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REVIEW ARTICLE

An Updated Review on Oxaliplatin Induced Peripheral Neuropathy

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ABSTRACT

Peripheral neuropathy (PN) is a common condition that affects roughly 5% of the general population after the age of 50. PN can be caused by a variety of factors, including chemotherapy medicines, heredity, diabetes, alcohol, vitamin deficiencies, and gluten sensitivity. This article concentrates on oxaliplatin-induced PN in this review. Oxaliplatin (OHP) is a significant component of colorectal, gastric, and pancreatic cancer chemotherapy, yet it frequently causes PN as a dose-limiting factor. OHP-induced neurotoxicity manifests as acute neuropathic symptoms exacerbated by cold exposure as well as chronic neuropathy that develops after several treatment cycles. Despite the fact that many basic and clinical researchers have investigated anticancer drug-induced PN, the mechanism remains unresolved. According to clinical data, more than 65% of patients reduce or discontinue OHP due to this adverse effect, reducing their chances of survival. This article reviews in detail aspects of OHP-induced PN such as risk factors, types of neuropathy, various animal models, mechanisms of OHP-induced peripheral neuropathy, pathophysiology, diagnosis, and management and additionally determines future research directions.

Keywords: Chemotherapy, neuropathy pain, oxaliplatin, peripheral neuropathy

INTRODUCTION

Oxaliplatin (OHP) is a highly active, third-generation platinum chemotherapeutic drug that is frequently used to treat advanced colorectal cancer (CRC) and as an alternate permanent for cisplatin in cases of ovarian, pancreatic, breast, lung, and most recently, prostate cancer.[1]

In this disease, OHP has shown clinically significant advantages in both the adjuvant and metastatic settings. However, its clinical use is associated with OHP-induced peripheral neuropathy (OIPN), which can be and major in certain patients. The prevalence of chronic OIPN ranges between 64 and 97%, with at least 12% of individuals suffering from severe neuropathy.[2]

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After repeated OHP injections, sensory impairment develops as chronic neuropathy, which is a dose-limiting factor. Clinical evidence indicates more than 60% of patients reduce or stop using OHP as a result of this side effect, which negatively affects their chances of survival.[3]

Peripheral Neuropathy (PN)

PN is referred to as disorders of the peripheral nerve system, PN is a frequent aliment that arises when the peripheral nervous system (PNS) is damaged. Peripheral nerves originate in the brain and spinal cord, and they extend to the skin, muscles, and tissues. Electrical impulses are transmitted from the body to the brain through the PNS. Peripheral nerves fall into three distinct categories.[4,5]

- Autonomic nerves – Control the functions of the internal organs and glands
- Sensory nerves – Transmit sensations such as heat, vibration, touch, and pain.

- Motor nerves – Regulate that how body moves.[6]

The clinical signs of PN differ depending on which nerve fibers are damaged. Most cases include varying degrees of altered sensation (paresthesia and dysesthesia), neuropathic pain (burning, stabbing, electric shock-like, heat and cold hyperalgesia, and allodynia), muscle weakness or atrophy, and autonomic dysregulation (i.e., altered sweating, bowel and bladder dysfunction, orthostatic hypotension, and so on). The degree and length of PN symptoms might vary, and they can resemble myelopathy, radiculopathy, neuromuscular illness, or even hyperventilation. Therefore, efficient therapy and treatment of PN depend on accurate diagnosis based on clinical symptoms, signs, relevant history, and electrodiagnostic investigations (such as nerve conduction, needle electromyography, and nerve excitability). When diagnosing PN, electrophysiological studies can help determine if the pattern of neuropathy is comparable to a mononeuropathy or polyneuropathy based on distribution, length, course, and whether the pathophysiology is axonal or demyelinating in origin.[7]

Epidemiology

PN is much more common in individuals who are over the age of 50, with prevalence rates ranging from 1% to 7% in the general population. The most prominent known causes of PN are diabetes mellitus, nerve compression or damage, alcohol use, toxin exposure, genetic disorders, and nutritional inadequacies.[8,9]

In India

Several epidemiological studies conducted in India discovered that the prevalence ranged from 5 to 2400 cases/10,000 people in various community studies. It happens less frequently in rural areas and is comparable to research from the East and South. According to a hospital-based study from Eastern India, of 225 patients with acute and chronic PN, Guillain-Barre Syndrome (GBS) was the most prevalent (24.8%), followed by diabetes (11.1%), hereditary sensory motor neuropathy (7.55%), chronic inflammatory demyelinating neuropathy (7.55%), Hansen (4.8%), alcoholic/nutritional neuropathy (3.55%), and entrapment neuropathy (3.55%). In 17.3% of patients, no etiology could be determined.[10,11]

Drug-induced toxic neuropathies

According to a study conducted in India, toxins or medication-related polyneuropathy affect between 2% and 4% of people. PN is a side effect of various chemotherapy medications such as OHP and cisplatin that is cumulative and dose-dependent. Acute or chronic symptoms might occur; within the first cycle of treatment, at least one acute neuropathy symptom appears in roughly 90% of patients. Depending on the kind and dosage of chemotherapy, the incidence of chronic chemotherapy-induced PN (CIPN) might range from 13% to 70% [Table 1].[10]

