Cisplatin : "The Impact in Cancer Therapy"

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Abstract

Cisplatin is called the "penicillin of cancer" because it is used so widely and it was the first big chaemotherapy drug, It is most widely prescribed as well as a first and effective treatment for many cancer diagnoses. Unlike many cancer drugs, which are organic molecules with complex structures, cisplatin is an inorganic molecule with a simple structure. In designing and evaluating new cancer treatments, researchers use cisplatin as the gold standard against which new medicines are compared. This drug is probably most widely known for its prominent role in in fighting multiple cancer types. Cisplatin is used to treat many types of cancer, but it is most widely prescribed for testicular, ovarian, bladder, lung, and stomach cancers.

Cisplatin, is a well-known chemotherapeutic drug. It has been used for treatment of numerous human cancers including bladder, head and neck, lung, ovarian, and testicular cancers. It is effective against various types of cancers, including carcinomas, germ cell tumors, lymphomas, and sarcomas. Its mode of action has been linked to its ability to crosslink with the purine bases on the DNA; interfering with DNA repair mechanisms, causing DNA damage, and subsequently inducing apoptosis in cancer cells.

However, because of drug resistance and numerous undesirable side effects such as severe kidney problems, allergic reactions, decrease immunity to infections, gastrointestinal disorders, hemorrhage, and hearing loss especially in younger patients, other platinum-containing anti-cancer drugs such as carboplatin, oxaliplatin and others, have also been used.

Furthermore, combination therapies of cisplatin with other drugs are to be highly considered to overcome drug-resistance and reduce toxicity. This comprehensive review highlights the physicochemical properties of cisplatin and related platinum-based drugs, and discusses its uses either alone or in combination with other drugs for the treatment of various human cancers. A special attention is to be given to its molecular mechanisms of action, and its undesirable side effects.

Keywords: Cisplatin, Platinum-based drugs, Mechanisms of action, cisplatin combination therapy, Cancer treatment, Cisplatin Pharmacology and Toxicological effects of Cisplatin.

1. Introduction

Cisplatin is called as a **cis-di ammin edi chloro platinum(II)**, and it is a metallic (platinum) coordination compound with a square planar geometry. It is a white or deep yellow to yellow-orange crystalline powder at room temperature. It is slightly soluble in water and soluble in di methyl primanide and N,N-di methyl formamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the trans-isomer. Cisplatin has a molecular weight of 301.1 gm/mol, a density of 3.74 g/cm^3, a melting point of 270° C, a log Kow of -2.19 and a water solubility of 2.53 g/L at 25° C (HSDB 2009).

Cisplatin was first synthesized by M. Peyrone in 1844 and its chemical structure was first elucidated by Alfred Werner in 1893. However, the compound did not gain scientific investigations until the 1960's when the initial observations of Rosenberg at Michigan State University pointed out that certain electrolysis products of platinum mesh electrodes were capable of inhibiting cell division in Escherichia coli created much interest in the possible use of these products in cancer chemotherapy.

Since the identification of cis-di chloro diammine platinum (II) (cisplatin, r) as the agent responsible for this activity, much interest has been generated in the use of coordination complexes of platinum, palladium, and other noble metals in the treatment of cancer. Cisplatin also has shown anticancer activity in a variety of tumors including cancers of the ovaries,' testes,' and solid tumors of the head and neck.

It was discovered to have cytotoxic properties in the 1960s, and by the end of the 1970s it had earned a place as the key ingredient in the systemic treatment of germ cell cancers. Among many chemotherapy drugs that are widely used for cancer, Cisplatin is one of the most compelling ones. It was the first FDA-approved platinum compound for cancer treatment in 1978. This has led to interest in platinum (II) - and other metal-containing compounds as potential anticancer drugs.

It is aimed to provide a comprehensive review of the physicochemical properties of cisplatin and related platinum-based drugs, to discuss its uses either alone or in combination with other drugs for the treatment of various human cancers, to examine its molecular mechanisms of action, and to discuss it potential side effects.

2. Platinum-Containing Drugs of Cisplatin

Cisplatin is the first platinum compound to be discovered and shows strong anti-tumour activity in various malignancies. However, its application in clinical practice is extremely limited due to its severe nephrotoxicity, high-frequency of vomiting, obvious peripheral neuropathy, as well as the requirement of intravenous hydration, especially for old patients.

