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A COMPREHENSIVE REVIEW OF CISPLATIN: FROM CHEMICAL EVOLUTION TO ADVANCED THERAPEUTIC STRATEGIES

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ABSTRACT

Cisplatin is a commonly used platinum-based chemotherapeutic agent that is effective in treating cancers such as lung, ovarian, and testicular malignancies; it primarily acts by binding to DNA, forming adducts, and inhibiting cell division while inducing apoptosis through both intrinsic and extrinsic pathways; it also generates oxidative stress via reactive oxygen species, contributing to tumour cell death; additionally, cisplatin influences important cellular signalling pathways, with nephrotoxicity being the most common dose-limiting toxicity. Drug resistance is still a significant problem because of decreased drug accumulation, improved DNA repair, and drug inactivation; combination therapies with other anticancer medications have been used to improve treatment outcomes; sophisticated drug delivery systems like nanoparticles and liposomal formulations help enhance efficacy and reduce side effects; and future approaches like targeted therapy and artificial intelligence-based optimisation aim to improve safety, precision, and overall therapeutic effectiveness.

KEYWORDS: Cisplatin, Antineoplastic Agents, Mechanism of Action, Nephrotoxicity, Pharmacokinetics, Clinical Uses, Resistances.

INTRODUCTION

According to a recent analysis, cancer is a primary cause of illness and death worldwide, with an estimated 20 million new cancer diagnoses and over 10 million deaths expected by 2025. An estimated 53.5 million people survived for at least 5 years after being diagnosed with cancer. In 2022, the five most frequently diagnosed malignancies globally were lung, breast, colon, rectum, prostate, and skin· Platinum-based anti-cancer medicines such as cisplatin, carboplatin and oxaliplatin, which have clear therapeutic effects and well-defined mechanisms of action are frequently utilised in clinical practice. Cisplatin, the first generation of platinum anti-cancer drugs, has demonstrated therapeutic efficacy on a wide range of malignant tumours, including breast, ovarian, and colorectal cancers. Cisplatin is a non-specific chemotherapy medication that causes systemic damage while destroying tumour cells. Platinum anti-cancer medications have significant negative side effects, including dose-limiting toxicity, nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression.[2]

Discovery And History of Cisplatin

Michele Peyrone discovered Cisplatin, one of the greatest and earliest metal-based chemotherapy medicines, in 1845.[3] Barnett Rosenberg found in 1965 that the platinum complex produced by electrolytes from platinum electrodes prevented binary fission in E. Coli bacteria.[4] Loretta Van Camp, Tom Krigas, Eugene Grimley and Andrew Thomson all made substantial contributions to the cooperative effort that led to the discovery of Cisplatin.[5] Rosenberg's lab reported encouraging findings about Cisplatin's anticancer properties in mice in 1969.[6] In the United States, some platinum compounds began clinical studies in 1971. Barnett Rosenberg worked at Michigan State University on analogues of platinum[7] and was shown to have cytotoxic qualities in the 1960s. By the end of the 1970s,

in 1978 it became the first platinum compound to be licensed by the FDA for the treatment of cancer.[8]

CHEMISTRY

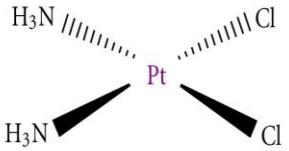

Figure 1: Structure of Cisplatin.

In terms of structure, Cisplatin is a coordination compound with square planar geometry. At room temperature, it is a white or pale yellow to yellow orange powder that resembles glass. Cisplatin is found to be stable at standard pressure and temperature, with a water solubility of 2.53g/L at 25°C.[9] Cisplatin's platinum anticancer complex contains three distinct ligand types. One is the non-leaving ligand type, which are nitrogen donors that create thermodynamically stable bonds with the central platinum atom and aid in the production of the final DNA-platinum adduct, which gives Cisplatin its anticancer effect. The cellular repair processes to avoid the DNA adducts are determined by the modification of those ligands. Leaving group ligands are the second sort of ligand that can change the platinum anticancer reaction complex's overall stoichiometry and aquation kinetics. Higher valency platinum complexes, platinum (III) and platinum (IV), are bound by the third category of ligands, known as axial ligands. They provide structural moieties for DNA adduction and nanoparticle attachment for targeted drug delivery, and they can separate following the biological reduction of the platinum complex.[10]