CAUSES

Etiologies of Peripheral Neuropathy by Pattern of Involvement

1. Focal
    - Acromegaly
    - Amyloidosis
    - Direct trauma to nerves, such as repeated minor trauma, traction, injection, cold exposure, burns, radiation

Symptoms

- Sensory and motor symptoms
- Predominantly sensory symptoms, including pain and paresthesias
- In severe or chronic cases, motor symptoms may include weakness and atrophy

2. Multifocal
    - Connective tissue diseases
    - Diabetes mellitus
    - Hereditary predisposition to pressure palsies

Symptoms

- Sensory symptoms include pain, paresthesias, vibration, and proprioception
- Motor symptoms may include weakness and atrophy
- Autonomic symptoms may be present

3. Symmetrical distal sensorimotor

Table 1: Causes of PN

1	Etiologies of PN by Pattern of Involvement	
	Focal	
	● Acromegaly ● Amyloidosis ● Direct trauma to nerves, such as repeated minor trauma, traction, injection, cold exposure, burns, and radiation	Symptoms ● Sensory and motor symptoms ● Predominantly sensory symptoms, including pain and paresthesias ● In severe or chronic cases, motor symptoms may include weakness and atrophy
	Multifocal	
	● Connective tissue diseases ● Diabetes mellitus ● Hereditary predisposition to pressure palsies	● Sensory symptoms include pain, paresthesias, vibration, and proprioception ● Motor symptoms may include weakness and atrophy ● Autonomic symptoms may be present
	Symmetrical distal sensorimotor	
	● Alcohol use ● Celiac disease ● Chronic kidney disease ● Connective tissue diseases ● Cryoglobulinemia ● Gouty neuropathy	Symptoms ● Sensory symptoms include pain, paresthesias, vibration, and proprioception ● Motor symptoms may include weakness and atrophy ● Autonomic symptoms may be present
	Less common patterns	
	● Diabetes ● Guillain-Barré syndrome ● Infections (HIV/AIDS, Lyme disease, diphtheria)	Symptoms ● Problems with speech, swallowing, taste, and sensory or autonomic functions; coughing; head, pharyngeal, or neck pain; and weakness of the trapezius, sternocleidomastoid, or tongue muscles
2	Medications and Toxins That May Cause PN	
	Antiepileptic drugs -– Lithium and Phenytoin Antimicrobial/antiviral drugs – Chloroquine, Dapsone, Didanosine, Ethambutol, Isoniazid Metronidazole (Flagyl), Nitrofurantoin, Stavudine, and Triazoles Cardiovascular drugs – Amiodarone, Hydralazine, Procainamide, and Statins Chemotherapy agents – Oxaliplatin, Cisplatin, Bortezomib (Velcade), Epothilones, and Paclitaxel Thalidomide Other drugs – Amitriptyline, Cimetidine, Colchicine, and Levodopa Metals – Arsenic, Gold, Lead, Mercury, and Thallium Solvents – Acrylamide, Carbon disulfide, and Carbon monoxide.[8]	

PN: Peripheral neuropathy

- Alcohol use
- Celiac disease
- Chronic kidney disease
- Connective tissue diseases
- Cryoglobulinemia
- Gouty neuropathy

Symptoms

- Sensory symptoms include pain, pare- sthesias, vibration, and proprioception
- Motor symptoms may include weakness and atrophy
- Autonomic symptoms may be present

4. Less common patterns
    - Diabetes
    - Guillain-Barré syndrome
    - Infections (HIV/AIDS, Lyme disease, diphtheria)

Symptoms

problems with speech, swallowing, taste, and sensory or autonomic functions; coughing; head, pharyngeal, or neck pain; and weakness of the trapezius, sternocleidomastoid, or tongue muscles

Medications and Toxins That May Cause Peripheral Neuropathy

Antiepileptic drugs - Lithium, Phenytoin

Antimicrobial/ antiviral drugs - Chloroquine, Dapsone, Didanosine, Ethambutol, Isoniazid

Metronidazole (Flagyl), Nitrofurantoin, Stavudine, Triazoles

Cardiovascular drugs – Amiodarone, Hydralazine, Procainamide, Statins

Chemotherapy agents- Oxaliplatin, Cisplatin, Bortezomib (Velcade), Epothilones, Paclitaxel

Thalidomide

Other drugs- Amitriptyline, Cimetidine, Colchicine, Levodopa

Metals -Arsenic, Gold, Lead, Mercury, Thallium

Solvents - Acrylamide, Carbon disulphide, Carbon monoxide.[8]

Sign and Symptoms

Patients describe a variety of mostly sensory complaints, including:

- Numbness,
- Paresthesia,
- Ongoing/spontaneous pain,
- Hypersensitivity to mechanical and/or cold stimuli in their hands and feet.
- The impact on function is exacerbated in more serious cases by the loss of vibration sense and joint position perception. There may also be motor and autonomic dysfunction.

