impact of taxane-induced neurotoxicity and adopting appropriate management strategies, healthcare providers can enhance patients' quality of life and minimize the effects of this debilitating side effect[5].

Several studies published between 2021 and 2023 have examined the effects of taxane-based chemotherapy on breast cancer patients, particularly in relation to peripheral neuropathy, quality of life, and symptom severity. In 2023, Erika Cimbro and colleagues conducted a single-center retrospective study on early taxane-induced neurotoxicity and its impact on quality of life in breast cancer patients. The majority of women treated with taxane-based chemotherapy for breast cancer reported experiencing neurotoxicity[6]. In another 2023 study by Meghna S. Trivedi and colleagues, which involved paclitaxel and docetaxel, patients aged 18 and above with stage I-III primary non-small cell lung cancer (NSCLC), breast cancer (BC), or ovarian cancer were assessed for chemotherapy-induced peripheral neuropathy (CIPN). This was measured using the patient-reported EORTC QLQ-CIPN20 and clinician-assessed NCI-CTCAE. In this diverse cohort of BC patients, the frequency of CIPN was higher than expected for both paclitaxel and docetaxel, with paclitaxel resulting in more severe cases[7]. A prospective, longitudinal observational study by Laura Grima and colleagues also focused on peripheral neuropathy, onycholysis, and quality of life in women with breast cancer treated with taxanes. The study concluded that taxanes negatively affect women's quality of life even six months after completing treatment, primarily due to the peripheral neuropathy and onycholysis they cause[8].

Pathophysiology of TIPN

Alterations in microtubule dynamics can negatively impact neuronal function, disrupting the transport of essential organelles, nutrients, and neurotransmitters along axons. This disturbance in microtubule function can lead to axonal degeneration or axonopathy, which contributes to the development of peripheral neuropathy. Mitochondrial dysfunction and oxidative stress are key factors in taxane-induced peripheral neuropathy. Research has shown that paclitaxel-induced peripheral neuropathy correlates with mitochondrial damage in both myelinated and C-fibers. This damage is marked by morphological changes, such as swelling and vacuolization, as well as alterations in calcium efflux due to the opening of the mitochondrial permeability transition pore.

Deficiencies in the mitochondrial respiratory chain have also been observed in rodent models of paclitaxel-induced peripheral neuropathy. These findings suggest that ongoing mitochondrial dysfunction in dorsal root

ganglia (DRG) neurons is a key mechanism behind taxane-induced peripheral neuropathy. Additionally, mitochondrial respiratory dysfunctions and ATP deficits are early events in paclitaxel neurotoxicity, occurring in DRGs before pain onset. While mitochondrial respiration is restored at the peak of pain severity, ATP deficits persist, alongside an increase in glycolytic activity. These bioenergetic changes in DRG neurons highlight the central role of mitochondrial dysfunction in the development of taxane-induced peripheral neuropathy. A deeper understanding of these mechanisms is crucial for creating effective strategies to prevent or alleviate this debilitating side effect[9].

Risk factors for TIPN

The development of taxane-induced peripheral neuropathy is influenced by various risk factors, such as the duration and intensity of taxane treatment, the patient's age, and the presence of underlying conditions like diabetes, alcoholism, or previous neuropathy. Additionally, genetic differences in specific genes related to potassium channels, cytochrome P450 enzymes, and solute transporters may contribute to an individual's risk of developing this neuropathy. These genetic variations can affect the metabolism, transport, and efficacy of taxanes, potentially increasing neurotoxicity in some patients. Key gene polymorphisms, including those in KCNN3, CYP2C8, CYP3A4, ABCB1, EPHA4, EPHA5, FGD4, FZD3, ARHGEF10, SLCO1B1, and TUBB2A, have been identified as possible risk factors for taxane-induced peripheral neuropathy. A deeper understanding of these genetic and clinical factors can help healthcare professionals predict and reduce the likelihood of this side effect in patients receiving taxane-based chemotherapy [10]

Diagnosis of TIPN

Clinical Assessment of Chemotherapy-Induced Peripheral Neuropathy (CIPN)
At present, there is no universally accepted method for evaluating CIPN. A thorough assessment should combine both objective neurological findings and symptoms reported by patients. Establishing a "gold standard" for CIPN measurement would enhance clinical trial designs and support the development of neuroprotective treatments. This standard should integrate clinical evaluations, neurophysiological measurements, and patient-reported outcomes. Assessments should be conducted at baseline, during treatment, and in long-term follow-ups (at least three months post-treatment).

Clinical Grading Scales :Commonly used tools for CIPN evaluation include clinician-administered grading scales, such as the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Neuropathy Sensory subscale. However, these scales have limitations in terms of interobserver reliability and sensitivity to changes over time.