In the preclinical and clinical development of cisplatin, several thousand analogues have been synthesized and tested for properties that would enhance its therapeutic index. About 13 of these analogues have been evaluated in clinical trials, but only one the **carboplatin** has provided definite advantage over cisplatin and achieved worldwide approval. Nine platinum analogues are currently in clinical trials around the world ormaplatin (tetraplatin), oxaliplatin, DWA2114R, enloplatin, lobaplatin, CI-973, 254-S, JM-216, and liposome-entrapped cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum (II) (LNDDP).

Figure 1 - presents the chemical structures of cisplatin and four of its analogs including carboplatin, oxaliplatin, ormaplatin and enloplatin.

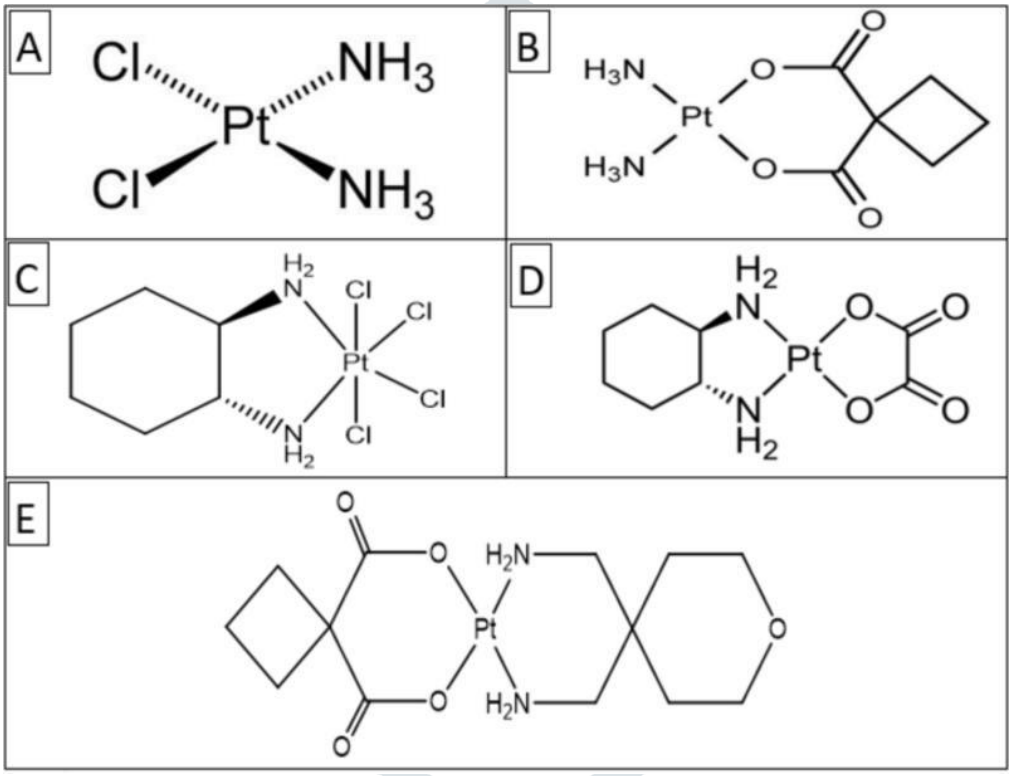


Figure 1 - Chemical structures of selected platinum drugs: A-cisplatin; B-carboplatin; C-oxaliplatin; D-ormaplatin; E-enloplatin.

From the molecular perspective, cisplatin represents a perfect example of how a small alteration in chemical structure can significantly affect biological activity in target cell.

Cisplatin, carboplatin and oxaliplatin are composed of doubly charged platinum ion surrounded by four ligands; with the amine ligands on the left forming stronger interactions with the platinum ion, and the chloride ligands or carboxylate compounds on the right forming leaving groups allowing the platinum ion to form bonds with DNA bases.

Carboplatin is a chemotherapeutic drug used for cancers of **ovaries, lung, head and neck.** In terms of its structure, carboplatin differs from cisplatin in that it has a bidentate dicarboxylate (CBDCA) ligand in place of the two chloride ligands, which are the leaving groups in cisplatin (Figures 1). It exhibits lower reactivity and slower DNA binding kinetics, although it forms the same reaction products in vitro at equivalent doses with cisplatin.

