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RECENT ADVANCES AND FUTURE OUT LOOKS OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY- REVIEW

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Abstract: Peripheral neuropathy is the result of damage to the nerves located outside the brain and spinal cord often causes numbness, weakness and pain. The usage of number of chemotherapeutic agents accelerated the induction of peripheral neuropathy as adverse effect. Anti-cancer drugs exhibited molecular changes in cellular level such as microtubule disruption, oxidative stress and mitochondrial damage, altered ion channel activity created neuro inflammation which in turn causes neuropathy. The advanced research studies are going the field of cancer biology is tried to eradicate the symptoms of chemotherapy induced peripheral neuropathy from cancer survivors. The discovery of newly emerged medicaments like duloxetine reduced the score of neuropathy during clinical trials.

Keywords : Microtubule, Chemotherapy, Peripheral Neuropathy, Clinical trial, Medicaments.

1. INTRODUCTION

Cancer is currently a leading cause of mortality worldwide. However, thanks to advances in medicine and modern technology, the availability of sensitive tests and diagnostic methods to detect cancer at an early stage and the use of increasingly effective treatments, including chemotherapeutic agents, the number of cancer survivors is rising: It is expected to increase by 35%, from 13.7 million in 2012 to 18 million, by 2022. Although these survivors may have beaten cancer, many of the have poor outcomes due to a number of syndromes that reduce the quality of life as a consequence of cancer treatment, including pain, which they often experience for a long time after completing their cancer treatment (Glare et al,2014).

Drugs used in cancer chemotherapy constitute an extremely effective tool in arresting the progression of cancer since they have numerous targets and mechanisms of action aimed at eliminating rapidly dividing cancer cells. Unfortunately, these drugs also affect normal cells and structures of the body, causing various deleterious and sometimes even devastating side effects (e.g., anaemia, diarrhoea, nausea, vomiting, infections, neurological changes, fatigue, hair loss, infertility, pain and peripheral neuropathy) may necessitate the tapering of chemotherapy regimens or even their cessation, thereby limiting the efficacy of cancer treatment (Cioroiu et al, 2017).

RISK FACTORS ASSOCIATED WITH CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY (CIPN)

A number of predisposing risk factors of CIPN have been identified, including patient age (higher risk in older patients); the co-occurrence of neuropathy before the start of chemotherapy (e.g., diabetic neuropathy); a history of smoking; impaired renal function with reduced creatinine clearance; exposure to other neurotoxic chemotherapeutic agents; Para neoplastic antibodies; and independent, direct cancer-associated neuropathy. Genome-wide association studies (GWAS) identified some single nucleotide polymorphisms (SNPs) associated with a higher risk of CIPN. The reported polymorphisms are associated with a range of proteins, including voltage-gated sodium channels, Schwann cell function–related proteins, and receptors for cell surface collagen, receptors involved in neuronal apoptosis, neuronal crest cell development and an enzyme involved in pyruvate metabolism. The cumulative dose of chemotherapeutic agents is another well-recognized major risk factor of CIPN (Seretny et al, 2014).

The pathological mechanism by which chemotherapeutics damage the nervous system structures and cause CIPN is multifactorial and involves microtubule disruption, oxidative stress and mitochondrial damage, altered ion channel activity, myelin sheath damage, DNA damage, immunological processes and neuro inflammation (Areti et al, 2014).

2. PATHOLOGICAL AND BIOCHEMICAL ROLE FOR DEVELOPMENT OF PERIPHERAL NEUROPATHY BY CHEMOTHERAPEUTIC AGENTS

Peripheral neuropathy is a result of damage to the nerves located outside the brain and spinal cord, often causes weakness, numbness and pain, usually in the hands and feet. It can also affect other areas and body functions including digestion, urination and circulation. Peripheral nervous system sends information from brain and spinal cord (central nervous system) to the rest of our body. The peripheral nerves also send sensory information to the central nervous system.

The mechanism of action of chemotherapeutic agents that lead to potent effects on tumor cell proliferation and cell death are well-studied and relatively well understood in following figure:

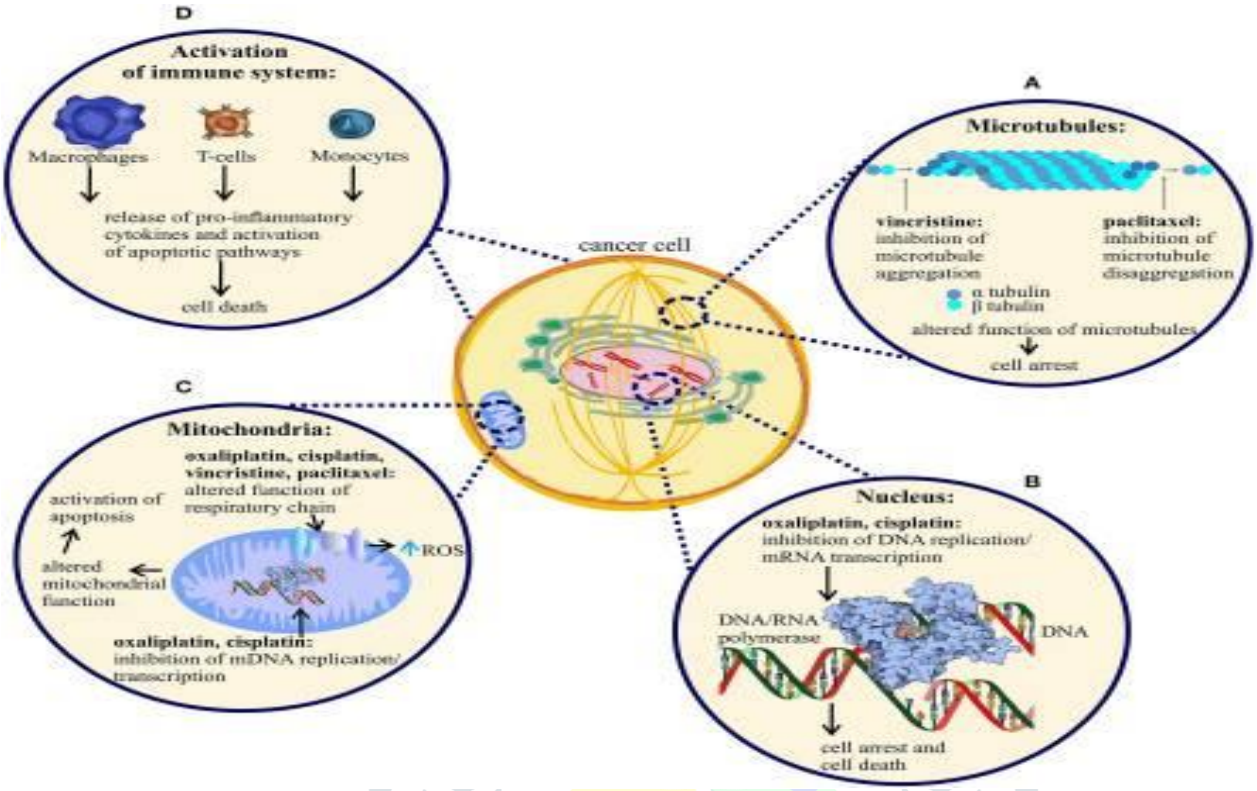

Figure 1: Mechanism of action of chemotherapeutic agents that lead to potent effects on tumor cell proliferation and cell death

3. IS VINCA ALKALOIDS ACCELERATED THE DEVELOPMENT OF PERIPHERAL NEUROPATHY AS ADVERSE EFFECT DURING CANCER THERAPY

All vinca alkaloids can cause CIPN, this side effect is most common with vincristine. Vincristine is one of the most important antineoplastic substances used for chemotherapy of several childhood and adult tumors, and it is administered by intravenous infusion .While the mechanisms of vincristine transport into the cell are still unclear, a carrier-mediated transport mechanism characterized by Michaelis-Menten kinetics, temperature dependence and competitive inhibition was demonstrated in different murine leukemia cells (Bleyer W et al, 1975). .The adenosine triphosphate (ATP) binding cassette (ABC) transporter family, ABCB1, ABCC1, ABCC2, and ABCC3 contribute to vincristine efflux from the cell cytosol and to the development of cancer cell resistance to the therapy (Huang R et al, 2006). Additionally, a relationship between cholesterol and phospholipid levels and vincristine uptake into murine leukemia cells has been demonstrated, showing that increased levels of cholesterol and phospholipids in the cell membrane accounts for lower vincristine accumulation (Gan P et al, 2010).

Vincristine binds to the β-subunit of tubulin and inhibits microtubule formation. The microtubules are cytoskeletal proteins that are involved in several important cell functions, for instance the regulation of cell shape, mitosis, chromosome segregation, cell division and retrograde as well as anterograde cellular transport. The proper function of microtubules depends on a balance between permanent aggregation and disaggregation of the α- and β-tubulin subunits. Therefore, the disruption of microtubule aggregation by bound vincristine can lead to mitotic arrest and cell death (Gregory R et al, 2000).