Total Neuropathy Score (TNS) :The TNS is a composite score that combines symptom ratings with objective assessments of sensory loss and neurophysiological data. It has been validated as an effective and sensitive measure of CIPN, consistently correlating with other sensory dysfunction indicators. Both the clinical version (TNSc) and a reduced version (TNSr) of the TNS have been validated.

Patient-Reported Outcomes in Chemotherapy-Induced Peripheral Neuropathy (CIPN)
Patient-reported outcomes are essential in understanding CIPN as they offer a comprehensive view of the severity and significance of the condition.

Available Questionnaires
EORTC QLQ-CIPN20: A validated tool that evaluates neuropathy symptoms and their impact on quality of life.
FACT/GOG-Ntx: A questionnaire that assesses neuropathy symptoms, daily functioning, and quality of life.
Patient Neurotoxicity Questionnaire (PNQ): A tool that gauges the functional impact of neuropathy symptoms.

Objective Assessment of Chemotherapy-Induced Peripheral Neuropathy (CIPN)
The gold standard for objective CIPN assessment is nerve conduction studies (NCS), which measure the amplitude and conduction speed of sensory and motor action potentials. NCS can provide critical information on axonal damage and confirm sensory neuropathy. However, NCS have limitations, including delayed

changes in parameters until later stages of chemotherapy, a need for specialized equipment and expertise, and potential discomfort for patients.

Quantitative Sensory Testing (QST) :QST assesses the sensory detection threshold to quantify changes in sensory perception. This includes vibration detection, thermal detection, and sharpness detection methods. Other objective evaluations of sensory loss include using calibrated tuning forks and monofilaments, which are quick, easy to perform, and require minimal training to assess nerve function[11].

Pharmacogenetic Assessment of Chemotherapy-Induced Neurotoxicity :Pharmacogenetic approaches are becoming increasingly useful for identifying genetic polymorphisms that may affect an individual's risk of chemotherapy-induced neurotoxicity. However, there is still no clear consensus on the link between genetic variations and neurotoxicity risk. Several studies have explored the connection between genetic polymorphisms and neurotoxicity risk in patients undergoing chemotherapy.

ABCB1 and CYP2C8: Genetic polymorphisms in these genes have been associated with increased neurotoxicity in patients treated with paclitaxel[12].

MANAGEMENT OF TIPN

Currently, the most effective strategies for preventing chemotherapy-induced peripheral neuropathy (CIPN) involve dose adjustments and treatment interruptions. Structured protocols for dose modifications may significantly reduce neurotoxicity, though additional research is needed to evaluate the effectiveness of specific reduction protocols for other neurotoxic chemotherapy agents.

Identifying patients who are at higher risk of developing severe neurotoxicity before treatment begins is essential to minimizing the occurrence of this side effect. Those with pre-existing neuropathy or conditions like diabetes, which predispose individuals to peripheral neuropathy, are typically at greater risk.

Neuroprotective Agents :Various antioxidant compounds, such as glutathione, glutamine, and N-acetylcysteine, have been studied for their potential to protect against neurotoxicity. However, none have yet demonstrated a proven clinical benefit, and further evidence will be needed to support larger clinical trials. Calcium and magnesium infusions have been suggested to reduce neurotoxicity and improve the reversibility of neuropathic symptoms. However, recent findings from a randomized placebo-controlled trial show these infusions did not effectively prevent or alleviate neurotoxicity.

Symptom Control :Medications like antiepileptics and antidepressants may help control symptoms in patients with CIPN, but many of these agents have not shown significant effects in clinical trials. Randomized clinical trials are needed to assess the effectiveness of these medications in managing CIPN.

Experimental Treatments :Several experimental treatments for CIPN symptoms are currently being investigated, including neurostimulation, topical pain relief creams, acupuncture, and dietary adjustments. However, the effectiveness of these interventions in treating CIPN is still unclear.

Clinical Management and Patient Education :Because there are no universally effective treatments for CIPN, there is an increased focus on clinical management and patient education to prevent further complications from neuropathy. Recommended strategies may include therapy to improve balance and walking difficulties and occupational therapy to help patients adjust their activities and environment to manage their symptoms.

CONCLUSION

Taxane-induced peripheral neuropathy (TIPN) is a debilitating side effect of taxane-based chemotherapy that greatly affects patients' quality of life. To develop effective prevention and treatment methods, it is essential to understand the mechanisms behind TIPN, such as disrupted microtubule dynamics, mitochondrial dysfunction, and oxidative stress. While dose adjustments and interruptions remain the most effective ways to prevent CIPN, more research is needed to identify genetic and clinical risk factors, create standardized assessment tools, and explore new treatments, including neuroprotective agents and experimental therapies. By recognizing the impact of TIPN and implementing thorough management strategies, healthcare providers can improve patient outcomes, lower the risk of long-term neurological damage, and enhance overall quality of life[13].

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