Patients may experience significant difficulty with essential daily functions such as fine finger movement, such as

- Buttoning clothing,
- Unsteady gait (numbness and loss of joint position sense);
- Pain when walking (mechanical hypersensitivity);

Inability to remove items from a fridge or exacerbation in cold weather (cold hypersensitivity).[12]

Risk Factors

Risk elements for PN include:

- High cumulative dose of chemotherapy
- Abuse of alcohol
- Deficits in vitamins, especially B vitamins.
- Infections, including HIV, hepatitis B and C, shingles, Epstein-Barr virus, Lyme disease, and Lyme illness.
- Diseases of the kidney, liver, or thyroid
- The presence of poisons
- Routine actions, such as those needed for some occupations
- Family members suffering from neuropathy
- Being born prematurely.[13]

Classification

Classification of neuropathy is mononeuropathy, mononeuropathy multiplex, or polyneuropathy. These three major categories can be further divided into further distinct groups by identifying differences based on the disease's origin (compressive or non-compressive), its progression through time (chronic or acute), or the kind of neuropathy (axonal or demyelinating neuropathy).[14]

Mononeuropathy

Mononeuropathy is a term used to describe a focused lesion of a peripheral nerve that is typically brought on by trauma, focal compression, or entrapment. The most prevalent peripheral mononeuropathies are entrapment neuropathies, which are marked by increased pressure on peripheral nerves that disrupts microcirculation and causes localized nerve ischemia before causing myelin alteration and axonal dysfunction. The median nerve flows through the carpal tunnel at the level of the wrist, where persistent localized compression of the median nerve results in carpal tunnel syndrome (CTS), the most frequent peripheral nerve entrapment neuropathy. As a result of damage to both big and tiny sensory fibers, patients with CTS report sensory abnormalities including severe paresthesia, numbness, hyperalgesia, mechanical allodynia, and a lack of temperature sensitivity.[15-17]

Mononeuropathy multiplex

The concept of "mononeuritis multiplex" refers to a set of disorders that frequently cause an uncomfortable, asymmetrical sensorimotor neuropathy in which at least two nerves in different body areas are impacted. A more or less symmetrical distribution of symptoms, similar to polyneuropathy, may eventually result from the disorder as it develops and much more nerves are afflicted. Multifocal motor neuropathy (MMN) is a demyelinating condition of the PNS that is immune-mediated and impacts motor nerves. Asymmetric, predominately distal muscle weakness and atrophy caused by MMN often begin in the arms and progress over the course of time. Whereas weakness in the arms will be most observable during the course of the disease, weakness can also develop further in the legs.[18]

Polyneuropathy

Polyneuropathies are a kind of neuropathy that affects all peripheral nerves, usually in the lower limbs, where the nerves are the longest. Polyneuropathy is caused by an underlying illness that can impact axons, myelin sheaths, or both. The most frequent type of polyneuropathy is distal symmetrical polyneuropathy, which is identified by length-dependent nerve degeneration and is related to acquire systemic illnesses, metabolic disorders such as diabetes mellitus, and medications such as chemotherapeutics. Distal symmetrical polyneuropathy symptoms are distal and symmetrical and may include a combination of positive (paresthesia, burning pain) and negative (a shortage of feeling) sensory abnormalities, as well as gait imbalance. Some individuals may also present with early distal lower limb muscular weakness, which frequently manifests as toe extension and foot dorsiflexion weakness.

Polyneuropathy may progress proximally over time, leading patients to have significant and common sensory loss and dysesthesia in the lower limb, upper limb, and abdomen, as well as distal muscle weakness and wasting, hyporeflexia or areflexia, and gait and proprioception problems.[19] Polyneuropathies are characterized according to the length and clinical history of the condition, the involvement of big and small fibers, and whether the neuropathy is axonal or demyelinating in origin. Rapidly growing neuropathies, for example, are commonly associated with GBS, vasculitis, or toxin exposure; early detection is required for proper treatment and therapy. Most polyneuropathies involve both small and big fibers, although, as seen in the specific case above, certain neuropathies damage one fiber type more than the other. While motor axons are generally big myelinated fibers (except for gamma efferents to muscle spindles), a neuropathy characterized by muscle weakness and atrophy indicates a large-fiber motor neuropathy. Small sensory fibers (thinly myelinated A and unmyelinated C fibres) are principally responsible for pain and temperature sensation, as well as peripheral autonomic function relating to thermoregulation, sudomotor, cardiovascular, gastrointestinal, urogenital, and other autonomic processes. Thus, neuropathies involving small nerve fibers can present with a wide range of positive and negative sensory and autonomic symptoms.[20] Polyneuropathies can also be classified depending on whether the neuropathy is acute or chronic and if the disease is axonal or demyelinating.

