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Review Article:

Cisplatin: Pharmacological and Toxicological Review

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ABSTRACT

Background: The chemotherapy medication cisplatin has been used to treat a variety of human cancers, including ovarian, lung, head and neck, testicular, and bladder tumors. Cisplatin has shown effectiveness against a number of cancer types, including lymphomas, sarcomas, germ cell tumors, and carcinomas. The mechanism of action of cisplatin has been associated with its ability to crosslink with the urine bases on the DNA to form DNA adducts. This prevents DNA damage from being repaired, which in turn causes cancer cells to undergo apoptosis. However, the medication shows certain signs of resistance, such as enhanced DNA damage repair, decreased drug accumulation intracellularly, and cisplatin cytosolic inactivation.

Aim: The current review presents a pharmacological review of cisplatin, including its mechanism of action, resistance mechanism, and toxicity, as well as its clinical applications.

Conclusion: In summary, researchers have frequently emphasized the significance of cisplatin therapy as the cornerstone of the treatment of various cancers. Strong evidence from research has shown that cisplatin-based chemotherapy regimens combined with other medications are more effective at reducing toxic side effects and overcoming drug resistance.

Keywords: Chemotherapy; Cisplatin; Toxicity.

INTRODUCTION

Antineoplastic medication called cisplatin (CIS) was first used in the late 1970s. CIS is exceedingly toxic and one of the most often used chemotherapy medications for solid tumors and hematologic cancers. It can be used either alone or in combination for induction and neoadjuvant therapy **[1].**

Chemical structure:

The CIS stands for cis-[Pt(NH3)2Cl2] square planar coordination complex. The CIS isomer, which has two similar ligands present in close proximity, is indicated by the prefix cis. This molecule's scientific name is CIS-diamminedichloroplatinum, where the second m in ammine denotes an ammonia (NH3) ligand as opposed to the first m in an organic amine **[2].**

Pharmacology:

1. Pharmacokinetics:

Absorption

The concentrations of platinum are highest in the liver, prostate, and kidney after cisplatin

doses of 20 to 120 mg/m2, somewhat lower in the bladder, muscle, testis, pancreas, and spleen, and lowest in the colon, adrenal, heart, lung, cerebrum, and cerebellum. 180 days after the final dosage, platinum is still found in tissues. Plasma proteins, including albumin, transferrin, and gamma globulin, can be bound to platinum itself. 90% of the plasma platinum is protein-bound three hours after a bolus injection and two hours after a three-hour infusion ends. Urine contains the parent substance, cisplatin, which is eliminated. The fecal excretion of platinum appears to be negligible, despite the fact that tiny levels of platinum are found in the bile and large intestine after administration of cisplatin **[2].**

Half-life

Following doses of 50 or 100 mg/m2, the monoexponential half-life of cisplatin is 20 to 30 minutes. The plasma half-life of cisplatin is 30 minutes. With a minimum half-life of five days or more, the complexes between albumin and the platinum from cisplatin are slowly removed but do not dissolve significantly **[1].**

Clearance

15–16 L/h/m2 (total body clearance, 100 mg/m2 infusion over 7 hours). 62 mL/min/m^2 [renal clearance, 2-hour infusion of 100 mg/m^2]. 50 mL/min/m2 [renal clearance, 100 mg/m2 infused over a 6- to 7-hour period]. The fact that the kidneys actively produce cisplatin or other platinum-containing compounds is demonstrated by the fact that the renal clearance of free (ultra filterable) platinum surpasses the glomerular filtration rate. Due to individual variations in the amount of active secretion and potential tubular reabsorption, the dose, urine flow rate, and renal clearance of free platinum are nonlinear and variable **[3].**

10% of the medication is eliminated in the bile and 90% in the urine. Its terminal half-life is 24 hours, with a beginning half-life of roughly 20 to 30 minutes. Albumin-bound platinum is administered gradually over a minimum of five days **[1].**

2. Pharmacodynamics:

The fastest-proliferating cells, which in theory are malignant, are killed when CIS disrupts DNA replication. Following delivery, a mechanism known as aquation causes one chloride ion to be gradually displaced by water to produce the aquo complex cis-[PtCl(NH3)2(H2O)]+. Because the intracellular chloride concentration is just 3-20% of the about 100 mM chloride concentration in the extracellular fluid, dissociation of the chloride is more likely inside the cell **[3].**