Mechanism of Action

Cisplatin penetrates the cytoplasm of a cell, water molecules replace its chloride atoms, activating the drug. Because of this displacement, it becomes a strong electrophile that develops an affinity for nitrogen atoms found in nucleic acids and proteins with sulfhydryl groups.[11] Cisplatin binds to purine rings at position N7, which damages DNA by preventing cell division and causing apoptosis.[12] The most prominent locations in DNA are the cross connections between purine and cisplatin at 1,2-intrastrand, which are composed of d(GpG) and d(ApG) adducts. These adducts may contribute to cytotoxicity, according to some theories.[13]

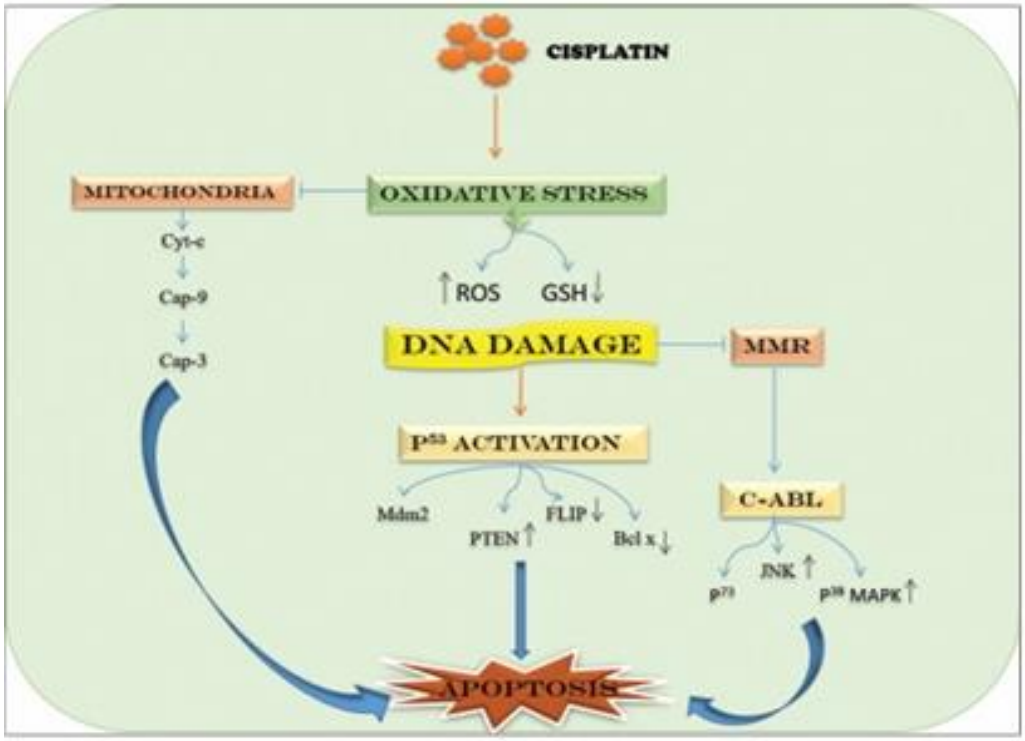

Figure 2: Mechanism of Action.

Oxidative stress induced by Cisplatin

Cells can balance reactive oxygen species (ROS) under normal circumstances by removing the scavenge system, which includes reduced glutathione, superoxide, and catalase. Under stressful circumstances, high ROS levels damage essential proteins, phospholipids, and DNA, resulting in abrasions that then aid in the development of tumours. Oxidative stress causes the loss of sulfhydryl groups, inhibits calcium absorption, and lowers mitochondrial membrane potential because mitochondria are extremely susceptible to ROS.[14] It is also hypothesised that high ROS levels can induce both necrosis and apoptosis in tumour cells.[15]

