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Cisplatin in Chemotherapy

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ABSTRACT

Chemotherapy is a cancer treatment used to halt the uncontrolled growth of cancer cells. Despite the increase in cancer survival rates due to aggressive treatments, new anticancer drugs often cause severe side effects that can last for years, sometimes leading to treatment discontinuation or dose reduction. Chemotherapy-induced peripheral neuropathy is the most dose-limiting side effect of anticancer agents like paclitaxel, vincristine, and platinum compounds commonly used in treating various tumors. Many of these drugs affect the nervous system, causing significant side effects such as neurotoxicity. Cisplatin, a platinum-based compound widely used in cancer treatment, exerts its effect by binding to purine residues in DNA, chelating, and triggering apoptosis in cancer cells. Due to this mechanism, it is used as an antineoplastic agent in the treatment of various solid tumors, including testicular, ovarian, bladder, head-and-neck, and lung cancers. One of the most serious issues associated with cisplatin chemotherapy is neurotoxicity, with oxidative stress being a major factor. Other mechanisms contributing to cisplatin neurotoxicity include DNA-mediated apoptotic pathways, mitochondrial damage, activation of pro-inflammatory cytokines, ion channel disruptions, and glial activation.

Research aimed at reducing cisplatin's neurotoxicity risk holds promise for making cisplatin a safer and more effective treatment option in the future.

Keywords: Chemotherapy, cisplatin, neurotoxicity,

1. Introduction

Chemotherapy is a powerful drug treatment used to destroy or stop the growth of cancer cells. It is commonly used in cancer treatment, with different chemotherapy drugs administered alone or in combination depending on the tumor type, disease stage, and patient's health status (Bray et al., 2018). Chemotherapy drugs generally target rapidly dividing cells, such as cancer cells, but they can also affect healthy, fast-growing cells in the body, including hair follicles, bone marrow, and digestive system cells.As a result, chemotherapy can cause side effects like hair loss, nausea, fatigue, and weakened immune function.

Chemotherapy can be used to directly treat cancer, slow disease progression, or shrink tumors to aid other treatments like surgery and radiotherapy. During treatment, drugs are typically administered intravenously, but some may be taken orally or via subcutaneous injection. The treatment process often spans several weeks or months, with patients receiving treatment at specific intervals followed by rest periods. Chemotherapy has shown efficacy in extending life expectancy in advanced cancer stages and, in some cases, in eradicating the disease. Personalized planning and supportive treatments (e.g., antiemetics or immune boosters) are

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often used to alleviate side effects. New strategies, including targeted therapies and immunotherapy, are under investigation to reduce chemotherapy's side effects (Calls et al., 2021).

Antimetabolites, alkylating agents, and tyrosine kinase inhibitors have neurotoxic effects, with doxorubicin and cisplatin known for their pronounced neurotoxicity (Ongnok et al., 2020). Platinum-based drugs, such as cisplatin, carboplatin, and oxaliplatin, are widely used in many types of solid tumors.. Their primary pharmacological mechanism involves binding to DNA to form intrastrand and interstrand cross-links, inhibiting DNA replication and transcription, and inducing double-strand DNA damage. As a first-generation platinum-based drug, cisplatin is used as a first-line therapy and has demonstrated strong inhibitory effects on solid tumors, including testicular, ovarian, lung, stomach, head and neck, cervical, and breast cancers. Cisplatin acts as a chelator by binding to purine residues in DNA, leading to apoptosis in cancer cells (Dasari and Tchounwou, 2014). Although cisplatin has a limited ability to cross the blood-brain barrier, it causes severe neurotoxicity.

One of the most significant issues associated with cisplatin chemotherapy is neurotoxicity (McWhinney et al., 2009). The mechanism of neurotoxicity is thought to involve cisplatin-induced oxidative stress in nerve cells, mitochondrial dysfunction, and weakening of antioxidant defense mechanisms. Oxidative stress and mitochondrial damage in nerve cells contribute to neurotoxicity by leading to cell death and impaired nerve function (Hashem et al., 2015).

Cisplatin-associated neurotoxicity can occur in both the central and peripheral nervous systems, and its severity depends on the dose and duration of use (Brouwers et al., 2009). The onset of cisplatin-induced neuropathy can vary, with the most prominent toxic effects observed in neurons within the dorsal root ganglia, leading to peripheral neuropathy. Patients undergoing cisplatin treatment may experience symptoms such as numbness, tingling, loss of sensation, and pain, particularly in the hands and feet (Lange et al., 2016).

Cisplatin-induced neurotoxicity is often permanent and can significantly impact patients' quality of life. Therefore, studies are being conducted on the use of neuroprotective agents (such as antioxidants, N-acetylcysteine, or vitamin E) in combination with cisplatin to prevent or reduce neurotoxicity. Additionally, treatment strategies such as dose reduction and extending dose intervals have proven effective in reducing neurotoxicity risk.

2. Cisplatin

Cisplatin, also known as cis-diamminedichloroplatinum (II) or cisplatinum, is a metallic (platinum) coordination compound with a square planar geometry. At room temperature, it appears as a white or dark yellow to yellow-orange crystalline powder that is sparingly soluble in water but soluble in dimethyl sulfoxide and N,N-dimethylformamide. Cisplatin is stable under normal temperature and pressure; however, over time, it can slowly convert into its trans-isomer form. Originally synthesized by M. Peyrone in 1844, its chemical structure was first described by Alfred Werner in 1893. Despite its early discovery, it was not involved in scientific research until later.

In the 1960s, biophysicist Barnett Rosenberg accidentally discovered its potential. While studying the effects of electromagnetic radiation on the proliferation of bacterial and mammalian cells, Rosenberg used platinum electrodes in his initial experiments with *Escherichia coli*. He observed the presence of unusually long filaments, around 300 times longer than normal, in the bacteria in the growth area with platinum electrodes. Shortly thereafter, Rosenberg demonstrated that this effect was not due to the electromagnetic field but was instead caused by electrolysis products from the platinum electrodes. Further chemical

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analysis revealed that the compound responsible for this effect was a neutral cis-isomer of platinum, first described by Peyrone in 1845 and later named cisplatin. It was found that this compound inhibited cell division in the bacteria without hindering other growth structures, which explained the appearance of extremely long filaments.

Scientific findings on cisplatin were published in 1965 (Rosenberg et al., 1965). In 1971, it was successfully used in cancer patients for the first time, and the U.S. Food and Drug Administration approved it as a cancer treatment in 1978 (Kelland, 2007). Today, cisplatin remains a widely used antineoplastic drug with a broad spectrum, particularly effective for treating solid tumors, including small-cell lung cancer, ovarian, testicular, bladder, and head and neck cancers, as well as refractory lymphomas (Links and Lewis, 1999).