Acute polyneuropathies

GBS and other acute polyneuropathies can cause rapidly progressing (days to weeks) limb weakness and areflexia with various sensory involvements. GBS is a clinical entity that comprises a group of acute autoimmune inflammatory neuropathies that usually manifest as acute motor and sensory axonal neuropathy, acute motor axonal neuropathy, and acute inflammatory demyelinating polyradiculopathy.[21]

Chronic symmetrical polyneuropathy

Chronic symmetrical polyneuropathy is the most prevalent type of polyneuropathy that develops over months or years. The rate and pattern of development (progressive or relapsing), the primary modalities involved in the pathology (predominantly sensory, motor, or mixed), the relative involvement of large and small sensory fibers (large fiber, small fiber, or mixed fiber neuropathy), and whether it is primarily axonal, demyelinating, or both, as determined by electrophysiological studies, are all diagnostic features of chronic polyneuropathy. Because these features are well described in chronic polyneuropathy, categorizing polyneuropathy as demyelinating or axonal (or both) is beneficial in identifying causes, therapy, and predicting prognosis.

Chronic demyelinating polyneuropathies

Chronic demyelinating polyneuropathies, a subset of chronic polyneuropathies with a predominantly demyelinating pathology, can be inherited (i.e., Charcot-Marie-Tooth [CMT] disease, metachromatic leukodystrophy, and Refsum disease) or acquired (i.e., Chronic inflammatory demyelinating polyneuropath [CIDP], MMN, and paraproteinaemic demyelinating polyneuropathy).

The most common acquired demyelinating polyneuropathies are CIDP and MMN. CIDP is an immune-mediated polyneuropathy that commonly appears as chronic progressive, stepwise progressive, or relapsing weakness, sensory impairments (numbness, tingling, gait instability, and rarely severe paresthesia), and hypo- or a-reflexia. MMN is a form of chronic demyelinating polyneuropathy that primarily affects motor axons and appears clinically as slowly progressing asymmetrical muscular atrophy and weakening.

Chronic axonal polyneuropathy

Chemotherapeutic medications, dietary deficits, chronic renal failure, and some cancers can all induce chronic axonal polyneuropathy. Furthermore, some hereditary neuropathies, such as the Type 2 version of CMT, might present with a similar type of neuropathy. However, in 10–18% of patients that appear with sensory and/or motor symptoms suggestive of PN (described previously), a conclusive cause cannot be established, and the illness is referred to as chronic idiopathic axonal polyneuropathy.[22]

Pain

Pain is defined as "an unpleasant sensory or emotional experience associated with or described in terms of actual or potential tissue damage." Although pain is defined as the sense of noxious stimuli, it is usually accompanied by a negative emotional experience. As a result, the experience of pain is always subjective and attached to the experiences learned by the individual as a result of an injury in childhood. The experience of pain offers information about tissue-damaging stimuli and aids in the prevention of further damage. Furthermore, pain learning cautions the patient to avoid stimuli that have resulted in pain. Pain is frequently the primary motivator for seeking immediate medical assistance for any ailment that would otherwise be ignored.[23,24]

Acute pain

Acute pain, also known as nociceptive pain, is a natural feeling caused by the activation of nociceptors in peripheral tissues. It alerts the nervous system to the possibility of harm and the need for medical attention. Acute pain can be caused by cutaneous (skin), deep somatic (muscle, bone), or visceral structures (organs within the chest and abdomen). Immediately following tissue injury, distinct anatomical and physiological changes occur. Healing normally occurs, but when these changes persist long after damage, the shift from acute to chronic pain occurs.[25]

Chronic pain

Every occurrence of tissue damage is inevitably accompanied by chronic pain. Deeper structures or the skin could be the point of origin. Inflammation (inflammatory pain) or nerve damage can be possible causes of chronic pain (neuropathic pain). Diabetes mellitus, herpes simplex infections, medications used to treat TB and HIV, and most significantly, cancer chemotherapy treatments, can all result in neuronal damage and neuropathic pain.[23]

Classification of pain

Pain may be further categorized experimentally into three categories, each mediated by a distinct mechanism: nociceptive pain, inflammatory pain, and neuropathic pain.

Nociceptive pain

It is caused primarily by the activation of nociceptors in peripheral tissues by severe heat, mechanical, or chemical stimuli. These nociceptors are primary afferent nerve terminals that send impulses to the spinal cord through the dorsal root ganglion (DRG). The portion of the signal that travels to the thalamus raises our conscious attention to the pain signal by making synaptic contact with secondary neurons from the brainstem, while the other half of the signal that goes to the brainstem improves the impact of the pain signal. The pain signal in the thalamus then goes to the somatosensory cortex to assist the organism in localizing the source of pain, and a portion of the signal also crosses over to the hypothalamus and limbic system to activate the behavioral and emotional responses to the pain stimuli. Nociceptors are classified based on their receptive modality and their response to stimuli.