Cisplatin-induced apoptosis

Cisplatin causes cell death primarily through apoptosis mediated by the extrinsic death receptor and intrinsic mitochondrial mechanisms. The extrinsic pathway involves TNF receptor-dependent caspase-8 activation, whereas the intrinsic system is activated by DNA damage-induced cytochrome-c release and caspase-9 activation via the APAF-1 apoptosome complex. Bcl-2 family proteins regulate mitochondrial cytochrome-c release, which controls DNA damage-induced death. Dysregulation of these signalling pathways increases cisplatin resistance and contributes to chemoresistance.[30]

Cisplatin and protein kinases

Protein kinase C is a phospholipid-dependent enzyme. Protein kinases play an important role in signal activity and cell regulation, including growth, differentiation, and cell arrest.[16] Protein kinases C are resistant to cisplatin due to the existence of distinct isozyme patterns and cellular conditions.[17]

Cisplatin and mitogen-activated protein kinase

MAPK is a broad family of kinases that includes extracellular signal-regulated kinases, c-Jun N-terminal kinases, p38 MAP kinases, and p90 ribosomal s6 kinase. p90 ribosomal s6 kinases are downstream proteins that play critical roles in cell cycle, translation, and localisation.[18] p90 ribosomal s6 kinase can stimulate cell proliferation and survival by activating anti-apoptotic activity and inhibiting the genes responsible for apoptosis. extracellular signal-regulated kinases have an active part in DNA damage caused by cisplatin.[19,20]

Cisplatin and p38 mitogen-activated protein kinase

The P38 MAPK pathway affects tumour cell migration and proliferation**.** inhibited p38 promotes apoptosis regulated by ROS and JNK in tumour cells, exhibiting resistance to cisplatin and 5-fluorouracil.[21] p38 inhibition increases ROS production, which activates the JNK pathway, resulting in cisplatin-induced death in cancer cells.[22]

Cisplatin induced DNA damage

Cisplatin's major target is DNA, where it binds to the N7 position of purine rings, producing covalent connections. Purine base modification at 1,2 intrastrand and cross-linking across strands inhibits replication and transcription. However, many mutations and environmental stress induce DNA damage, which results in delayed cell cycle progression and activated check points to ensure cell repair or apoptosis. Cisplatin acts in the same way, producing DNA damage and bringing cells to death.[17]

Pharmacokinetics of Cisplatin

Cisplatin has a t1/2 of 25–50 minutes for initial plasma clearance following intravenous administration; concentrations of total (bound and unbound) drug then decrease, with a t1/2 of ≥ 24 hours. Platinum is covalently attached to plasma proteins in about 90% of the blood. The parent drug makes up the majority of the unbound portion, which decreases in a matter of minutes.

Cisplatin is present in high amounts in the tissues of the kidney, liver, intestine, and testes, but it has little effect on the central nervous system. During the first six hours, just a little amount of the medication is eliminated by the kidneys; by 24 hours, up to 25% is eliminated; and by five days, up to 43% of the dose is found in the urine, primarily covalently attached to proteins and peptides. There is very little biliary or intestinal excretion.

Table 1: Pharmacokinetic Parameters of Cisplatin.

Half-life elimination (terminal):	24hr to 47days
Protein bound:	>90%
Excretion:	Urine (90%); feces (10%)
Clearance:	15L/hr/m^2
Vd:	11L/m^2

[23]

Clinical Uses

Table 2: Cisplatin Doses for Different Types of Cancer.

Metastatic testicular cancer	20mg/m^2 once a day for five days per cycle IV
Metastatic ovarian Cancer	75–100mg/m^2 day 1, every 4weeks (taken with Cyclophosphamide 600mg/m^2 day 1, every 4weeks) IV 100mg/m2per cycle once every 4weeks (As single agent) : 70mg/m^2
Advanced bladder cancer	70mg/m^2 on day 2, every 4weeks (with Gemcitabine) IV
Head and Neck cancer	75–100mg/m^2 on day 1, every 3–4weeks IV