2.1. Molecular Structure of Cisplatin

The chemical structure of cisplatin is distinct from that of other typical organic anticancer agents. It is a metal (platinum) coordination compound with a square planar geometry. The doubly charged platinum ion is coordinated with four ligands: on the left side, there are amine ligands that form strong interactions with the platinum ion, while on the right side, chloride ligands allow the platinum ion to bind to DNA bases. At room temperature, cisplatin appears as a white or dark yellow-orange crystalline powder. Although stable under normal temperature and pressure, it can gradually transform into its trans isomer over time.

Cisplatin has a molecular weight of 301.1 g/mol, a specific gravity of 3.74 g/cm³, and a melting point of 270°C. Its half-life is 1.05 hours at 35.5°C.

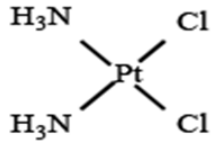

Figure 1 Chemical structure of cisplatin (Dasari and Tchounwou, 2014).

Table 1. Molecular structure of cisplatin (Dasari and Tchounwou, 2014).

Chemical Name	Cis-diamminedichloroplatinum
Molecular Formula	$C1_2H_6N_2Pt$
Molecular Weight	301.1 g/mol
Color	Dark yellow crystalline powder/clear solution
Water Solubility:	2.53 g/L (25°C 'de)
Melting Point:	270 °C

2.2. Pharmacokinetics of Cisplatin

The platinum center in cisplatin can interact with various biomolecules. Platinum is a soft acid, and cisplatin hydrolysis products tend to form stable bonds with soft bases. It can react with nucleobases in DNA and RNA, as well as histidine residues in proteins and peptides (Jung and Lippard, 2007).

Immediately following intravenous injection, cisplatin rapidly distributes to all tissues. High concentrations are found in the kidneys, liver, and prostate, while lower concentrations are found in the bladder, testis, pancreas, and spleen. The lowest concentrations are observed in the

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heart, lungs, intestines, and cerebrum/cerebellum. As it is not absorbed through the gastrointestinal system, cisplatin is administered only via the intravenous route (Links and Lewis, 1999). Platinum can be detected in kidney tissue for up to about four months post-treatment. The elimination half-life is approximately sixty hours. Within two hours of administration, over 90% of plasma cisplatin irreversibly binds to proteins and is converted to metabolites in a non-enzymatic manner. Reported half-lives in humans are a distribution half-life (t1/2) of 10–60 minutes and a terminal half-life (t1/2) of about 2–5 days. Within the first five days after administration, only 27–45% of the drug is excreted unchanged (DeConti et al., 1973). Due to its high protein binding, the total dose is expected to be excreted in the urine over a period exceeding 84–120 hours. Fecal excretion is minimal. Plasma half-life increases with reduced kidney function (Urien and Lokiec, 2004), and cisplatin is theoretically highly bound to plasma proteins, which may increase ascites in the abdomen (Links and Lewis, 1999).

2.3. Mechanism of Action of Cisplatin

Cisplatin uptake into cells occurs through various mechanisms. Initially, passive diffusion was described as the method of entry, but today an active transport system has been identified, which is associated with tumor resistance. Studies have shown that the facilitated transport system related to cisplatin's nephrotoxicity operates through the organic cation transporter (OCT2) and the copper transporter (CTR1). (Pabla et al., 2009; Hu et al., 2017).

This transport mechanism is electrical, voltage-dependent, bidirectional, and independent of pH and sodium. There are three types of OCTs: OCT-1 in the liver, OCT-2 in the kidneys, and OCT-3 in the placenta. OCT-1 does not transport cisplatin, which highlights cisplatin's organ-specific toxicity. Other cisplatin analogs, such as carboplatin and oxaliplatin, are not transported by OCT-2, which may explain their lower nephrotoxicity.

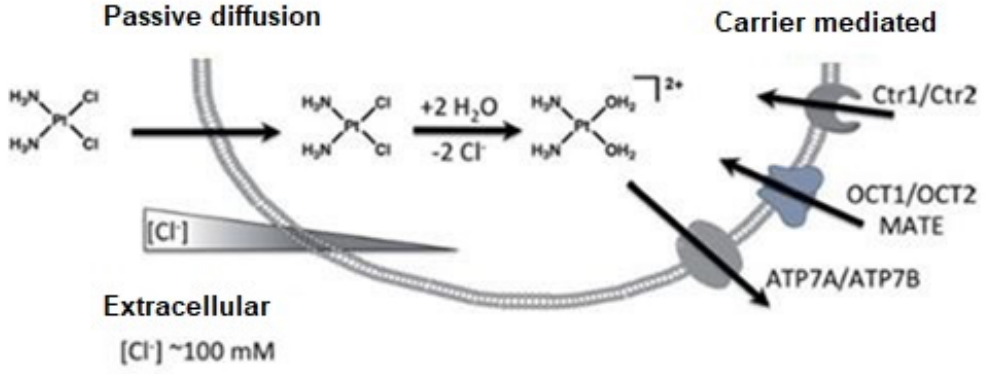

Figure 2 The pathways of platinum drug entry into cells involve both passive diffusion, which is dependent on the reduced intracellular chloride concentration, and carrier-mediated transport involving copper transporters (CTR1 and CTR2) and organic cation transporters (OCTs) like Ctr1 and Ctr2. For the efflux of platinum drugs from cells, P-type ATPases, including ATP7A and ATP7B, play a crucial role (Qi et al., 2019).

It has been shown that the cytotoxic effect of cisplatin occurs by suppressing DNA synthesis, without being specific to the cell cycle. Due to the high chloride ion concentration in the extracellular environment and blood, cisplatin is not prone to hydrolysis in these areas. Inside the cell, approximately 10% of cisplatin binds to genomic DNA, while the rest binds to proteins and other cellular structures. The reactivity of cisplatin changes depending on the chloride ion concentration in the environment. Since the chloride ion concentration in the extracellular environment and blood is approximately 100 mM, cisplatin is relatively less active in these environments. However, its reactivity increases in the cell, where the chloride ion concentration

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is lower. In this environment, water molecules replace the chloride ions, and nucleophilic groups bind to the platinum. These compounds act as highly reactive hydrolytic products of cisplatin in target organs (Jamieson and Lippard, 1999; Qi et al., 2019).