There are two types of nociceptors: Aδ fibers and C fibers. Aδ fibers are myelinated afferents with a medium diameter that mediate rapid pain. C-fibers are unmyelinated fibers with a tiny diameter that transmit progressive pain. They are found at different levels of density in the skin, muscles, tendons, joints, and viscera and help to detect cutaneous, somatic, and visceral pain. Nociceptors are activated only when stimulus intensities approach the noxious range, demonstrating the presence of biophysical and molecular features that allow them to detect and respond selectively to potentially harmful stimuli.[25,26]

Inflammatory pain

It is caused mostly by tissue damage (e.g., inflamed joints) and the ensuing inflammatory process, which results in increased excitability of peripheral nociceptive sensory fibers as a result of inflammatory processes. It is adaptive in nature, meaning that it causes physiological reactions that encourage recovery. However, in certain pathological settings, the sensory nerve system may overreact to non-painful stimuli and create pain that is not beneficial. It now detects non-painful stimuli as excessively painful (allodynia) or responds to painful stimuli in an exaggerated manner (hyperalgesia). This unusual development might be related to flexibility in nociceptors and central pain pathways. Typically, inflammatory pain improves as a result of "healing" and inflammation resolution.[25]

Neuropathic pain

It is caused by nerve damage or inflammation. Any injury to neurons in the PNS or central nervous system (CNS) causes sensitivity in these systems, resulting in neuropathic pain. Peripheral sensitization causes increased activation of peripheral nociceptors, which amplifies pain signals to the CNS. Central sensitization causes hyperstimulation of neurons in the dorsal horn of the spinal cord, improving pain signals to the brain and therefore increasing pain sensations. This damage might be caused by a variety of factors, including acute injury or surgical intervention, infection (herpes zoster), or disease (cancer, diabetic neuropathy, multiple sclerosis, etc.). It is a chronic, debilitating disease characterized by allodynia, hyperalgesia, and spontaneous pain.[4]

Pain processing

Primary afferent neurons (Aβ-, Aδ-, and C-sensory neurons) have the responsibility of transmitting sensory information from the periphery to the CNS (dorsal horn of the spinal cord) via the DRG and of converting external stimuli (mechanical, chemical, and electrical information) into electrical activity. Under physiological conditions, C (dull pain-slow pain) and Aδ- (sharp pain-fast pain) fibers send nociceptive information from PNS to CNS, and Aβ -fibers can only respond to non-noxious mechanical stimuli. These sensory neurons may interact with secondary neurons in the grey matter of the dorsal horn of the spinal cord. The grey matter of the spinal cord horn is divided into 10 laminae (I–X). A-fibers project to lamina I (the marginal layer), while C-fibers project to lamina II (substantia gelatinosa). A-fibers emerge from laminae III and V (nucleus propius). Along with transmission, second-order neurons divide pain signals in the dorsal horn into excitatory and inhibitory types. When the pain signal reaches the dorsal horn, it ascends through the thalamus and interacts with limbic circuits on the way to the cortex.[25]

Ascending projection neurons extend contralaterally to supraspinal targets such as the caudal ventrolateral medulla, the nucleus of the solitary tract, the lateral parabrachial region, the periaqueductal grey matter, and the thalamus. Important ascending routes are the tractus spinothalamicus lateralis, which controls sensory discriminative dimensions of pain, the spino-parabrachio-amygdaloid pathway, and the spinoparabrachio hypothalamic system, which controls emotional-cognitive components of pain.[25] Descending pathways start in the cortex and/or midbrain and provide modulatory feedback signals to the spinal cord, where they influence nociceptive sensation. A delicate balance of excitation and inhibition signals is required for appropriate representation of pain stimulus all along the pain processing pathway, from primary afferent nociceptors to the dorsal horn of the spinal cord, supraspinal processing sites, and

descending pathways. Any miscommunication at any of these specific points may result in the shift from acute pain to chronic pain.[25]

Animal Models of Neuropathic Pain

1. Peripheral nerve injury models
   - Axotomy model (complete sciatic nerve transection; neuroma model)
   - Chronic constriction injury
   - Partial sciatic nerve ligation (Seltzer Model)
   - Spinal nerve ligation
   - Spared nerve injury
2. Drug-induced neuropathy models
   - OHP induced neuropathy
   - Cisplatin-induced neuropathy
   - Vincristine-induced neuropathy
   - Docetaxel-induced neuropathy
   - Anti-HIV drugs-induced neuropathy
3. Disease-induced neuropathy models
   - Diabetes-induced neuropathy
   - Cancer pain model
   - Post-herpetic neuralgia model.[27-29]

Pathophysiology

The pathobiology and main processes involved in developing chemotherapy-induced PN include mitochondrial failure and oxidative stress. The associated structural alterations are neuronopathy, axonopathy, and myelinopathy, particularly intraepidermal nerve fiber (IENF) degeneration. The DRG is the primary anatomic target for neurotoxic chemotherapeutic drugs, and disruption of axoplasmic microtubule-mediated transport, known as Wallerian degeneration, causes direct damage to the cell bodies of the DRG's sensory neurons. Its excitotoxicity causes neuronal damage, followed by neuropathic pain [Table 2].[30]

Diagnosis of PN

Chemotherapy-induced PN is a common adverse effect of cancer treatment. Multiple evaluations have concluded that the present techniques for assessing chemotherapy-induced PN are insufficient. The careful assessment was performed using a mix of invasive and non-invasive approaches, such as medical history, neurologic examination, electrodiagnostic tests, and basic laboratory testing, which will produce an etiologic diagnosis in 74%–82% of polyneuropathy participants.[30,31]

OHP

OHP is a platinum-based anticancer drug. It is approved for the treatment of stage III CRC

Table 2: Diagnostic procedures for the established clinical patterns are based on clinical history and neurological examination