Oesophageal cancer	75–100mg/m^2 on day 1, every 3–4weeks (with Fluorouracil) IV
Gastric cancer	60mg/m^2 on day 1, every 3weeks, (with Epirubicin, Capecitabine) IV
Lung cancer	75–100mg/m^2 on day 1, every 3–4weeks (with Vinorelbine) IV 50mg/m^2 on days 1 and 8, every 4weeks (with Etoposide, Radiation therapy) IV
Hodgkin's or non-Hodgkin's lymphoma	75mg/m^2 on day 1, every 3weeks (with Dexamethasone, Gemcitabine) IV
Osteosarcoma	100mg/m^2 on day 1, every 3weeks (with Doxorubicin) IV

[10]

Renal Dose Adjustments

Creatinine clearance between 10 to 25: Decrease dose by 25%

Creatinine clearance below 10 : Decrease dose by 50%

Haemodialysis : Decrease the dose by 50% without any supplement

Peritoneal dialysis : Decrease the dose by 50% without any supplement.[24]

ADMINISTRATION

The cisplatin can be administered by intravenous infusion over a period of 6-8 hrs.

Preparation of Cisplatin Solution for Infusion

The required amount (dose) of the cisplatin concentrate may be diluted with mixture of sodium chloride 0.9% or glucose 5% or mannitol solution and administered by intravenous infusion with only clear & colourless to yellowish solution without visible particles.

Pre Treatment

Patients are prehydrated with at least 500 ml of an intravenous fluid containing salt in order to reduce the risk of nephrotoxicity. To increase urine flow, mannitol (12.5–25 g) is given parenterally. To avoid nausea and vomiting, patients need to undergo parenteral antiemetic medication, usually dexamethasone combined with a 5-HT3 receptor antagonist.

Post Treatment

IV hydration continue after treatment with the aim to administer 2 litres of sodium chloride IV infusion 0.9% or glucose-saline over a period of 6-12 hours.

Handling Precautions

Cisplatin injection should be prepared by qualified staff. A cytotoxic laminar flow cabinet is the ideal location for this procedure. It is important to take precautions to avoid breathing in particles and exposing the skin to cisplatin. When handling cisplatin, one should wear a protective gown, mask, gloves, and the proper eye protection. If the solution comes into contact with the eyes, rinse with water or saline; if it inadvertently gets on the skin or mucosa, wash the afflicted area well with soap and water right away; and in both situations, get medical help. If the medication is swallowed or inhaled, get medical help right away. It is advised that pregnant women do not handle cytotoxic drugs such as cisplatin. Luer-Lock fitting syringes and giving sets are recommended to prevent spillage. To reduce pressure and the possibility of aerosol production, use large diameter needles. Using a venting needle during preparation can also help to lower aerosol levels**.**

Spills And Disposals

If a spill occurs, restrict access to the affected area. Wear two latex rubber gloves, a respirator mask, a protective gown, and safety eyewear. Covering the spill with an absorbent cloth or adsorbent granules will help to limit its spread. Spills can also be cleaned with 5% sodium hypochlorite. Collect absorbent/adsorbent material and other spill debris and place in a leak-proof plastic container with appropriate labelling.

Clearly marked "CYTOTOXIC WASTE FOR INCINERATION AT 1100°C," cytotoxic waste should be treated as toxic or dangerous. It is recommended that waste materials be burnt for at least one second at 1100°C**.**[25]

Incompatabilities

Cisplatin reacts with aluminium which results in production of a black precipitate .therefore any device containing aluminium that may come in contact with (sets for iv infusions, needles, catheters, syringes) must be avoided.

Cisplatin decomposes with solution in media with low chloride content, the chloride concentration should at least be equivalent to 0.45% of sodium chloride.

Cisplatin not mixed with other medicinal products.

Antioxidants such as sodium metabisulphite, sodium bicarbonates, sulfates, fluorouracil and paclitaxel may inactivate cisplatin in infusion systems.[26]

Use of Cisplatin for Cancer Treatment

Lung Cancer

Lung cancer is among the most prevalent and deadly cancers. There are two forms of lung cancers. SCLC and NSCLC are both types of lung cancer. These two forms of cancer can be distinguished by how they grow and spread. SCLCs are the most aggressive and rapidly developing of all lung cancers.[27] Chemotherapy is the best treatment for SCLC. The two most crucial medications typically used in SCLC treatment are cisplatin and carboplatin. However, cisplatin is preferred over carboplatin due to its significant anticancer efficacy, despite having some side effects including as renal damage, nausea, and vomiting.[28]