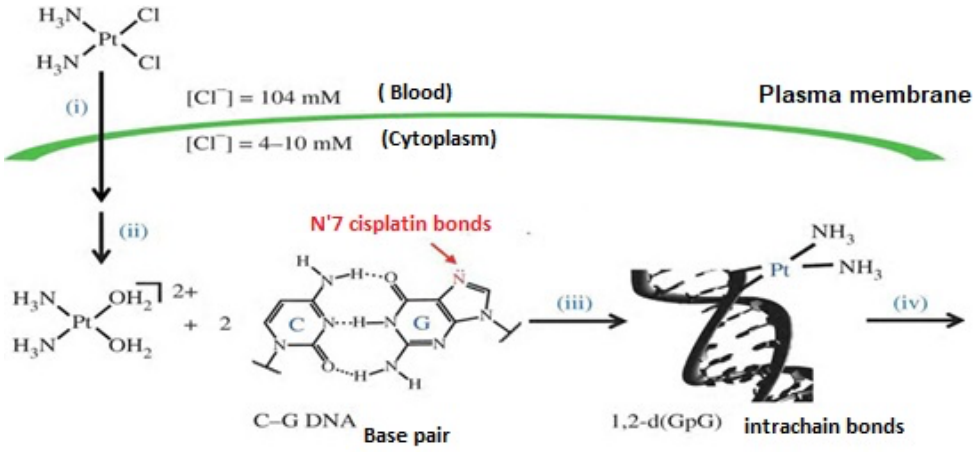

Figure 3 Mechanism of action of cisplatin: (i) Cellular uptake, (ii) Hydration/activation, (iii) DNA platination, and (iv) Cellular processes leading to apoptosis (Johnstone et al., 2015).

The mechanism of action of cisplatin is similar to that of alkylating agents. However, only the cis isomer is cytotoxic. It is a cell cycle-independent drug and can affect cells during all phases. The primary target of cisplatin's chemotherapeutic effect is DNA. By interacting effectively with DNA, cisplatin disrupts tumor cell proliferation. Cisplatin creates cross-links between adjacent guanines on the same DNA strand, which is a major interaction with DNA. Additionally, cisplatin damages the mitochondria, inhibits ATPase activity, arrests the cell in the G2 phase, and suppresses cellular transport systems (Parker et al., 1991; Pabla and Dong, 2008).

Cisplatin and its hydrolyzed products react with the nitrogen at the N7 position of the purine rings in DNA, forming cross-links between two purine bases. These cross-links inhibit DNA transcription and replication. The resulting DNA damage leads to the initiation of apoptosis and also inhibits protein and mRNA synthesis to some extent (Dasari and Tchounwou, 2014). These cross-links can be intrachain or interchain. Intrachain binding is more prominent. Typically, 1,2 intrachain adducts such as guanine-guanine are formed. Less frequently, 1,3 guanine-guanine linkages and interchain guanine-guanine linkages can be observed (Jamieson and Lippard, 1999).

Cisplatin’s cross-linking of DNA alters its structure. The High Mobility Group Box 1 (HMG1) protein, which normally protects DNA, recognizes the cisplatin-DNA complex and forms a DNA-platin-HMG1 complex. This leads to the inhibition of DNA replication and the halting of the cell cycle (Jordan and Carmo-Fonseca, 2000).

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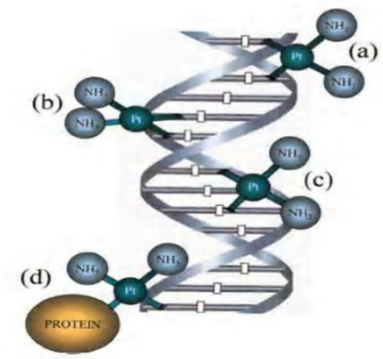

Figure 4 DNA-cisplatin intra- and interstrand cross-links: (a) Interstrand cross-link, (b) 1,2-intrastrand cross-link, (c) 1,3-intrastrand cross-linking, (d) Protein-DNA cross-link (Qi et al., 2019).

In addition to its genomic effects, cisplatin also exerts non-genomic effects in its chemotherapeutic action. These effects can increase the production of reactive oxygen species (ROS) due to changes in mitochondrial functions, and they can influence both intrinsic and extrinsic apoptotic pathways. Furthermore, cisplatin can affect Ca^{2+} signaling pathways and various protein kinases (such as MAPK, JNK, PKC, and AKT), leading to cell death (Dasari and Tchounwou, 2014).

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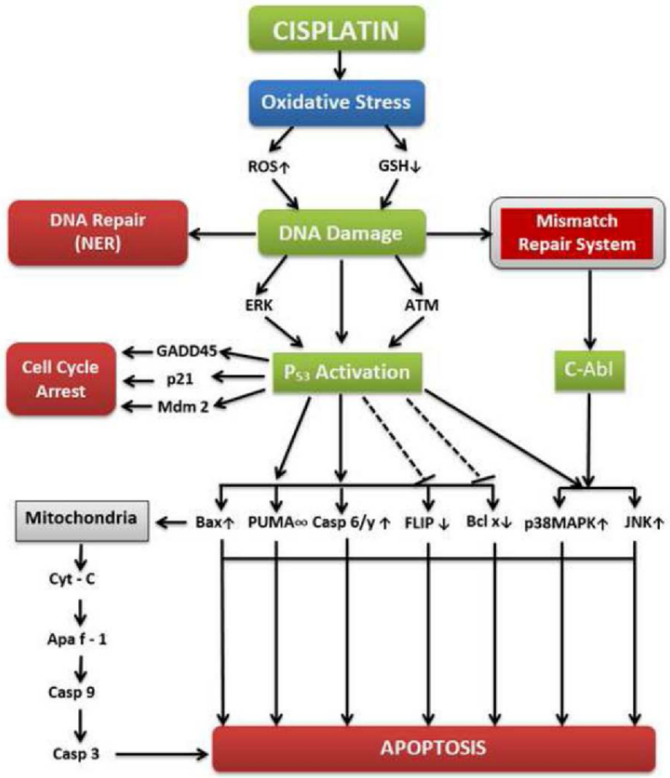

Figure 5. Cisplatin mechanism of action (Dasari and Tchounwou, 2014).

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2.4. Cisplatin Toxicity

While cisplatin exerts toxic effects on cancer cells, it also causes significant side effects in normal tissues. Platinum compounds, which contain metal ions, form binding sites for proteins, nucleic acids, and other cellular molecules. These properties are responsible for much of their effects, as well as their toxicity. Although different mechanisms have been proposed for each side effect, the main mechanisms include oxidative stress, mitochondrial dysfunction, DNA damage, alterations in cellular transport systems, inflammation, protein kinase activation, and apoptosis activation (Cepeda et al., 2007).

Cisplatin treatment can cause various toxic side effects. The most common side effect is nephrotoxicity. Clinical studies frequently observe elevated serum creatinine levels, reduced glomerular filtration rate, hypomagnesemia, and hypokalemia (Kidera et al., 2014). About one-third of patients receiving cisplatin therapy experience nephrotoxicity.

Another side effect is ototoxicity. Hearing loss and tinnitus (ringing in the ears) can occur early after cisplatin administration. Hearing loss is more common in patients receiving frequent and high doses of cisplatin (Rademaker-Lakhai et al., 2006).

Gastrointestinal toxicity can manifest as nausea, vomiting, appetite loss, and diarrhea. This side effect is also frequently observed with other chemotherapeutic agents (Shahid et al., 2018).

Hematological side effects include thrombosis, leukopenia, neutropenia, thrombocytopenia, and anemia. These side effects are related to cisplatin's suppression of bone marrow function (Astolfi et al., 2013).