The water molecule in CIS-$[PtCl(NH_3)_2(H_2O)]+$ is itself easily displaced by the N-heterocyclic bases on DNA, especially guanine, which can bind. Accordingly, formation of [PtCl(guanine-DNA)$(NH_3)_2$]+ and crosslinking can happen when another guanine replaces the other chloride, generally. Cisplatin alters DNA in a number of ways that prevent mitosis, which is the process by which cells divide. Damaged DNA triggers DNA repair processes, which, when repair is unsuccessful, initiate apoptosis **[4].**

Most notable among the changes in DNA are the 1,2-intrastrand cross-links with purine bases. These include 1,2-intrastrand d(GpG) adducts, which form nearly 90% of the adducts, and the less common 1,2-intrastrand d(ApG) adducts. 1,3-intrastrand d(GpXpG) adducts occur but are readily excised by the nucleotide excision repair (NER**)** (Figure 1) **[1].**

Inter-strand crosslinks and inactive adducts are other adducts that may also be involved in the activity of cisplatin. Another proposed method of interfering with mitosis involves interacting with cellular proteins, particularly those with the high-mobility group (HMG) domain **[5].**

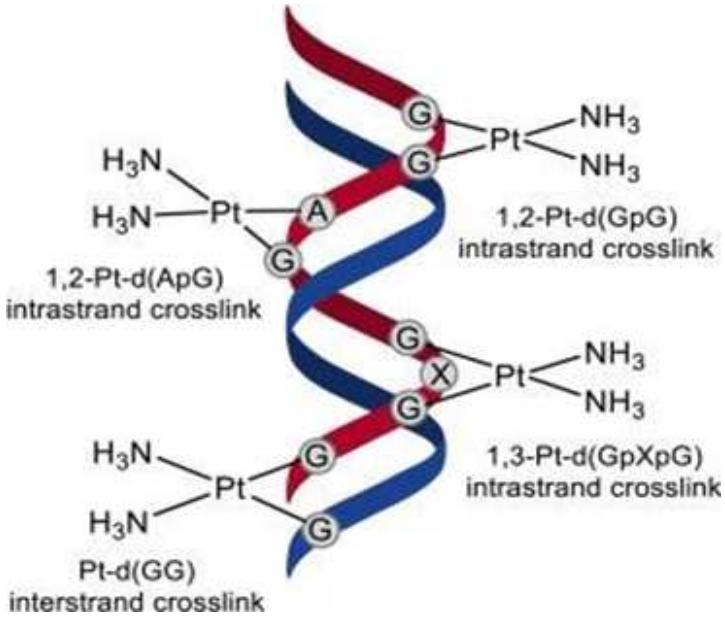

Figure 1: Cisplatin pharmacology **[7].**

Mechanism of action:

Cisplatin works by causing non-specific cytotoxicity in the cell cycle, which is made possible by the purine bases guanine and adenine being covalently attached to platinum. After strand separation brought on by intra- and inter-strand crosslinks created by this covalent binding **[6],** even when DNA repair systems are in action, cells frequently experience cell death that is either apoptotic or not as a result of residually damaged proteins, RNA, and DNA. Cisplatin treatment is especially effective at killing off cells that divide quickly, as seen in malignant tumors that grow quickly. Theoretically, slow-growing cancers may not benefit as much from cisplatin **[7].**

Mechanism of resistance:

Chemotherapy resistance is divided into two categories: primary resistance (resistance before drug treatment) and secondary resistance (resistance after drug exposure). The following processes contribute to chemotherapy drug resistance: efflux, drug inactivation, drug target modification, and suppression of cell death **[8].**

A specific efflux mechanism includes the tumor-manufacturing p-glycoprotein, a molecule that essentially removes the medication from the tumor cell. The Goldie-Coldman hypothesis, on the other hand, states that every tumor cell has a variable degree that is inversely proportionate to tumor growth **[9].** Tumor cell heterogeneity is another mechanism that adheres to this theory.