Ovarian Cancer

Ovarian cancer is the most frequent type of cancer in women and the leading cause of mortality among gynaecologic cancers.[29] Most ovarian cancers are

treated primarily with surgery, and the patient is then given systemic chemotherapeutic treatment to destroy any remaining cancer cells.[30] Despite a number of side effects, cisplatin is the most effective chemotherapeutic drug for treating ovarian cancer. One of the most significant disadvantages of cisplatin therapy in ovarian cancer is that even after successful treatment, there is a considerable risk that the cancer will return within a few years, and its resistance to chemotherapy will develop considerably. To avoid this problem, combination therapy is utilised in which cisplatin is administered in conjunction with one other chemical agent such as honey venom, trichostatin A,5-aza-2′-deoxycytidine, aferin.[31]

Testicular Cancer

Two significant forms of testicular cancer that affect young men are seminoma and non-seminoma. All age groups are susceptible to seminomas, which typically grow and spread more slowly than non-seminomas. Seminomas are best treated with regimens based on cisplatin. Three to four cycles of cisplatin-based therapy result in cures for 85% of patients with advanced seminoma.[32]

Non-seminomas are most common in men between their late teens and early thirties, and they are classified into four subtypes: embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, and teratoma. Teratoma patients benefit from combined therapy with bleomycin, etoposide, and cisplatin, which has a cure rate of at least 90%.[33]

Cisplatin is a chemotherapeutic drug that is highly effective in treating a number of malignancies, including ovarian, breast, testicular, head and neck, cervical, prostate, bladder, lung, and resistant non-Hodgkin's lymphomas.[34]

Adverse Effects

A reduction in erythroid stem cells or ethropoietin may be the cause of anaemia seen with cisplatin use. Cisplatin has also been demonstrated to sensitise red blood cells, which can lead to direct coomb's positive haemolytic anaemia. One of the most frequent side effects of chemotherapy is nausea and vomiting.[35] Abnormalities of electrolytes, including hypokalaemia, hypocalcaemia, hyponatraemia, and hypomagnesamia . Constipation, diarrhoea, dysphasia, postprandial belly bloating, white tongue, impaired taste, leukopenia, neutropenia, thrombocytopenia, alopecia, itching, skin rash, oedema, mucositis, cough, polypnea, and chest pain are some other side effects.[36]

Toxicity

Cardiotoxicity

Changes in electric heat activity are the main cause of cardiotoxicity, which typically manifests as atrial fibrillation, supraventricular tachycardia, ventricular aarhythmia, and occasionally sinus bradycardia.[37]

Neurotoxicity

Cisplatin primarily damages the neurones in the dorsal root ganglia, resulting in symptoms like paraesthesia, diminished deep tendon reflexes, numbness and tingling, and weakness in the legs. The nucleoli of spinal root ganglion cells become aberrant when cisplatin builds up in the dorsal root ganglia.[38]

Ototoxicity

Ototoxicity typically occurs in younger people; approximately 31% of patients experience tinnitus and bilateral high-frequency hearing loss following a 50 mg/m^2 dosage of cisplatin. Bilateral, progressive, and permanent hearing problems result with larger cumulative doses and higher dosages (150 mg/m^2) administered over shorter time periods.[39] cisplatin-induced ototoxicity results from inner ear damage caused by elevated ROS and decreased GSH concentrations. This cisplatin adverse effect has not yet been successfully treated.[40]

Nephrotoxicity

The incidence of renal insufficiency in more recent experience using saline hydration and diuresis is in the range of 20-30% patients. The toxicity of cisplatin in the kidney is due to its accumulation in high concentrations in the proximal tubules and manifested by decreasing GFR rate, increase in serum creatinine and decrease in magnesium and potassium levels.[41]

Gastrointestinal And Hepatotoxicity

Cisplatin-induced gastrointestinal toxicity includes emetic symptoms, such as dyspepsia and chemotherapy nausea and vomiting (CINV). Cachexia may result from anorexia in certain people.[42] Cisplatin and other platinum-based medications have the potential to harm the liver's sinusoid arteries. Benign liver tumours and nodular hyperplasia may arise from this sinusoidal injury.[43,44]