Cardiotoxicity is rarely observed in clinical practice but may be dose-dependent. Electrophysiological changes, arrhythmias, myocarditis, pericarditis, blood pressure changes, myocardial infarction, cardiomyopathy, heart failure, and angina have been reported in connection with cisplatin (Pai and Nahata, 2000).

Cisplatin can damage liver sinusoids and has been shown to have hepatotoxic effects. Hepatocyte degeneration and significant necrosis in the portal area, along with inflammatory cell infiltration, have been reported (Karale and Kamath, 2017).

Other side effects may include visual disturbances, photosensitivity, and reproductive system disorders (Chovanec et al., 2017).

In peripheral neuropathy, cisplatin therapy remains the most common dose-limiting side effect, and an effective treatment for this side effect has not yet been found.

2.5. Cisplatin and Neurotoxicity

Cisplatin neurotoxicity is dose-limiting and includes significant side effects such as ototoxicity and polyneuropathies. Polyneuropathies manifest as distal symmetric sensory neuropathy, characterized by impaired position and vibration sense in thick fibers, while pain and temperature sensations are partially preserved. Paresthesias are a significant clinical symptom.

Approximately 30% of patients receiving cisplatin treatment may develop neurotoxicity. It has been shown that cisplatin, through copper transporter receptors (CTR), minimally crosses the blood-brain barrier and accumulates in dorsal root ganglion (DRG) neurons, which do not have a blood-brain barrier, especially after repeated doses, and becomes effective in brain tissue (Rzeski et al., 2004).

The onset of cisplatin-induced neuropathy can vary. In some patients, symptoms appear after the first dose, while in others, they develop after extended treatment cycles. Neuropathy caused by cisplatin typically appears after a cumulative dose of 350 mg/m². At a cumulative dose of 500-600 mg/m², neuropathy has been observed in 92% of patients (Krarup-Hansen et al., 2007).

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Neurotoxicity may persist for several months after the drug is discontinued and can sometimes worsen over time (coasting phenomenon) (Starobova and Vetter, 2017). The higher the cumulative dose and the longer the treatment duration, the greater the risk of chronic and irreversible neuropathy.

Certain clinical and genetic factors may increase the risk of neurotoxicity during cisplatin treatment. Factors such as the patient's age, gender, tumor type, the concurrent use of other chemotherapeutic agents, and especially polymorphisms in the glutathione S-transferase gene may increase this risk (Cavaletti et al., 2011).

In a study evaluating the long-term effects of neurotoxic chemotherapeutic agents, it was shown that about 50% of long-term survivors (average 8.5 years) continued to experience neuropathy. In this group, patients treated with cisplatin and vinca alkaloids had a higher prevalence of long-term neuropathy compared to those treated with other chemotherapeutic agents (Kandula et al., 2018).

The clinical signs of peripheral neuropathy caused by cisplatin are well-defined, and its early identification has been documented. However, its effects on brain functions have been known since 1990. The most commonly observed symptoms include memory impairment, attention deficits, learning difficulties, inability to perform tasks, and locomotor activity disorders. Similar neurotoxic effects have also been demonstrated with other chemotherapeutic agents. This side effect is often classified as "chemo brain" within the context of neuropathy. Among all chemotherapeutic agents, doxorubicin and cisplatin exhibit the highest "chemo brain" effects (Ongnok et al., 2020).

In some small-cell and non-small-cell lung cancer patients treated with platinum-based chemotherapy, significant cognitive impairments have been reported compared to controls after treatment (Simó et al., 2015). In Simo et al.'s study, brain volume differences in various regions were compared with healthy individuals using T1-weighted volumetric magnetic resonance imaging (Voxel-based morphometric analysis) one month after the treatment was discontinued.

In this study, lower gray matter density was observed bilaterally in the insula, parahippocampal gyrus, and left anterior cingulate cortex. Structural brain abnormalities caused by cisplatin may include the loss of branching in major myelin protein fibers and a reduction in white matter (Chiu et al., 2017). These findings confirm the potential toxic effects of cisplatin on oligodendrocytes.

2.5.1. Mechanisms of Neurotoxicity Formation

Although cisplatin crosses the blood-brain barrier to a limited extent, it is known to be effective in treating brain tumors and brain metastases. The passage of cisplatin across the blood-brain barrier is related to the copper transporter protein (CTR1). CTR1 expression is found in the neurons and endothelial cells of the blood-brain barrier (Eljack et al., 2014).

The exact mechanism of neurotoxicity is not fully understood, although several mechanisms have been proposed. One of the most important proposed mechanisms is oxidative stress, while other key mechanisms include mitochondrial dysfunction, DNA damage, changes in cellular transport systems, inflammation, protein kinase activation, axonal degeneration, and activation of apoptosis (Cavaletti et al., 1994; Dasari and Tchounwou, 2014; Chtourou et al., 2015; Abdel-Wahab and Moussa, 2019). These mechanisms contribute to cisplatin's neurotoxic effects, leading to structural and functional changes in the nervous system and associated neurological symptoms.

2.5.1.1. Oxidative Stress:

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The brain uses more oxygen than other tissues and lacks a strong antioxidant system to combat free radicals, making it particularly sensitive to oxidative stress. Cisplatin disrupts oxidative balance, leading to the accumulation of free radicals. These radicals not only have toxic effects on cells but also compromise the integrity of the blood-brain barrier.

Inside the cell, cisplatin transforms into aquated cisplatin and acquires a positive charge. It then conjugates with glutathione (GSH) through the negatively charged sulfur on cysteine. These cisplatin-GSH conjugates are unstable structures that can turn into reactive thiols via beta-lyases. Additionally, it has been shown that cisplatin increases the production of superoxide anions and hydroxyl radicals while reducing antioxidant enzymes (Townsend and Hanigan, 2002). This mechanism is often involved in nephrotoxicity, which typically arises from the high levels of gamma-glutamyl transpeptidase in tubular cells.

Mitochondria are a major source of oxidative stress. Healthy cells can eliminate low levels of reactive oxygen species (ROS) produced in the mitochondria through antioxidant enzymes, but neurons, being rich in mitochondria, are highly sensitive to free radicals. Damage repair within mitochondria is difficult, and dysfunction here can lead to irreversible damage due to the disruption of energy production. Increased ROS production and oxidative stress have been demonstrated in brain tissue, hippocampus, and peripheral nervous system in cisplatin-induced neurotoxicity (Abdel-Wahab and Moussa, 2019; Areti et al., 2014; Chtourou et al., 2015; Dasari and Tchounwou, 2014; Hashem et al., 2015; Khadrawy et al., 2019). The increased ROS production disrupts the structure of biomolecules such as enzymes, proteins, lipids, and nucleoproteins, leading to serious consequences. Oxidative stress contributes to demyelination, mitochondrial dysfunction, microtubule damage, neuronal damage, and apoptosis via activation of the caspase system. The resulting neuropathy is typically irreversible (Areti et al., 2014).