Clinical uses:

1. **Adult indications:** for the treatment of ovarian, testicular, and advanced bladder cancer, cisplatin has FDA approval. But when the advantages may outweigh the dangers of negative pharmacological side effects, practitioners regularly employ cisplatin which is used off-label for a variety of malignancies, including those listed below **[4].** Cisplatin is occasionally combined with other medications to treat diseases that frequently affect women, such as breast cancer, cervical and

endometrial cancer, and gestational trophoblastic neoplasia. These additional medications include taxane derivatives, 5-FU, and doxorubicin. Targeted therapy may be beneficial for tumors that are hormone-sensitive, but cisplatin is also useful as a single-agent neoadjuvant therapy for triple-negative breast cancer **[2].**

Also treated off-label with this drug and radiation are gastrointestinal cancers such as gastric, hepatobiliary, and esophageal cancer. Advanced cervical cancer is yet another off-label application. Small-cell and non-small-cell lung cancer can be treated off-label with etoposide and cisplatin **[5].** Other off label uses include the treatment of metastatic, advanced, and resistant malignancies, such as osteosarcoma, multiple myeloma, mesothelioma, penile cancer, thymoma, head and neck cancers, and Hodgkin and non-Hodgkin lymphomas **[4].**

2. **Pediatric indications:** There are no pediatric therapy applications for cisplatin **[10].**

Adverse effects:

The infusion should be stopped right away if extravasation is detected. Aspirate for any evident fluid accumulation and elevate the affected extremity. It is necessary to provide sodium thiosulfate, the antidote. Following cisplatin therapy, leukemia is the most frequent subsequent malignancy, and it often develops many years after the end of the initial course of treatment. After receiving treatment with a variety of chemotherapy drugs, tumor lysis syndrome can develop and present as hyperuricemia, hemodynamic changes, hyperkalemia, and azotemia. Treatments to lower uric acid levels could be required**.** These adverse effects include mild nausea, vomiting, diarrhea, temporary hair loss, loss of the ability to taste food, hiccups, dry mouth, dark urine, decreased sweating, dry skin, and dehydration **[4].**

Contraindications:

There is evidence that CIS crosses the placenta and could be harmful to an unborn child. Women of reproductive age need to use an effective form of contraception both throughout treatment and for up to a year after the final day of treatment. Breastfeeding women using cisplatin also had CIS in their milk. It is not advised to breastfeed while receiving therapy. If hypersensitivity manifests, CIS should be stopped right away **[2].**

Toxicity:

Mechanism of toxicity

It is thought that the toxicity of cisplatin mediates its cytotoxic effects through its contact with DNA. The chloride ligands of cisplatin are swapped out for water molecules in an aqueous environment, creating an electrophile that is positively charged. This electrophile forms DNA, RNA, and protein adducts when it interacts with nucleophilic sites on intracellular macromolecules. In rapidly proliferating cells, cisplatin binds to DNA and causes the creation of inter- and intrastrand cross-links, which stop DNA synthesis and replication **[11].**

Also, one of the mechanisms of cisplatin's toxicity is oxidative stress. It refers to an imbalance between the production and consumption of free radicals. The three mechanisms that cause the generation of ROS have been proposed. A powerful antioxidant molecule like glutathione is first depleted from the cell as a result of cisplatin's interaction with glutathione during its activation as a more potent nephrotoxin. The formation of ROS is caused by Cisplatin's second effect on the mitochondrial respiratory chain, while the third effect is due to the microsomes' cytochrome p450 system. It is unclear what the ROS's downstream target is. Given its extremely dynamic nature, it appears to operate through a variety of processes **[12-14].**

As previously mentioned, free radicals and oxidants can cause oxidative stress if they are present in excess. This detrimental process

occurs when there is an imbalance between the ability of cells to eliminate free radicals and the rate at which they generate them **[15].** For instance, an overabundance of peroxynitrite and hydroxyl radicals can lead to lipid peroxidation, which harms lipoproteins and cell membranes. Malondialdehyde (MDA) and conjugated diene compounds, which are known to be cytotoxic and mutagenic, will then arise as a result of this **[16].**

Lipid peroxidation spreads rapidly, damaging a huge number of lipidic molecules since it is a radical chain reaction. Oxidative stress can also cause protein damage, resulting in structural changes that may result in the loss or reduction of an enzyme's activity **[17].**

Even DNA is susceptible to oxidative stress-related lesions, with 8-oxo-2′-deoxyguanosine (8-OHdG) production serving as the most prominent example. This specific DNA lesion is extremely pernicious and capable of causing mutations. It can also result in the loss of epigenetic information, most likely as a result of a deficiency in the CpG island methylation capacity of gene promoters **[18].**

To protect themselves against DNA damage, cells can employ a variety of defense mechanisms, such as base excision repair (BER) or antioxidants. Several chronic and degenerative diseases, as well as the body's accelerated aging process and acute pathologies, can be brought on by oxidative stress if it is not rigorously controlled (i.e., trauma and stroke) **[19].**