Strategies To Prevent Cisplatin Induced Toxicities

Nephrotoxicity

Hydration protocol which are used for prevention of CIN, $MgSo_4$ and KCl add to intravenous fluid for prevention of hypomagnesaemia, hypokalmia and their side effects. Mannitol is an osmotic diuretic, conjunction with hydration, reduces renal cisplatin concentrations and has traditionally been used to prevent nephrotoxicity.[45]

Neurotoxicity

Glutathione may reduce neurotoxicity caused by cisplatin without changing its anticancer properties. Similarly, it is known that the thiol-containing molecule BNP7787 and Vitamin E functions as a neuroprotector against the neurotoxicity caused by cisplatin. ORG 2766 can also reduce the neurotoxicity caused by cisplatin, Additionally, substances like Colestipol, Fosfomucin, Acetylcysteine, and Ditiocarb sodium are utilised to reduce the various cytotoxicity caused by cisplatin.[46]

Hepatoxicity
Reducing oxidative stress, inflammation and apoptosis through natural antioxidants (Honey, Royal jelly, Silymarin), Pharmacological agents (L carnitine, Gliclazide, Dapagliflozin) and hydration to manage systemic toxicity.[47]

Gastrotoxicity
Strategies to overcome these effects involve a combination of antiemetic medications to control nausea and vomiting, nutritional support and the use of antioxidant rich compounds to protect the gastric mucosa.[48]

Haemotological Disorders
Cisplatin induced hematological disorders is treated by supportive care, Haematopoietic colony stimulating factors, Erythropoietin replacement .platelet growth factors, blood tranfusions, hydration, antioxidants, sodium thiosulfate, curcumin, dose modification, avoiding nephrotoxic drugs and monitoring parameters.[49]

Combination Drugs
Cisplatin And Paclitaxel
It is an anticancer medication that binds to microtubules and stabilises them by preventing the microtubule web complex from reforming.[50] Paclitaxel medication therapy is a successful treatment for a number of malignancies, including ovarian cancer.[51] Because of its low therapeutic index and increased transportation, paclitaxel is a good treatment option for women with ovarian cancer who have higher survival rates.[52]

Cisplatin And Gemcitabine
Gemcitabine functions as a nucleoside analogue and is a beta isomer. Gemcitabine can be used to treat cancer since it has an antiviral impact and causes minimal harm.[53] Gemcitabine's mechanism demonstrates how it induces apoptosis within DNA.[54] Gemcitabine and cisplatin combination therapy is frequently used to treat biliary malignancies.[55]

Cisplatin And Doxorubicin
The anticancer medication doxorubicin has a low level of toxicity. Endometrial patients are frequently treated with doxorubicin in conjunction with cisplatin.[56] Due of its cytotoxicity, doxorubicin is actively employed either alone or in combination.[57]

Cisplatin And Tegafur-Uracil
Tegafur uracil (UFT) is an oral anticancer medication that is further absorbed in the small intestine.
For the treatment of advanced stage non-small cell lung cancer, UFT is used with cisplatin.

Table 3: Drug Composition with Type of Cancer.

DRUG COMPOSITION	TYPE OF CANCER
Cisplatin + Etoposide	Non-small cell lung cancer
Cisplatin + Honey bee venom	Ovarian carcinoma
Cisplatin + Cyclophosphamide	Advanced stages of salivary glands
Cisplatin + Bleomycin	Ovarian carcinoma
Cisplatin + Capecitabine	Gastric carcinoma
Cisplatin + Tetra arsenic oxide	Cervical carcinoma
Cisplatin+ Irinotecan	Gastric cancer Esophageal cancer
Cisplatin + Osthol	Lung cancer
Cisplatin + Mitomycin + Vindesine	Non-small cell lung cancer
Cisplatin + Oxaliplatin + Quercetin + Thymoquinone	Ovarian cancer
Cisplatin + Gemcitabine	Biliary tract cancer
Cisplatin + Everolimus	Advanced pancreatic cancers
Cisplatin + BV10	Lung cancer Ovarian cancer Cervical cancer
Cisplatin + Cilastatin	Non-small cell lung cancer [58]