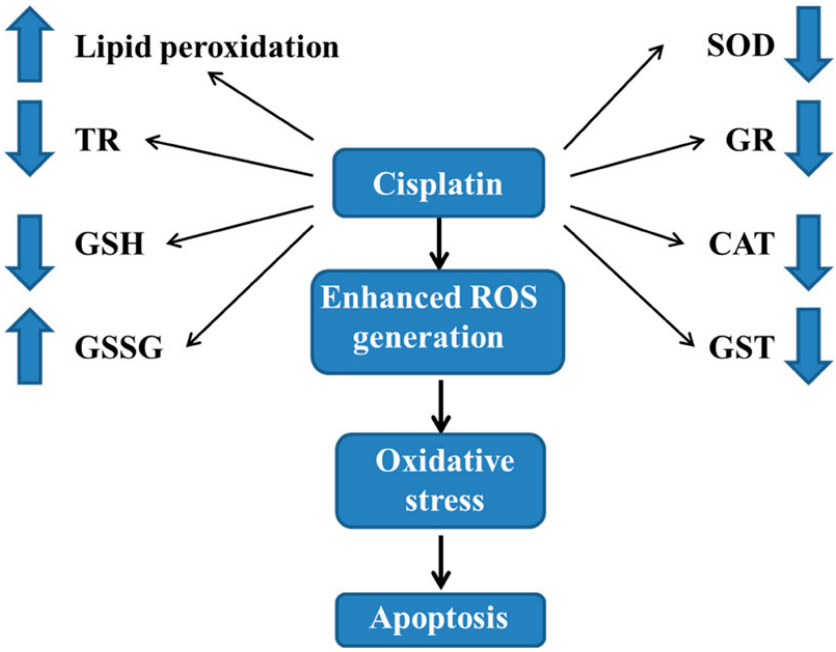

Figure 5 Apoptosis resulting from oxidative stress associated with cisplatin (Qi et al., 2019).

With the increase in ROS production, changes occur in the antioxidant enzyme system. Studies have shown a decrease in antioxidant enzyme levels. A reduction in glutathione (GSH), the most important antioxidant system in the brain, has been associated with cisplatin (Abdel-Wahab and Moussa, 2019; Areti et al., 2014; Chtourou et al., 2015; Dasari and Tchounwou, 2014; Hashem et al., 2015; Khadrawy et al., 2019). Increased ROS production can also lead to an increase in the production of proinflammatory cytokines. The rise in inflammatory cytokines further enhances ROS production and accelerates oxidative events (Areti et al., 2014). The

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elevated ROS can react with DNA to produce 8-hydroxyguanine, eventually causing DNA damage. ROS also affects the cholinergic system through lipid peroxidation of the cell membrane. The central cholinergic system plays an important role in learning and memory regulation in the hippocampus. Dysfunction of the cholinergic system is a sign of neurotoxicity. In cisplatin-induced neurotoxicity, a significant increase in acetylcholinesterase (AChE) activity has been observed. ROS is one of the major contributors to this increase (Abdel-Wahab and Moussa, 2019; Chtourou et al., 2015; Jangra et al., 2016). An increase in monoamine oxidase (MAO) activity has been found in the brain. MAO catalyzes the oxidative deamination of monoamine neurotransmitters, producing hydrogen peroxide. This could also contribute to the increase in oxidative stress (Chtourou et al., 2015).

2.5.1.2. Mitochondrial Dysfunction:

Platinum-based agents cause adducts not only in nuclear DNA but also in mitochondrial DNA. This disrupts the replication and transcription mechanisms of mitochondrial DNA and leads to morphological changes within the mitochondria. Since mitochondrial DNA lacks the ability to repair itself, the mitochondria become irreparable and deteriorate completely. Histological studies show that mitochondria become enlarged, vacuolized, and lose their function (Lomeli et al., 2017; Podratz et al., 2011). An important consequence of this is the disruption of the electron transport chain, leading to increased ROS production (Choi et al., 2015; Lomeli et al., 2017). Mitochondrial dysfunction affects mitochondrial permeability and increases calcium influx into the cell, which can lead to apoptosis. Morphological abnormalities in the mitochondria result in mitochondrial dysfunction (Guo et al., 2013). The neurotoxic mechanism of platinum-based drugs through mitochondrial dysfunction was first demonstrated by Podratz and colleagues (Podratz et al., 2011).

Cisplatin can also disrupt the expression of proteins related to mitochondrial fusion and fission in peripheral nerves. This can lead to changes in the shape, size, and number of mitochondria (Bobylev et al., 2017). These changes eventually stimulate microglial cells, leading to the release of proinflammatory mediators and growth factors at the damaged site, thereby increasing peripheral sensitization. It has also been reported that these chemotherapeutic agents increase peripheral sensitization through NMDA receptors, transient receptor potential vanilloid (TRPV) channels, and protein kinase C (PKC). This leads to spontaneous discharge and increased excitability. Other proinflammatory mediators can also damage the myelin sheath. All of these effects may contribute to neuropathic pain characterized by hyperalgesia and allodynia, and can also damage sensory neurons, such as Aδ and C fibers. Therefore, it has been reported that the mechanism induced by cisplatin leads to neurotoxicity through DNA damage and apoptosis in cells (Khadrawy et al., 2019).

2.5.1.3. Nuclear DNA Damage:

Cisplatin can cause both intrastrand and interstrand cross-links in DNA, not only in cancer cells but also in healthy cells and neurons. These modifications can impair cell replication and the cell cycle, often halting the cell cycle in the G2/M phase, which is a significant mechanism in neurotoxicity. This effect becomes more prominent, especially after chronic cisplatin use. Dorsal root ganglion (DRG) neurons are among the most affected. A correlation exists between the DNA adducts and the resulting damage (Ta et al., 2006). Neuronal toxicity, caused indirectly by binding to DNA, can lead to axonal changes.

DNA repair pathways play a crucial role in limiting toxicity. The nucleotide excision repair pathway (NER) serves as the primary repair mechanism by allowing the repair of certain intrastrand cross-links. Another repair pathway is the mismatch repair pathway. Deficiencies in

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these repair pathways can prevent the proper transcription of ribosomal RNA and disrupt protein synthesis. DNA adducts serve as binding sites for various cellular proteins such as transcription factors, histones, and high-mobility group proteins. As a result, the functions of these proteins may be affected (Ongnok et al., 2020).

2.5.1.4. Neuroinflammation

Chemotherapeutic drugs may have an immunosuppressive effect by suppressing myeloproliferation. However, these drugs can also activate the immune system (Zitvogel et al., 2008). This activation can lead to neuroinflammation, which can occur not only through the immune system but also via Schwann cells, astrocytes, and most importantly, microglial cells.