Unlike cisplatin, carboplatin may be susceptible to alternative mechanisms. Some studies shows that cisplatin and carboplatin cause different morphological changes in MCF-7 cell lines while exerting their cytotoxic behavior. The diminished reactivity limits protein-carboplatin complexes, which are excreted. The lower excretion rate of carboplatin means that more is retained in the body, and hence its effects are longer lasting. Relative to cisplatin, the greatest benefit of carboplatin is its reduced side effects, particularly the elimination of nephrotoxic effects. The main drawback of carboplatin is its myelo suppressive effect which causes the blood cell and platelet output of bone marrow in the body to decrease quite dramatically, sometimes as low as 10% of its usual production levels.

Carboplatin is less potent than cisplatin; depending on the type of cancer, carboplatin may only be 1/8 to 1/45 as effective. The clinical standard of dosage of carboplatin is usually a 4:1 ratio compared to cisplatin; that is, for a dose that usually requires a particular dose of cisplatin, four times more carboplatin is needed to achieve the same effectiveness.

Oxaliplatin, a third-generation platinum with a 1,2-diaminocyclohexane (DACH) carrier ligand, has been confirmed to have comparable efficacy and less nephrotoxicity and gastrointestinal toxicity compared to cisplatin 8-9. Thus, it is now widely used in patients with colorectal cancer, GC (Gasrtic cancer), and relapsed or refractory lymphoma.

As both oxaliplatin and cisplatin showed significant anti-tumour activity in advanced GC, researchers began to pay attention to the difference between oxaliplatin-based and cisplatin-based regimens.

3. Cisplatin uses in the treatment of cancer

1. Cisplatin in the treatment of Lung Cancer

Lung cancer remains one of the most common types of fatal malignancies. Small cell lung cancers (SCLCs) represent 15% of all lung cancers. At present, platinum based treatments are key drugs for SCLC. Cisplatin and carboplatin are two of the most common types of platinum based treatments used in SCLC chemotherapy. In clinical trials, cisplatin is often selected due to its strong antitumor activity, but its adverse effects include renal toxicity, nausea and vomiting. Therefore, to avoid renal toxicity, urine volumes should be monitored and large-dose infusion is mandatory in cisplatin based chemotherapy. In

clinical practice, carboplatin has been considered to be a substitute for cisplatin without any apparent loss of therapeutic efficacy since aggressive hydration is often problematic.

2. Cisplatin in the trestment of Ovarian Cancer

Ovarian cancer has the highest mortality among gynecologic cancers. Most patients with ovarian cancer are diagnosed at late stages due to lack of effective screening strategies and specific symptoms associated with early-stage disease. Conventional treatment for late stages of ovarian cancers is surgical excision followed by platinum/ taxane combination chemotherapy. Although this treatment regime is effective as the first-line treatment, recurrence occurs in up to 75% of ovarian cancer patients.

Patients with recurrent ovarian cancer ultimately develop resistance to chemotherapy and eventually succumb to the disease. About 90% of ovarian cancers arise originally from ovaries with an unknown reason, while the remainder has hereditary background, or are associated with breast and colon cancers. Cisplatin derivatives are used as the mainline treatment of ovarian cancer, despite their severe side effects and development of resistance. Cisplatin is used in combination with other chemical agents or compounds to treat ovarian cancer in both the resistant and sensitive cell lines.

3. Cisplatin in the treatment of Carcinoma

Head and neck squamous cell carcinoma (HNSCC) is a common malignant disease with more than 600,000 new cases registered worldwide every year. Despite improved treatment options, including surgery, radiation and chemotherapy, HNSCC is associated with a high mortality rate. The overall 5-year survival rate of approximately 50% has not changed over the last decades. Cisplatin alone is not an effective drug in treating the disease. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, doxorubicin, and or gemcitabine in patients with metastatic urothelial carcinoma has been reported.