Monitoring
Prior to starting treatment, an evaluation of renal function, Sr BUN, and Crcl electrolytes is necessary and take a complete blood count (CBC) before initiating treatment. An evaluation of audiology should ideally take place both before and after the administration of ototoxic drugs.
To check for infection and extravasation, the infusion site should be examined both before and after medication administration.[25]

Contraindications
Hypersensitivity
Myelosuppression
Pregnancy
Lactation
Renal Impairment
Hearing Impairment[24]

Drug Interactions
Cisplatin + Aminoglycoside Antibiotics (Gentamicin, Amikacin): Both drugs are nephrotoxic drugs and accumulate in renal tubular cells. They produce additive

or synergistic nephrotoxicity by increasing oxidative stress and mitochondrial damage in proximal tubular cells and it can increases serum creatinine and BUN.[59]

Cisplatin + Loop Diuretics: Loop diuretics enhance ototoxicity by increasing Cisplatin accumulation in the cochlear hair cells and reducing inner ear blood flow, therefore it increases risk of hearing loss and tinnitus.[60]

Cisplatin + Paclitaxel
Pharmacokinetic interaction occurs when Cisplatin is given before Paclitaxel, reducing Paclitaxel clearance and increasing its systemic exposure, therefore it increased myelosuppression and neurotoxicity.[61]

Cisplatin + Bleomycin
Combination therapy leads to enhanced oxidative stress and DNA damage, increasing toxicity in tissues such as lungs and kidneys, therefore it increases pulmonary toxicity and nephrotoxicity.[62]

Cisplatin + Amphotericin B
Both drugs cause direct tubular cell injury and renal vasoconstriction, resulting in severe additive nephrotoxicity and it leads to rapid decline in eGFR and electrolyte disturbances.[63]

Cisplatin + Phenytoin
Cisplatin reduces gastrointestinal absorption and plasma concentration of phenytoin, possibly due to chemotherapy induced mucosal damage and altered hepatic metabolism, therefore it leads to risk of seizures.[64]

Use In Special Populations
Pediatric Use
Paediatric patients receiving cisplatin injections may experience more severe and harmful ototoxic effects, especially if they are younger than five years old. Every patient getting an injection of cisplatin should have their vestibular and audiometric functions monitored. It is estimated that between 40 and 60 percent of paediatric patients have hearing loss**.** Early identification of hearing loss can reduce the possible negative effects of hearing loss on a child's social and cognitive development.

Geriatric Use
Compared to younger patients, older patients also had higher rates of leukopenia and severe thrombocytopenia. The kidney is known to eliminate cisplatin in significant amounts. Elderly patients are more likely to have impaired renal function, hence dose selection and renal function monitoring should be done carefully.[65]

Cisplatin Resistance
Cisplatin resistance is caused by a number of different methods. The first is a decrease in the drug's intracellular accumulation.[66] Two separate routes controlling intracellular drug uptake and export may be responsible for the decrease in cellular CDDP accumulation.[67] Increased DNA repair is another method that may sustain cisplatin resistance in tumour cells.[68] Platinum-DNA damage triggers a complicated biological reaction that includes identification and repair processes. One of the two main repair pathways—mismatch repair and nucleotide excision repair—will be implicated, depending on the type of platinum-DNA lesion.[69] The cytosolic inactivation of cisplatin is the third mechanism of resistance to cisplatin. Because cisplatin's capacity to react with DNA is impaired when it is inactivated, less DNA adducts are produced, which reduces DNA damage and increases the survival of cancer cells.[70]

Strategies To Overcome Cisplatin Resistance
Cisplatin resistance-overcoming techniques, such as combining cisplatin with medications that particularly target cancer cells, cisplatin with modulators of players implicated in cisplatin resistance, and lastly, creating novel platinating drugs.