Animal studies on cisplatin-induced neurotoxicity have shown high levels of proinflammatory cytokines both in brain tissue and serum (Zaki et al., 2018; Abdel-Wahab et al., 2019; Khadrawy et al., 2019;). In experimental neurodegenerative disease models, activation of microglial cells leads to the release of neurotoxic molecules such as IL-1β, IL-6, TNF-α, nitric oxide, and ROS. Cisplatin-induced oxidative stress can increase the release of proinflammatory cytokines, thereby activating immune system cells (Almutairi et al., 2017; Abdel-Wahab and Moussa, 2019; Arafa et al., 2020; Ongnok et al., 2020). Cisplatin causes changes in the release of interleukins, activation of the innate immune system, and inflammation in microglial cells. As a result, all these effects contribute to neuronal inflammation.

There is limited information on cisplatin-induced neuroinflammation in the spinal cord (Fumagalli et al., 2020). Regarding cisplatin-induced peripheral neuropathy, Park and colleagues reported no change in astroglia or microglia activation in cisplatin-treated mice, but there was a significant increase in activated transcription factor 3 (ATF3) in the dorsal root ganglion (Park et al., 2013). In contrast to these findings, it has been reported that the increase in spinal microglia immune-reactive cells is associated with an increase in the expression of proinflammatory cytokines such as interleukin 1β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and chemokine CCL3 (Fumagalli et al., 2020). Additionally, another study showed that microglia, the macrophages of the central nervous system, were activated in the spinal cord in several rat mononeuropathy models (Raghavendra et al., 2003).

2.5.1.5. Calcium Imbalance and Ion Channel Alterations:

Oxaliplatin, a platinum derivative, causes acute neurotoxicity. In its pathogenesis, dysfunction of voltage-gated sodium channels has been associated with changes in calcium ion levels. This effect may be related to its oxalate group structure. In contrast to oxaliplatin, cisplatin does not significantly cause dysfunction in sodium and potassium channels (Argyriou et al., 2013). However, cisplatin affects calcium channels.

Calcium ions play a crucial role in regulating physiological processes within the cell. Small changes in intracellular calcium levels can lead to alterations in membrane excitability, neurotransmitter release, and gene expression in both neuronal and glial cells. Changes in calcium balance and calcium signaling have been shown due to cisplatin. Specifically, cisplatin has been found to reduce calcium channel currents in small neurons (Tomazevic and Büsselberg, 2007). Further studies have reported that cisplatin increases the expression of N-type voltage-gated calcium channels in sensory neurons, thereby increasing calcium influx into the cell. Elevated intracellular calcium levels may lead to apoptosis by activating caspases (Leo et al., 2017). However, the role of these channels in the pathogenesis of cisplatin-induced neurotoxicity remains unclear.

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Sensory neurons express various types of transient receptor potential (TRP) channels, which contribute to inflammation and the development of pain.

Ta and colleagues demonstrated that cisplatin treatment increases the expression of transient receptor potential vanilloid 1 (TRPV1), TRPA1, and TRPM8 channels (Ta et al., 2010). Specifically, they observed an increased expression of TRPV1 and TRPA1 in the trigeminal nerves after cisplatin treatment, which led to increased sensitivity to thermal and mechanical stimuli.

2.5.1.6. Axonal Degeneration:

Numerous studies in humans and animals have reported that prolonged use of chemotherapeutic agents leads to degeneration in large myelinated and smaller unmyelinated (more rarely) axons associated with sensory-motor peripheral neuropathy (Cavaletti et al., 1992; Bennett et al., 2011; Boehmerle et al., 2014;). Intraepidermal nerve fibers are unmyelinated or thinly myelinated nociceptors in the skin, playing a role in sensing pain from the periphery. Furthermore, myelin loss and axonal cytoskeleton changes alter the structure and function of peripheral nerves, potentially contributing to the development of altered sensation. However, the contribution of demyelination and peripheral nerve degeneration to chemotherapy-induced peripheral neuropathy pathology is not fully understood. Electron microscopy images of peripheral nerves obtained from cisplatin-treated patients show degeneration in large myelinated nerve fibers and a decrease in vibration sensitivity. Studies in mice have also shown that cisplatin causes damage to myelinated sciatic nerves, reduces action potential amplitude, and decreases conduction velocity in the caudal sensory nerve (Boehmerle et al., 2014).

There is limited information about the molecular mechanisms responsible for axonal functional and structural changes. Under physiological conditions, axonal transport ensures the movement of ions from the neuron to the target cell or in the reverse direction. After cisplatin treatment, in addition to axonal degeneration, this transport process is impaired. Chemotherapeutic agents that cause peripheral neuropathy can also have indirect effects by altering gene expression in addition to direct toxic effects on axons (Boehmerle et al., 2014). Moreover, cisplatin treatment has been found to reduce alpha-tubulin acetylation by increasing histone deacetylase 6 activity (Ma et al., 2018). Disruption of tubulin structure is a significant cause of axonal damage.

In conclusion, cisplatin-induced neurotoxicity arises from various mechanisms such as oxidative stress, mitochondrial dysfunction, inflammation, DNA damage, channel alterations, and apoptosis. (Brouwers et al., 2009; Zajaczkowska et al., 2019).

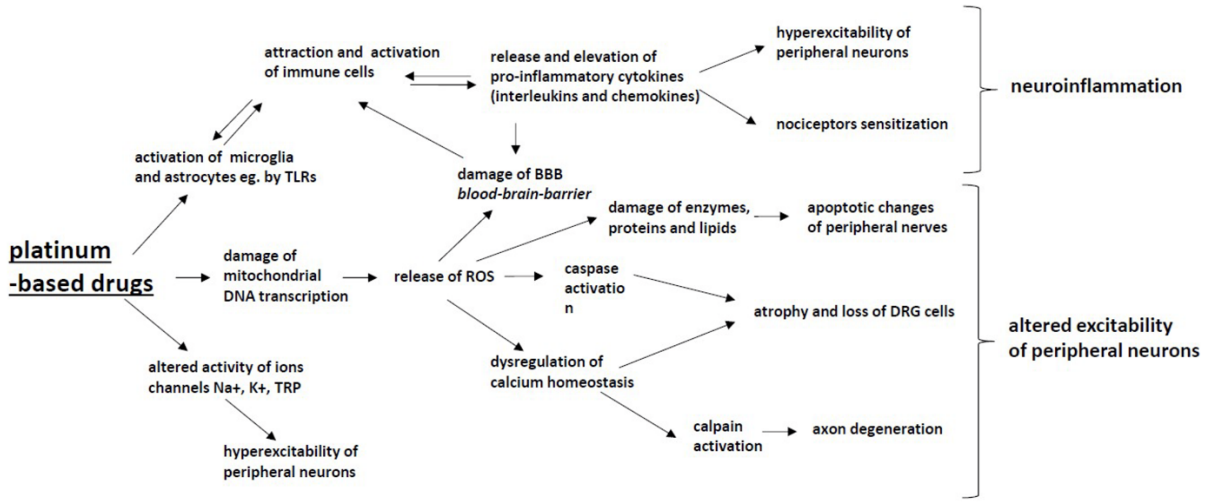

Figure 6 Mechanisms of Neurotoxicity Induced by Cisplatin (Zajaczkowska et al., 2019).