VIPN can be divided into sensory, motoric and autonomic components, with tendon reflexes, vibration sensitivity and strength most affected in the first year of treatment .Vincristine-induced sensory neuropathy is characterized by numbness, tingling and neuropathic pain in the upper and lower extremities. In addition, patients receiving vincristine experience loss of sensory discrimination, specifically an inability to detect light touch, pinprick sensations or vibration, and an inability to differentiate between hot and cold temperatures (Mora E et al, 2016) .Vincristine-induced motor neuropathy is characterized by weakness in the upper and lower extremities and the development of wrist- or foot-drop due to impaired dorsiflexion that arises from damage to peripheral nerves. This is accompanied by gait abnormalities, cramps, and loss of or reduction in deep tendon reflexes which can be severe .Typical symptoms of autonomic neuropathy are constipation, urinary retention, and orthostatic hypotension. As would be expected, these symptoms can significantly reduce the quality of life of these patients (Lavoie smith et al, 2013).

The mechanisms contributing to development of VIPN include disruption of calcium homeostasis, activation of the immune system and subsequent neuro inflammation, membrane remodeling of peripheral neurons and loss of large myelinated fibers.

Vinca alkaloids are natural (vincristine and vinblastine) and semi-synthetic (vindesine and vinorelbine) chemotherapeutics derived from the periwinkle plant and are used either alone or in combination therapy to treat haematological malignancies, testicular cancer, myeloma, sarcoma, non-small cell lung cancer and tumours of the kidney, liver, lung, brain and breast .Vincristine is arguably the most neurotoxic vinca alkaloid, with a majority of patients developing vincristine-induced neuropathy (VIPN) , the severity of which is dose-dependent (Madsen et al, 2019).

Anterograde transport of organelles and membrane proteins and retrograde transport of signalling molecules depends on microtubule based transport. Vinca alkaloids interfere with and disrupt microtubule assembly and mitotic spindle formation . They also increase the stability of microtubules, which impacts negatively on the ability of the cell to dynamically alter the structure of the cytoskeleton affecting axonal transport. Additionally, vincristine is mitotoxic and can impair the mitochondrial electron transport chain, resulting in defective energy production . Axonal degeneration requires both sterile alpha and TIR motif-containing proteins SARM1 and MAPK, and the deletion of SARM1 protects mice from developing VIPN . Other intracellular targets include the NF-E2- related factor and haeme oxygenase 1/carbon monoxide system (Nrf2/HO-1/CO) which modulates the expression of connexin 43 (Cx43), protecting against nerve damage and reducing vincristine-induced neuroinflammation . Increased expression of inflammatory markers TNF-a and IL-1b and increased expression of TRPA1 were recently identified in models of VIPN (Gertdts et al, 2016). Moreover, mRNA gene ontology has identified the inflammatory role of vincristine on microglia and upregulation of pro-inflammatory genes including frizzled-related protein 2 (SFRP2) and C-X-C motif chemokines (CXCL) 10 and 9.

3.CURRENT EPIDEMOLOGICAL STATUS OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY.

The survival rates of patients treated with antitumor agents are increasing. Hence, CIPN and CIPN-related neuropathic pain episodes have become a significant clinical issue among cancer survivors. Chemotherapy-induced peripheral neuropathy (CIPN) is a common and challenging complication of several frequently administered antineoplastic agents. The development of CIPN may result in prolonged infusion times, dose reduction or premature cessation of chemotherapy, which may negatively impact both treatment efficacy and patient survival. A meta-analysis of randomised controlled trials and cohort studies showed that around half of all patients develop CIPN during treatment. It is estimated that approximately 70% of patients receiving chemotherapy develop CIPN during the first month of treatment , whereas in approximately 20–30% of these patients, CIPN might be converted to a chronic, persistent and highly pharmacoresistant form [51] that can be observed 6 months or even longer after therapy cessation(Miltenburg et al, 2014)..Importantly, the symptoms of these delayed complications may persist for several months and can be progressively aggravated; this phenomenon in which either mild neuropathy worsens or a new form of CIPN develops is termed ‘coasting’. Since chemotherapeutics are not being applied when this disorder develops, coasting is a great challenge for clinicians; patients may be cancer-free but suffer from neuropathy evoked by previously received anticancer treatment

Importantly, CIPN tends to occur both in adults and in younger patients. In children, most cases of CIPN are due to the use of vincristine and platinum derivatives, as other CIPN-inducing chemotherapeutics are not routinely used in this population. It should also be noted that the prevalence and symptoms of CIPN seem to be age-related. This is thought to result from the distinct neurobiology of the peripheral nervous system in children and adults. The diameter, density and myelination of axons in the dorsal root ganglion significantly change during childhood to achieve full maturation, and this may have a strong influence on the risk of development and severity of CIPN. This notion is supported by previous observations that vincristine causes motor deficits more frequently in pediatric patients than adults. The reason for this seems to be unclear, and several potential mechanisms, including the use of higher doses, altered pharmacokinetics, different neuronal biology, and the lack of early detection of neurotoxic symptoms, should be considered. The treatment of CIPN symptoms, recovery, and the delayed effects of chemotherapy may also vary between adult and pediatric populations. Importantly, drugs commonly used to treat neuropathic pain in adult patients (e.g., duloxetine) have not been widely studied in children. Also, physical and exercise-based therapies have not been evaluated in children receiving CIPN-inducing drugs. Thus, both the symptoms of CIPN and methods for alleviating them might be different between these two populations (Stillman et al, 2006).