Patent presenting with clinical history and signs of PN

⇩

Clinical history:	Neurological examination:
● Time course and evolution	Types of nerve fiber involvement
● Family history	● Sensory/sensory motor
● Pain	● Pure motor
● Fever, night sweats, and weight loss	● Autonomous nerve fiber involvement
● Exposure to neurotoxic medications (previous chemotherapies)	Distribution of symptoms:
● Alcohols	● Distal symmetric
● Diabetes	● Proximal
	● Asymmetric/multifocal
⇩	⇩
Electrodiagnostic studies	Laboratory testing
Needle electromyography and nerve conduction studies are used to	● Nerve biopsy
● The confirmation of the clinical diagnosis of PN	● Peripheral nerve imaging [Table 3][31]
● Exclude neuropathy (e.g., radiculopathy, distal myopathy).	
● Determine the severity of the illness and the principal mechanism of damage (axonal vs. demyelinating)	

PN: Peripheral neuropathy

Table 3: Characteristics of both acute and chronic OIPN

S. No.	Characteristics	Acute OIPN	Chronic OIPN
1	Incidence rate	85–96%	40–93%
2	Duration	Within hours of infusion and lasting for the following 7 days	Within 6–12 months, or even lasting for 5 years
3	Typical feature	Cold-sensitive peripheral paresthesia, motor symptom's	Acute OIPN symptoms and the "coasting" phenotype
4	Mechanism	Na channel activation	Sensory neurons death, mitochondrial damage, oxidative stress, glia activation, and neuroinflammation.

OIPN: Oxaliplatin-induced peripheral neuropathy

following primary tumor elimination as well as for the treatment of metastatic CRC. It is FDA-approved in conjunction with infusional 5-fluorouracil (5-FU) and leucovorin in the 5-FU/folinic acid and OHP (FOLFOX) regimen. OHP varies from cisplatin in that diaminocyclohexane (DACH) is used in instead of the amine groups in cisplatin.[9,32]

- Drug name – OHP
- Drug Classes – Cytotoxic medicines
- Indication – CRC
- Chemical formula – $C_8H_{12}N_2O_4Pt$

Formulation - Parenteral – General injections – IV: 50 mg in vial powder for injection; 100 mg in vial powder for injection; 50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; and 200 mg/40 mL in 40 mL vial

Mechanism of action

OHP has been linked to several different modes of action. Like other platinum-based substances, OHP primarily causes deoxyribonucleic acid (DNA) damage, resulting in its cytotoxic effects. DNA damage, a decrease in DNA production, the suppression of ribonucleic acid (RNA) synthesis, and the induction of immune responses can all lead to cancer cells apoptosis. There is apparently synergy between OHP and other cytotoxic medicines, although the underlying mechanisms are less clear.[33]

Therapeutic application

In comparison, OHP, cisplatin, and carboplatin have no discernible therapeutic efficacy in treating CRC. At present, advanced metastatic CRC patients receiving combination chemotherapy receive OHP. It used to be that the first line of treatment for metastatic CRC was 5-FU, either alone or in combination with leucovorin (LV). However, more recently, it has been proven that adding OHP to the mix dramatically improves patient response and survival after treatment. In several combination chemotherapy regimens, such as FOLFOX, 5-FU/folinic acid, OHP, and irinotecan, and capecitabine and OHP, OHP has become a key component. The conventional therapy for metastatic CRC currently includes the first- and second-line usage of OHP.[34]

Pharmacokinetics

The intravenous administration of OHP results in significant non-enzymatic biotransformation of a large number of transitory platinum-containing intermediates. OHP's biotransformation is enhanced in a chloride-rich environment, such as the extracellular environment, by the displacement of the oxalate group by water and endogenous nucleophiles such as Cl-, HCO_3-, and H_2PO_4- ions. Monoaqua-1,2 DACH-monochloroplatinum, 1,2-DACH-platinum dichloride, and 1,2-DACH diaquo platinum are the transitory reactive species that are produced. The extremely reactive intermediate that interacts with DNA is produced when water replaces the oxalate group. Plasma proteins and erythrocytes are widely and permanently bound by these reactive platinum intermediates. Following the injection of OHP, the distribution of ultrafilterable platinum seems to be triphasic, consisting of two initial, brief distribution phases with average durations of 0.43 h and 16.8 h each and a protracted terminal elimination phase, with a duration of 391 h. OHP's biotransformation metabolites are mostly eliminated in urine.[34]

Pharmacodynamics

OHP has a number of modes of action, although the generation of DNA lesions appears to be the

predominant cytotoxic impact. Others include nucleic acid synthesis stops and inhibitions, as well as immunologic mechanisms. OHP causes many forms of DNA crosslinks (intra and interstrand as well as protein), with DNA intrastrand crosslinks being most probable to cause DNA lesions. DNA synthesis is inhibited by direct inhibition of thymidylate synthase, which is comparable to the antimetabolite action of FPs but is not accumulative when both medications are administered. Platinum DNA adducts inhibit messenger RNA synthesis through binding to transcription factors or inhibiting RNA polymerase. Furthermore, OHP appears to produce immunogenic signals on the surface of cancer cells before apoptosis, resulting in the immunogenic death of cancer cells through interferon-gamma production and exposure to toll-like receptor 4 on dendritic cells.[35]