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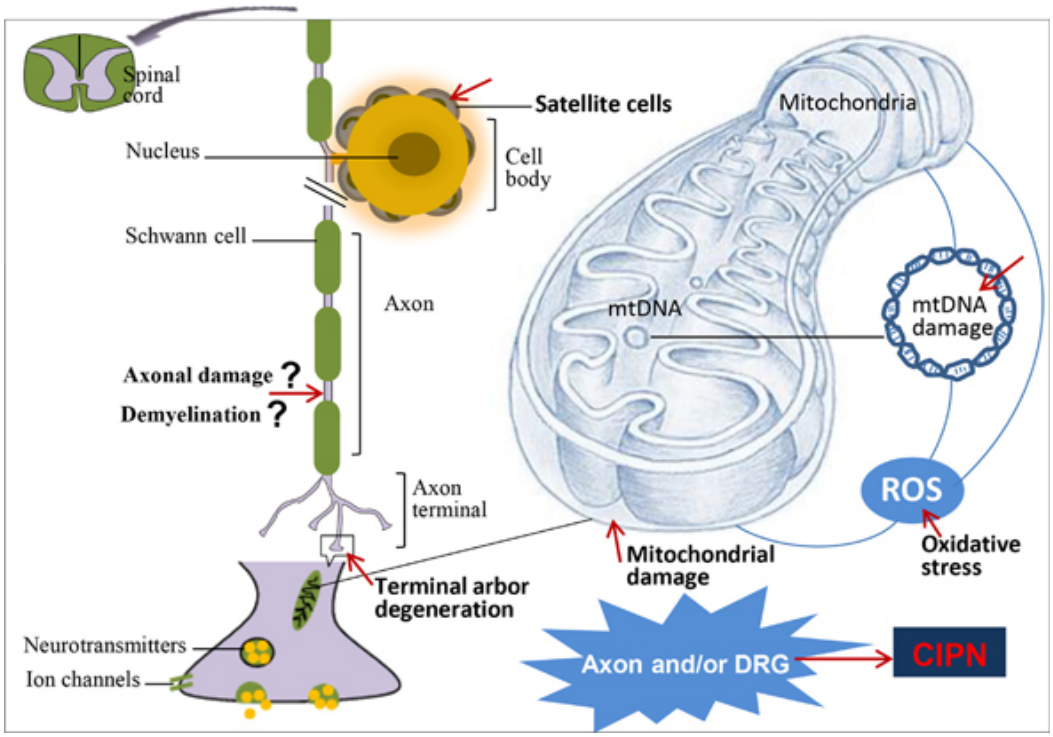

Figure 7 Cisplatin Pathogenesis and Associated Morphological Changes (Han and Smith, 2013).

2.5.1.7. Cisplatin Apoptosis

Like other platinum-based compounds, cisplatin exerts its therapeutic effects by initiating apoptosis (programmed cell death) in cancer cells. This process begins with the entry of cisplatin into the cell. Once inside the cytoplasm, cisplatin binds to DNA, creating cross-links that inhibit DNA replication. This leads to DNA damage in the cell nucleus and triggers the apoptotic pathway.

The apoptosis process involves a series of molecular events. The DNA damage caused by cisplatin upregulates tumor protein p53 (p53) and prevents cell division in DKG neurons. Changes in the cell cycle promote the upregulation of cyclin D1 and activation of CDK4/6 complexes, and phosphorylation of Rb. All of these events lead to the translocation of Bcl-2/Bax to the mitochondria, the release of cytochrome c, activation of caspases, and ultimately apoptotic cell death (Podratz et al., 2011; Dasari and Tchounwou, 2014).

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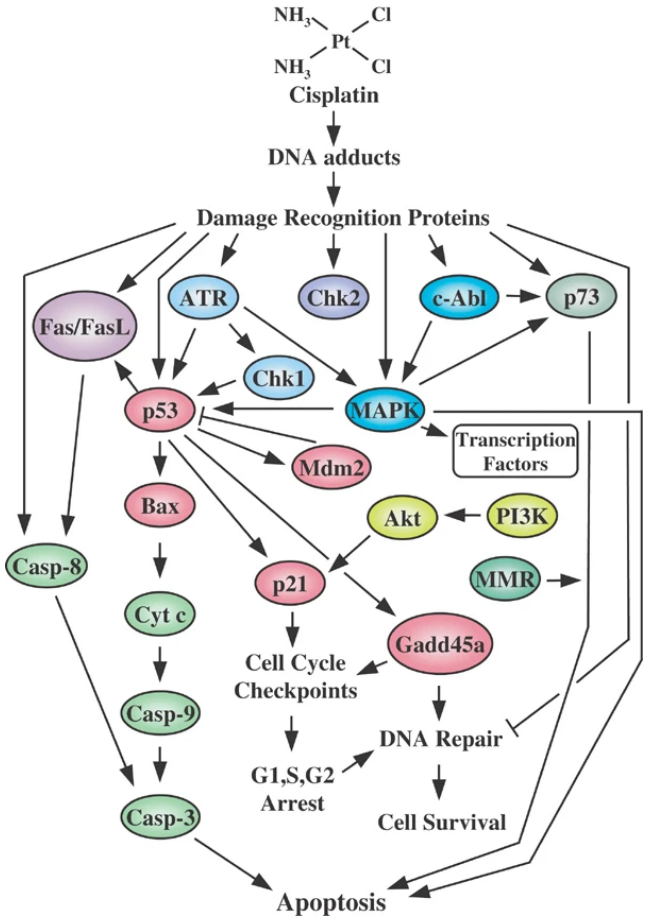

Figure 1.8. Apoptosis Induced by Cisplatin in the Cell and All Apoptotic Pathways (Siddik, 2003).

However, the apoptosis mechanism is complex, and many different factors regulate apoptosis. The apoptotic effect of cisplatin can vary depending on the cell type, dose applied, and treatment duration. Therefore, the impact of cisplatin on the apoptotic process can change based on specific conditions.

2.5.2 Types of Neurotoxicity

Cisplatin-induced neurotoxicity can manifest in various ways:

1.Peripheral Neuropathy: The most common form is characterized by numbness, tingling, and pain, typically in the hands and feet. This condition can worsen over time and lead to difficulties in walking and handling objects.

2.Ototoxicity: Cisplatin can damage the auditory system, leading to hearing loss or tinnitus (ringing in the ears).

3.Cognitive Impairment: Some patients experience issues with memory, concentration, and other cognitive functions, particularly with higher doses or prolonged treatment regimens.