4. Cisplatin in the treatment of Breast Cancer

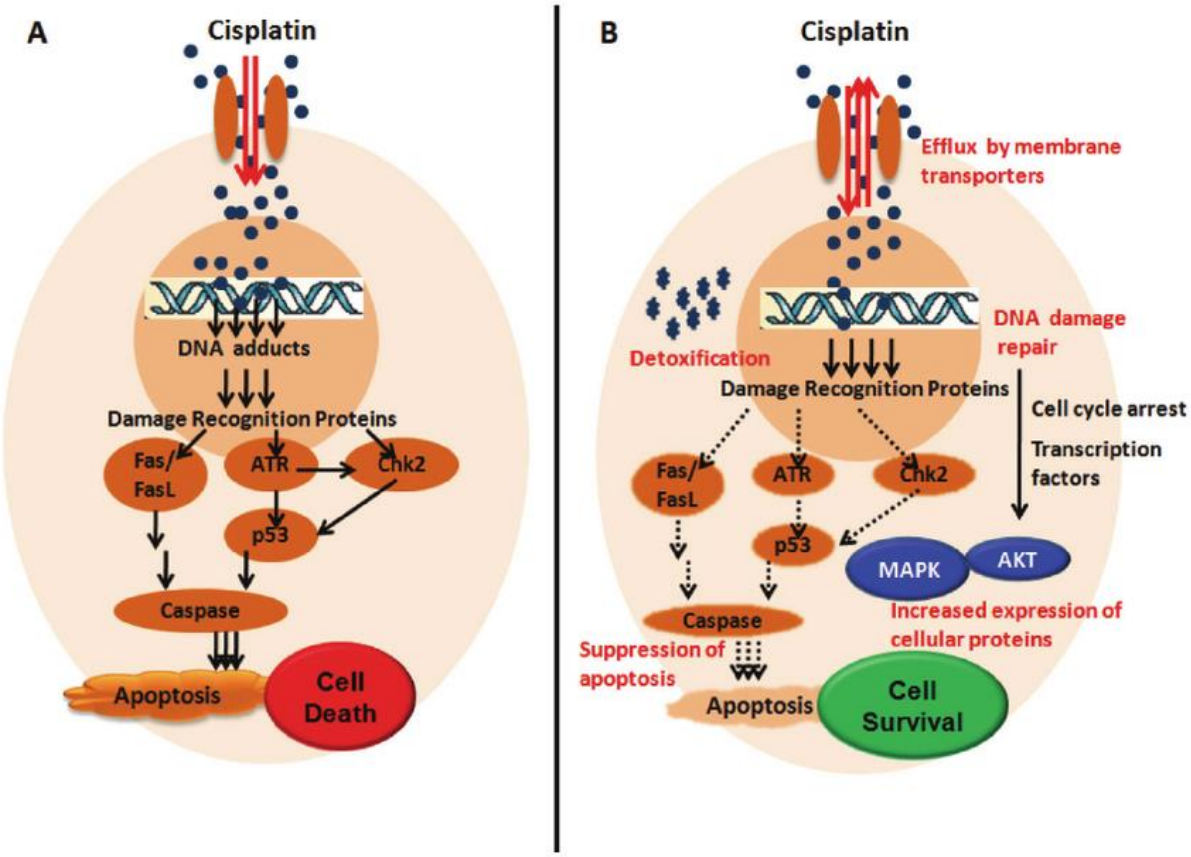
Breast cancer is one of the leading causes of women mortality worldwide. Chemotherapy is the only option for treating the malignant breast cancer and condition for increases the lifespan of the patient. Chemotherapeutic agents have been developed to counter the continuing breast cancer problem. However, most chemotherapeutic drugs effectively target rapidly dividing cells causing damage and are thus referred to as “cytotoxic drugs.”

Cisplatin is an important chemotherapeutic agent used widely or the treatment of a variety of malignancies, including breast, testicular, ovarian, cervical, prostate, head and neck, bladder, lung and refractory non-Hodgkin's lymphomas.

The cytotoxic effect is likely a result of inhibition of replication by cisplatin-DNA adducts and induction of apoptosis.

5. Cisplatin in the treatment of Brain Cancer

Glioblastomamultiforme (GBM) is the most common primary malignant brain tumor, and with rare exception, is invariably fatal. The current standard of care for patients with GBMs consists of surgery and radiotherapy in combination with temozolomide, followed by repetitive cycles of temozolomide. Although the survival advantage of this combined treatment regimen was still evident at 5 years, the increase in overall median survival was only for 2.5 months. Cisplatin therapy is also used for recurrent childhood brain tumors, as well as in other cancers such as gastric cancer, anal cancer, and leukemia.