Toxicities

OHP toxicity affects a number of healthy tissues, although peripheral sensory neurotoxicity is the main dose-limiting harm. Other common toxicities include diarrhea, neutropenia, thrombocytopenia, nausea, and vomiting. These side effects are often mild to moderate and go away promptly after therapy. In addition, some uncommon toxicities, including laryngospasm, may be experienced by patients. OHP has no discernible renal or auditory effects, in contrast to carboplatin and cisplatin. When administered in conjunction with other chemotherapeutic drugs, OHP's side effects are more pronounced and frequent. Nevertheless, most side effects, with the exception of neurotoxicity, are typically tolerable by patients without necessitating dosage reductions of additional drugs when taken at levels below those defined for single-agent treatment.[34]

OHP-induced PN

The platinum compound OHP is a commonly used cytostatic drug that has been shown to be effective in a variety of solid tumors, specifically CRC. OHP, which was originally used successfully to treat advanced CRC, is now also the regimen of choice for adjuvant therapy in patients with curative resected node-positive colon cancer. However, the most prevalent dose-limiting adverse effect of OHP is OHP-induced PN (OIPN). The process that causes neuropathy is unknown. OHP is known to produce two forms of neuropathy: Acute neuropathy and chronic neuropathy. Acute neuropathy (e.g., distal paresthesias, dysesthesias, and minor muscular contractions of the hands, feet, and perioral area) is mostly cold-triggered, affects around 90% of patients, and typically resolves within a week. Furthermore, chronic cumulative O-IPN continues between and after therapy and severe O-IPN disappears in the majority of patients 13 weeks following treatment [Table 4].[9,36-38]

OIPN mechanism

The primary clinical features of acute OIPN are cold-sensitive sensory symptoms and neuropathic pain in the limbs. Chronic OIPN results in autonomic nerve dysfunction in addition to the symptoms described previously. The most essential mechanism involved in acute OIPN is the change of oxidative stress and nuclear DNA damage in chronic OIPN.

Oxidative stress

Oxidative stress and OXA-induced neuropathy may be related, according to a number of lines of evidence. In preclinical models as well as in real-world clinical situations, antioxidant regimens have been shown to be effective in lowering neuropathic symptoms. Researchers have discovered a connection between TRPA1 and oxidative processes, both of which are influenced by Pt drug exposure. Since both oxidative stress and cold temperatures are sensed by TRPA1, it may be hypothesized that TRPA1 may be an important mediator of the cold hypersensitivity induced by OXA through oxidative stress-related processes. The function of TRPA1 as a sensor of electrophilic and reactive chemicals produced during oxidative stress at areas of tissue damage and inflammation has actually been well recognized. Indeed, oxidative stress byproducts created following OXA exposure might gate TRPA1, cause nociceptive responses, and cause neurogenic inflammation. The potential of OXA to cause mechanical and cold hypersensitivity has been found to be replicated by these oxidative

Table 4: OIPN mechanism

S. No.	Targets	Mechanisms
1	Na+ channel	In acute OIPN, the Na+ channels are in a prolonged open state and gradually inactivate.
2	K+ channel	Increasing the pro-excitatory K+ channel expression Reduced expression of TREK-1 and TRAAK, two-pore domain K+ channels, in the DRG
3	Ca2+ channel	The acute type of OIPN is facilitated by oxalate, a calcium chelator. In cases of cold hypersensitivity, the mRNA and protein for the Cavα2δ – 1 subunit are expressed more.
4	Oxidative stress-related mitochondrial damage	Nitro-oxidative stress is the outcome of dysfunctional mitochondria in neurons, which create adducts by binding to mitochondrial DNA. Oxidative stress may gate TRPA1, trigger neurogenic inflammation and nociceptive responses, demyelinate peripheral nerves, and damage their cytoskeleton. Lead to cellular energy failure in DRG neurons and disruption of the electron transport chain.
5	Schwann cells	Schwann cell mitochondrial dysfunction
6	Glia activation	Neurotransmission is changed as a result of increased neuroimmune activation. In the spinal cord and supraspinal regions, microglia and astrocytes are rapidly activated.
7	MicroRNA regulation	The down-regulation of BACE1 by the miR-15b gene is a factor in persistent neuropathic pain.
8	Nuclear DNA damage	Formation of platinum DNA adducts
9	Transporters	The absorption of OHP is mediated by CTRs (CTR1) and OCTs (OCT2). The cellular outflow of OHP is facilitated by ATP7A and ATP7B.
10	Transient receptor potential channels	TRPV1, TRPA1, and TRPM8 mRNA expression is increased in cultured DRG neurons. It was discovered that OHP-induced cold allodynia *in vivo* increased TRPM8 and TRPA1 sensitivity and expression.[39]