In addition to age, a number of other potential risk factors for CIPN development have been identified. These include the cumulative dose of a chemotherapeutic agent, genetic factors, a history of neuropathy before the start of chemotherapy (e.g., painful diabetic neuropathy or neuropathy due to viral infections), impaired renal function with reduced creatinine clearance, and smoking history.

4. RECENT ADVANCES AND FUTURE DIRECTIONS IN BIOPSYCHOSOCIAL ASSESSMENT IN TREATMENT OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY:

Chemotherapy-induced peripheral neuropathy (CIPN) is a common cause of pain and poor quality of life for those undergoing treatment for cancer and those surviving cancer. Many advances have been made in the pre-clinical science; despite this, these findings have not been translated into novel preventative measures and treatments for CIPN. This review aims to give an update on the pre-clinical science, preventative measures, assessment and treatment of CIPN(Arnold et al, 2019).

The last decade has heralded improvements in cancer survival. However, persistent effects following the treatment of cancer can lead to pain and an impaired quality of life long after treatment has finished or cancer has been cured [64]. Chemotherapy- induced peripheral neuropathy (CIPN) is one of those effects that can lead to a continuing symptom burden after treatment (Mols et al,2014).

CIPN is characterised by the classic "glove and stocking" distribution of symptoms. After chemotherapy, 68% of patients have painful neuropathy at 6 months, improving to 33% at 1 year . Although different chemotherapies have variable characteristics, symptoms tend to be predominantly sensory. Sensory toxicity is the predominant feature as dorsal root ganglion (DRG). Sensory features are characterised by so-called "positive" and "negative" symptoms. "Negative" symptoms include numbness, loss of vibration sense, proprioception and deep tendon reflexes, whereas paraesthesia, dysaesthesia, and cold and mechanical hypersensitivity are referred to as "positive" symptoms.

Animal models of CIPN have increased understanding of the pathophysiology of CIPN, yet a recent meta-analysis highlights problems with the current models and may help deliver more robust and valid models . For example, how do studies assessing short-term pain behaviours in animals without tumour burden model chronic CIPN? Pre-clinical studies often focus on the gain-of-function symptoms rather than the loss of function (for example, numbness) more common with chronic CIPN. paclitaxel model of CIPN for 28 days with ethologically relevant behavioural tests that better mirror the clinical picture (Bhatnagar et al, 2014).

7. SUMMARY AND FUTURE OUTLOOK

A number of agents, including amifostine, glutathione, and vitamin E, were evaluated as prevention strategies for CIPN, with no agent demonstrating efficacy. Calcium and magnesium are effective for the prevention of CIPN. Venlafaxine, a serotonin–norepinephrine reuptake inhibitor (SNRI), was evaluated for the prevention of neuropathy in a randomized, double-blind, placebo-controlled Phase III trial of patients receiving an oxaliplatin-based regimens every two weeks and demonstrated significantly less acute neurotoxicity compared with the control group. Treatment options for CIPN include reducing the dosage of the chemotherapy, changing the chemotherapy, and treating CIPN with adjunct therapy. Adjunct therapy with topical agents, tricyclic antidepressants, and anticonvulsants, such as pregabalin and gabapentin, have shown limited efficacy. However, a randomized, double-blind, crossover, Phase III trial of duloxetine versus placebo for the treatment of CIPN caused by paclitaxel or oxaliplatin found that patients treated with duloxetine 60 mg daily had a larger average decrease in pain score than those receiving placebo, regardless of the chemotherapy used.

Despite an ever-expanding body of literature behind the pathophysiology and treatment of CIPN, new treatment options are still limited, and a proportion of patients continue to have difficulty controlling symptoms causing a significant impact on quality of life. Guided by the pre-clinical literature, novel targets that may help prevent CIPN are beginning to emerge. However, with continual advancements in chemotherapeutic agents with novel mechanisms, it is important that ongoing development of treatments for CIPN continue.

Pre-clinical studies have shown that antagonism of the sigma 1 receptor (present on mitochondrial endoplasmic reticulum) is able to reduce mitochondrial structural changes and pain behaviours that occur in CIPN. A phase II clinical trial found that sigma 1 antagonist treatment during FOLFOX chemotherapy diminished cold hypersensitivity, reduced the dropout rate and allowed a higher cumulative dose of oxaliplatin [201]. Although the long-term pain outcomes are not known, this highlights a pathway for potential therapeutics that could improve CIPN.

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