4. Cisplatin Combination Therapy

Cisplatin combination chemotherapy is the basis of treatment of many cancers. Platinum responsiveness is high primarily but many cancer patients will ultimately relapse with cisplatin-resistant disease. Hence, drug resistance has been observed in many patients who have relapsed from cisplatin treatment. The proposed mechanisms of cisplatin resistance include changes in cellular uptake and efflux of cisplatin, increased biotransformation and detoxification in the liver, and increase in DNA repair and anti-apoptotic

mechanisms. To overcome resistance, cisplatin is commonly used in combination with some other drugs in treating ovarian cancer, biliary tract cancer, lung cancer, gastric cancer, carcinoma of salivary gland origin, breast, colon, lung, prostate, melanoma and pancreatic cancer cell lines, squamous cell carcinoma of male genitial tract, urothelial bladder cancer, and cervical cancer. The given table presents a synopsis of Cisplatin combination therapy with other cancer drugs and targeted cancers.

Cisplatin and other cancer drugs for combination therapy

1. Honeybee venom	Ovarian cancer
2. Anvirzel	Breast, Colon, Lung, Prostate, Melanoma and Pancreatic cancer
3. Bevacizumab	Non small lung carcinoma
4. Vinbalstine and bleomycin	Metastatic granulosa cell tumors in ovary
5. Methotrexate and bleomycin	Advanced squamous cell carcinoma of the male genital tract
6. Tetra arsenic oxide	Cervical cancer
7. Vindesine	Non small lung carcinoma
8. Combination Drug(s)	Cancer Type
9. Paclitaxel	Ovarian carcinoma Breast carcinoma Lung carcinoma Melanoma Head and neck carcinoma
10. Paclitaxel and 5-FU	Gastric and Esophagogastric adenocarcinoma
11. UFT	Non small lung carcinoma
12. Doxorubicin	Diffuse malignant pleural mesothelioma

13. Cyclophosphamide and doxorubicin	Salivary gland advanced carcinoma
14. Gemcitabine	Biliary cancer
15. Osthole	Lung cancer
16. Everolimus	Urothelial bladder cancer
17. Fluorouracil, doxorubicin and cyclophosphamide	Salivary gland carcinoma
18. Metformin	Lung adenocarcinoma
19. Oxaliplatin, quercetin and thymoquinone	Ovarian cancer
20. Olaparib	PTEN deficient Lung cancer

1.Cisplatin and Paclitaxel

Paclitaxel is a mitotic agent that binds preferentially to microtubules and the resulting stabilization of microtubules inhibits the reorganization of the microtubule network. Paclitaxel has been demonstrated to be active against previously treated ovarian carcinoma, breast carcinoma, lung carcinoma, and melanoma as well as for head and neck carcinoma.

The combination chemotherapy with paclitaxel, cisplatin and **fluorouracil** is an active and tolerable as first-line and second line therapy in Chinese patients with advanced gastric and esophagogastric junction adenocarcinoma which showed a better tolerance has also been reported.

2. Cisplatin and **Tegafur-uracil (UFT)**

UFT is an oral anticancer agent comprised of tegafur and uracil in a 1:4 fixed molar ratio and is absorbed very well from the small intestine. Combination chemotherapy comprised of oral UFT and cisplatin was shown to be an effective regimen for the treatment of advanced non-small cell lung carcinoma.

3. Cisplatin and Doxorubicin

The combination of **doxorubicin** and cisplatin is effective and well tolerated. It might be considered for palliation of symptomatic patients with diffuse malignant pleural mesothelioma DMPM.

Cyclophosphamide, doxorubicin, and cisplatin combination chemotherapy for advanced carcinomas of salivary gland origin showed encouraging results.

4. Cisplatin and Gemcitabine

As compared with **gemcitabine** alone, cisplatin plus gemcitabine was associated with a significant survival advantage without the addition of substantial toxicity. Cisplatin plus gemcitabine is an appropriate option for the treatment of patients with advanced biliary cancer.