OIPN: Oxaliplatin-induced peripheral neuropathy, DRG: Dorsal root ganglion, OHP: Oxaliplatin

stress byproducts, such as H_2O_2, nitroleic acid, hypochlorite, and other endogenous chemicals, through their impact on TRPA1. Consequently, OXA has an indirect effect on TRPA1, which is most likely caused by byproducts of oxidative stress. In addition to modulating Na+ channel activity, it has been demonstrated that the ROS produced by OXA therapy also increases nociceptors' sensitivity. In addition, OXA has the potential to have negative effects on axonal mitochondria, which can disrupt the electron transport chain and impair the ability of DRG neurons to create energy. Increased ROS formation may begin as a result of mitochondrial injury. In fact, prophylactic administration of the antioxidant substance acetyl-l-carnitine reduces the onset of OHP-evoked hyperalgesia by avoiding damage to the respiratory chain and maintaining the integrity of the mitochondria. However, further clinical trials and verifications are required to fully understand the effects of Vitamin C and other antioxidants.[39,40]

Management of OIPN

Neurotransmitterbased therapies

Duloxetine

Based on preclinical and clinical research, the antidepressant medicine duloxetine, which functions as a serotonin-norepinephrine reuptake inhibitor (SNRI), can effectively reduce OIPN symptoms without lowering the anticancer activity of OHP. Despite American Society of Clinical Oncology recommendation, there is currently insufficient data to support the use of duloxetine as an achievable therapy for CIPN. Due to the fact that duloxetine is not 100% successful and does not work for everyone, figuring out predictors of response and improving the treatment plan should be the primary concerns. According to an exploratory responder analysis, patients with OIPN are more likely than those with paclitaxel-induced neuropathy to benefit from duloxetine, which raises the possibility that the pharmacodynamic effects of duloxetine are closely related to the specific molecular mechanisms underlying OIPN. Furthermore, compared to the use of venlafaxine, duloxetine has been reported to have fewer side effects. In addition, duloxetine performed better than venlafaxine in terms of lowering the intensity of neuropathic pain and the grade of motor neuropathy. The optimal dose of duloxetine and how effectively it prevented pain sensations brought on by OHP in Stage II–III CRC patients were the subjects of a Phase II/III trial that drug recently started.

Venlafaxine

It has been used to stop CIPN and use venlafaxine, a more focused SNRI. Venlafaxine demonstrated

clinical benefit in a randomized Phase III study against acute neurosensory toxicity brought on by OHP, but it is important to be aware of its adverse effects, which include nausea (43.1%) and asthenia (39.2%). Clinical studies indicated that duloxetine may be more effective at treating CIPN symptoms than venlafaxine; however, SNRI analgesia benefits were stronger in patients receiving platinum treatment than in those receiving taxanes treatment. Furthermore, important is a side-by-side comparison of duloxetine and venlafaxine. Sadly, a 50-patient randomized pilot study that was meant to prove venlafaxine's effectiveness in CIPN patients fell short of expectations.

Minocycline

The development and symptoms of OIPN are reduced by minocycline, a matrix metallopeptidase 9 (MMP9) blocker and microglia inhibitor that also suppresses the generation of cytokines that are pro-inflammatory. The loss of IENFs and mechanical sensitivity in OIPN animals has been found to be effectively avoided by minocycline therapy. According to a 2017 pilot study, minocycline did not reduce overall sensory neuropathy in CIPN. However, it reduced the patients' average pain score and exhaustion when compared to the placebo. Because of this, minocycline may be an effective option for the management of CIPN. Large-scale clinical trials and preclinical research are required to better assess its impact on CIPN.[40]

Metformin

The impact of metformin on the management of chemotherapy- and diabetic-induced neuropathy. Metformin has been proven in *in vitro* and animal studies to be helpful in preventing the onset and progression of diabetic neuropathy and chemotherapy-induced neuropathy. However, there is inconsistent clinical evidence about the efficacy of taking metformin either alone or in combination with other medications to treat the symptoms of diabetic neuropathy. In fact, further clinical research is necessary before we can definitively say if metformin is useful for treating peripheral neuropathies of any type.

CONCLUSIONS AND FUTURE RESEARCH PERSPECTIVES

Many of the chemotherapeutic drugs were discontinued even though they had good therapeutic potential because of PN as an adverse effect. Therefore, there is still a strong need to find effective drugs for the prevention and treatment of PN. The most common non-hematological dose-limiting side effect of OHP-based chemotherapy is PN. It is difficult to assess and diagnose OIPN. Many pharmacological and non-pharmacological treatment techniques, such as blocking ion channels, lowering oxidative stress, and targeting inflammatory cytokines, have been investigated in preclinical and clinical investigations to alleviate OIPN symptoms. To treat OIPN, many medicines are employed, including duloxetine, an antidepressant drug that acts as a SNRI and may be useful in the prevention of OIPN without reducing OHP's anticancer effectiveness. Duloxetine was not completely successful and it did not function in every patient who participated. A priority area of study is the identification of strong predictors of duloxetine response. New treatment techniques may considerably enhance future research; medication targets should be evaluated; and improved clinical trials should be created in the search for pharmaceuticals for OIPN prophylaxis. Nanotechnology is becoming increasingly important in sectors ranging from medical to engineering. The use of nanotechnology in medication delivery is a highly promising technique for overcoming such constraints and improving the therapeutic impact of natural and chemical agents.

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