4.Autonomic Nervous System Dysfunction: In some cases, cisplatin affects the autonomic nervous system, leading to issues with blood pressure regulation, heart rate, and digestive system function.

2.6 Clinical Use of Cisplatin

Cisplatin is a chemotherapy drug commonly used for treating solid tumors. It can be administered alone or in combination with other drugs. One of its most common applications

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is in the treatment of lung cancer (Pignon et al., 2008). It is highly effective in early-stage ovarian cancer (Hess et al., 2007). In addition to ovarian carcinoma, cisplatin is also used in combination treatments for testicular tumors and metastatic urothelial carcinoma (Pinto-Leite et al., 2013).

Head and neck cancers are among the types of cancer where cisplatin is frequently used. It is recommended to be combined with radiation and surgery, along with other drugs (de Castro et al., 2018). Another cancer type where cisplatin is used is breast cancerIt has been reported that survival rates are particularly improved in patients with metastatic breast cancer. Combination therapy with cisplatin is still one of the most effective treatment methods, especially in advanced-stage breast cancer (Decatris et al., 2004).

Cisplatin has also proven effective in patients with primary brain cancer and metastatic brain cancer. It is used in the treatment of testicular cancer, cervical cancer, esophageal cancer, neuroblastoma, mesothelioma, and lymphomas (Dasari & Tchounwou, 2014).

2.7 Treatments Used to Prevent Cisplatin-Induced Neurotoxicity in Clinical Studies

Attempts to adjust cisplatin dosing regimens have not significantly affected the severity of the resultant neurotoxicity (Hilkens et al., 1995). Efforts to reduce side effects without affecting cisplatin's anti-tumor activity have led to the search for effective agents that could enhance its therapeutic efficacy. Several agents have been explored for their potential to prevent neuropathy associated with platinum-based drugs. Various drug treatments for cisplatin-induced neurotoxicity have been tried in cancer patients, with antioxidants being the most commonly used. A prospective, randomized, placebo-controlled, double-blind study using alpha-lipoic acid did not show a significant reduction in the severity or incidence of neurotoxicity (Guo et al., 2014).

The ACTH analogue Org 2766, glutathione (GSH), amifostine, and various neurotrophic growth factors have been tested in experimental and clinical models to prevent cisplatin-induced neurotoxicity (Links & Lewis, 1999). Acetyl-(DDTC) has been considered as a chelating agent that binds with platinum without interfering with cisplatin's anti-tumor effects (Gandara et al., 1995). Glutathione's thiol nucleophilic region has a high affinity for heavy metals and has been suggested to prevent platinum accumulation in dorsal root ganglia (DRG) (Cascinu et al., 2002). A neuropeptide called Org2766 has been proposed to improve cisplatin neuropathy by enhancing trophic effects and repair mechanisms in endogenous nerve cells (van Gerven et al., 1994). Vitamin E, an antioxidant molecule, has been suggested to have protective effects against cisplatin-induced ototoxicity, nephrotoxicity, and neurotoxicity (Pace et al., 2010).

In a clinical study involving 108 patients with various solid tumors, vitamin E use resulted in significant reductions in the severity and incidence of grade 3 and 4 neurotoxicity in a randomized placebo-controlled study. A limitation of this study was the exclusion of a high number of patients. The same group also evaluated the neuroprotective effects of vitamin E treatment in a small group of patients with lung, ovarian, pharyngeal, gastric, testicular, esophageal, and tongue cancers. Significant reductions in the incidence and severity of neurotoxicity were observed in the control group, along with a reduction in median synaptic amplitudes (Pace et al., 2010).

Vitamin E has also been used in a protective capacity in a group of 189 patients with colorectal, breast, and lung cancers. Eight of these patients received cisplatin, two received carboplatin, 50 received oxaliplatin, and 109 received taxanes or their combinations. In a randomized double-blind placebo-controlled study, confounding factors were found in the taxane group. Due to the

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insufficient sample size in the platinum group, a definitive assessment could not be made (Kottschade et al., 2011).

N-acetylcysteine (NAC), a nutritional supplement that increases glutathione levels, has been thought to prevent platinum accumulation and reduce neurotoxicity in clinical cases of oxaliplatin (Lin et al., 2006). BNP7787 (disodium 2,2'-dithio-bis-ethanesulfonate) is considered an advanced chemoprotective agent (Miller et al., 2008).

Infusions of calcium and magnesium have been suggested to reduce the effects of oxalates on voltage-dependent sodium channels by chelating oxalates (Gamelin et al., 2004). A drug similar to carbamazepine, oxcarbazepine, blocks voltage-sensitive sodium channels and some calcium channels, and has been developed as a neuroprotective molecule against oxaliplatin neuropathy (Argyriou et al., 2006).

Reduced glutathione is a natural neuroprotective and antioxidant agent. It may prevent platinum accumulation in DRG neurons and also acts as a natural free radical scavenger. It may stimulate nerve growth factor receptors (Barhwal et al., 2008). However, three prospective randomized placebo-controlled studies did not find a significant effect (Cascinu et al., 1995; Colombo et al., 1995; Smyth et al., 1997).

Nimodipine, a Ca++ channel blocker, did not show significant neuroprotective effects on cisplatin-induced neurotoxicity in ovarian cancer patients (Cassidy et al., 1998). In patients with colon cancer, a prospective randomized open-label study using oxcarbazepine (Na+ channel inhibitor) showed a significant reduction in the incidence and severity of cisplatin-induced neurotoxicity (Argyriou et al., 2006).

Retinoic acid, which stimulates the expression of nerve growth factor and its receptor, has been used to prevent neurotoxicity in patients with advanced non-small cell lung cancer who were treated with cisplatin and paclitaxel. However, due to the short follow-up period, there was a decrease in the incidence and severity of grade 2-4 neuropathy (Arrieta et al., 2005).

Amifostine, an organic thiophosphate, has cytoprotective and detoxifying effects. It has been used in some clinical studies to treat cisplatin-induced neurotoxicity. However, there are differing views on its effectiveness, with some claiming it works (Planting et al., 1999) and others finding it insufficient (Gallardo et al., 1999).

Conclusion

Cisplatin, although highly effective in cancer treatment, is limited by severe side effects and drug resistance. The uptake of cisplatin into cells occurs through various mechanisms. Initially thought to occur via passive diffusion, an active transport system has now been identified, which is associated with tumor resistance. Understanding the mechanisms behind cisplatin resistance is crucial for developing new drug targets and predicting clinical responses. Advances in molecular biology have shed light on the intracellular pathways cisplatin follows, such as DNA damage recognition, damage signal transduction, cell cycle arrest, DNA repair, and the induction of apoptosis. This growing knowledge will aid in creating more effective combination therapies and developing new platinum-based drugs. Furthermore, research aimed at reducing cisplatin's neurotoxicity risk aims to make cisplatin a safer and more effective treatment option in the future.

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