Toxic effects of CIS:

Black box warnings for CIS include ones for myelosuppression, severe nausea and vomiting, and nephrotoxicity (Figure 2) **[11].**

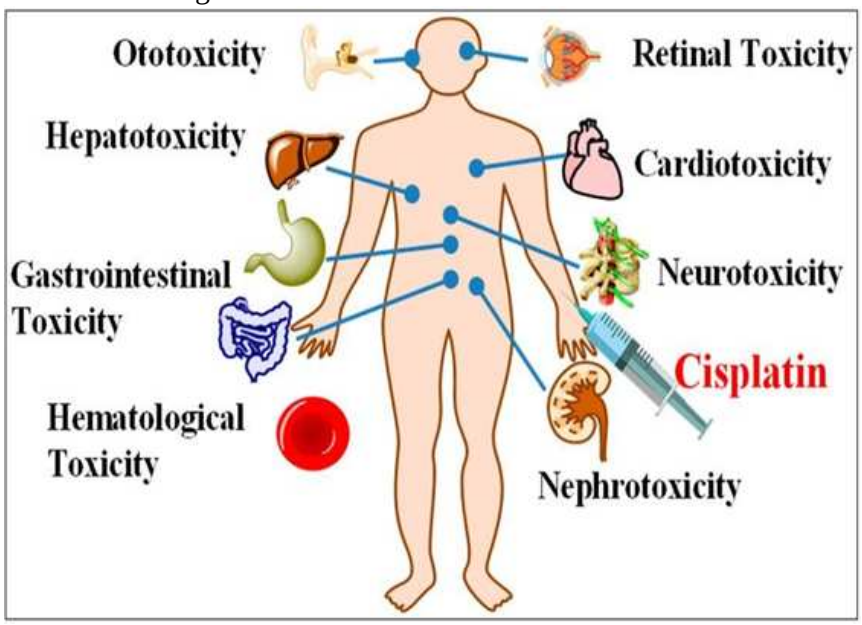

Figure 2: Cisplatin toxicity **[4].**

Gastrointestinal toxicity:

The side effects of it can take up to a week to recover from severe nausea and vomiting that are dose-related, linger for a long time, and cause metabolic abnormalities following treatment. The use of antiemetic medications as a preventative measure is strongly advised **[5].**

Myelosuppression:

The morbidity and mortality related to infection are the main issues with myelosuppression brought on by the use of

cisplatin. Keep an eye on your CBC and check for infection signs frequently. A thorough workup is required for infection and requires high clinical suspicion. Hematologic toxicity can require complete treatment discontinuation. If treatment is to continue, dose adjustment is frequently necessary **[4].**

Neurotoxicity:

The neurotoxic cisplatin is dose dependent. Peripheral neuropathy is the most frequent symptom of dose-related neurotoxicity. After withdrawal, this neuropathy may worsen and, in some cases, become irreversible. While neuropathy may necessitate adjusting the dosage, high-grade peripheral neuropathy may necessitate completely stopping treatment **[12].**

Nephrotoxicity:

With the administration of cisplatin, severe renal damage, including acute renal failure, is possible. These effects build up over time and are dose-dependent. Hydration prior to treatment is crucial to reducing renal toxicity. Depending on renal function and meticulous glomerular filtration rate monitoring, the dosage of cisplatin may need to be adjusted (GFR) **[1].**

Ocular toxicity/retinopathy:

These negative effects may take many different forms, such as loss of color perception or cortical blindness. After stopping cisplatin, patients typically get better, and in some circumstances, complete recovery is achievable **[2].**

Ototoxicity:

Examining the patient's ability to follow conversations, high-frequency hearing loss, and ringing in the ears are all part of the ototoxicity monitoring process. Although it has been documented, cisplatin use does not frequently result in deafness. In children, language development may be harmed by hearing loss **[3].**

Gonadotoxicity:

Cisplatin can decrease ovarian failure caused by dose-dependent spermatogenesis that results in early menopause since it is toxic to the gonads **[13].**

CONCLUSION

In summary, the importance of cisplatin therapy as the cornerstone for the treatment of many cancers has been repeatedly stressed by researchers. Strong evidence from research has shown that cisplatin-based chemotherapy regimens combined with other medications are more effective at lowering harmful side effects and beating drug resistance. Future research on combining strategies that target different pathways, such as cisplatin absorption decrease and inflammation, could improve the effectiveness of cisplatin.

Declaration of interest

The authors report no conflicts of interest.

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