Modulators of cisplatin resistance
In lowering cisplatin resistance, the GST inhibitor NBDHEX and the GST-activated prodrug Canfosfamide (TLK286) have demonstrated potent action, including clinical effectiveness in platinum-resistant ovarian cancer. Further enhancing cisplatin activity is the inhibition of DNA damage response pathways; cisplatin toxicity is increased by the Chk1 inhibitor UCN-01, which also breaks down ERCC1–XPA connections. The DNA demethylating drug Decitabine may also reverse resistance by reviving genes that have been epigenetically silenced.[71]

Combination of cisplatin with drugs targeting cancer cells
Combining cisplatin with other medications has been shown to be an effective therapeutic strategy. Clinical activity in individuals with advanced breast cancer has been encouraging when cisplatin and Trastuzumab, an antibody produced against the EGF receptor subtype HER2, are combined.[72] Adding Bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, to platinum-based chemotherapy increased response and survival in patients with non-small cell lung cancer.[73]

Development of new platinum drugs
A different strategy to get around cisplatin resistance is the introduction of novel cisplatin analogues that are partially or totally non-cross resistant.[74] In osteosarcoma and ovarian cancer cell lines, acquired cisplatin resistance can be overcome by the new generation cisplatin analogues Satraplatin and Picoplatin.[75] Picoplatin appears to be less reactive than cisplatin toward compounds that contain thiols, allowing it to avoid GSH and MT detoxification.[76] Satraplatin and Picoplatin have demonstrated promising clinical efficacy in prostate cancer and non-small cell lung cancer.[77]

Future Perspectives

Nanoparticle Delivery

Nanotechnology plays a significant role in medication development and delivery, as well as diagnosis and focused therapeutic management. Nanoparticles improve chemotherapy efficacy by reducing side effects, targeting cancer cells, and affecting pharmacokinetics. Combining chemotherapy medications with nanoparticles is more effective than using pharmaceuticals alone. Combination approaches offer benefits such as accurate drug distribution, minimal toxicity, and reduced resistance.[58]

Targeted Therapy

The goal of targeted therapy for cisplatin is to overcome drug resistance and lessen serious systemic effects such neurotoxicity and nephrotoxicity. Important targeted cisplatin delivery strategies include oral administration platforms, folate/boron modified particles, Platinium (IV) prodrugs, nanoparticle encapsulation, and aptamer targeted systems.[78]

Liposomal Cisplatin

Liposomal cisplatin enhances targeted drug distribution while lowering systemic toxicity associated with conventional cisplatin therapy. Liposomal formulations, such as Lipoplatin, offer promise in increasing tumour accumulation while minimising nephrotoxicity. Future research should focus on optimising liposome composition, improving drug release and stability, and creating trustworthy models to predict in-vivo performance. Furthermore, multifunctional liposomal systems capable of delivering cisplatin with other anticancer drugs may improve therapeutic efficacy and overcome drug resistance.[79]

Ai In Chemotherapy Optimization

AI has the ability to significantly improve chemotherapy by analysing huge clinical, genomic, and molecular information to predict treatment response and drug resistance. AI-based models can help identify the most effective medications and personalise dosing regimens for specific patients, boosting therapeutic outcomes while minimising harm. Furthermore, AI platforms may dynamically change chemotherapy regimens based on patient-specific data, enabling precision oncology and improving clinical decision-making in cancer treatment.[80]

CONCLUSIONS

Cisplatin is still one of the most significant and commonly used chemotherapy drugs for the treatment of a variety of cancers, including lung, ovarian, bladder, and head and neck cancers. Its potent anticancer activity and wide clinical application have made it a staple of many chemotherapy regimens. However, cisplatin's therapeutic use is limited by considerable side effects, including nephrotoxicity, neurotoxicity, and drug resistance, which may have an impact on treatment outcomes and patient well-being. Despite these limitations, ongoing research is to enhancing cisplatin's therapeutic efficacy and safety profile. To reduce toxicity and overcome resistance, strategies such as targeted drug delivery systems, liposome formulations, combination therapies, and biomarker-based personalised treatment approaches are being investigated. Future research should focus on developing safer cisplatin alternatives, optimising toxicity-prevention techniques, and incorporating modern technologies like as nanomedicine and artificial intelligence-guided therapy. These developments could improve treatment precision and maximise the therapeutic benefits of cisplatin in cancer care.

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