5. Other Possible Drug Combinations

Cisplatin is also used in combination with natural compounds like osthole in lung cancer cell lines, **honey bee venom** in ovarian cancer cells, **anvirzel** in breast, colon, lung, prostate, melanoma and pancreatic cancer cell lines, **bevacizumab** in non-small cell lung cancer-mediated malignant pleural effusion, **vinblastine and bleomycin** in metastatic granulosa cell tumor of the ovary, **methotrexate, bleomycin** and cisplatin for advanced squamous cell carcinoma of the male genital tract.

Everolimus combined with cisplatin has a potential role in treatment of urothelial bladder cancer, **Fluorouracil, doxorubicin, cyclophosphamide**, and cisplatin combination chemotherapy has been used in advanced or recurrent salivary gland carcinoma.

Tetraarsenic oxide and cisplatin induce apoptotic synergism in cervical cancer. Vindesine and cisplatin combination chemotherapy compared with vindesine as a single agent in the management of non-small cell lung cancer seemed to be more effective.

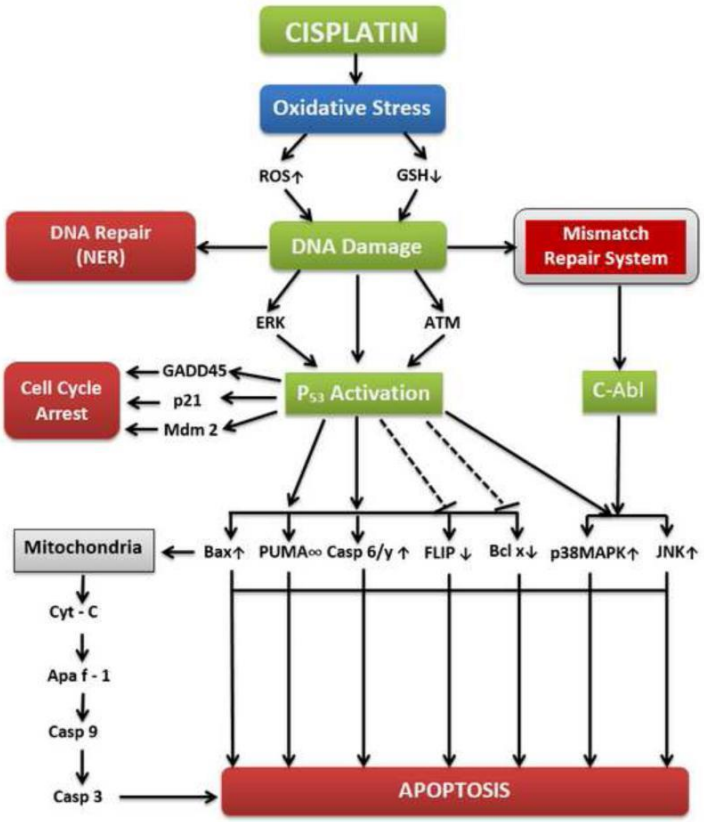
5. Molecular Mechanisms of Cisplatin Pharmacology

Cisplatin becomes activated once it enters the cell. In the cytoplasm the chloride atoms on cisplatin are displaced by water molecules. This hydrolyzed product is a potent electrophile that can react with any nucleophile, including the sulfhydryl groups on proteins and nitrogen donor atoms on nucleic acids.

Cisplatin binds to the N7 reactive center on purine residues and as such can cause deoxyribonucleic acid (DNA) damage in cancer cells, blocking cell division and resulting in apoptotic cell death. The 1,2-intrastrand cross-links of purine bases with cisplatin are the most notable among the changes in DNA. These include the 1,2-intrastrand d(GpG) adducts 1,2-intrastrand d(ApG) adducts representing about 90% and 10% of adducts, respectively.

1,3-intrastrand d(GpXpG) adducts and other adducts such as inter-strand crosslinks and nonfunctional adducts have been reported to contribute to cisplatin's toxicity. Hence, published research from many laboratories has implicated DNA as a critical target for cisplatin cytotoxicity, the most revealing evidence being the hypersensitivity to cisplatin by both prokaryotic and eukaryotic cells deficient in DNA repair.

Several molecular mechanisms leading to apoptosis have been implicated in cisplatin treatment of human cancers.



Overview of molecular mechanisms of cisplatin in cancer treatment.

Cisplatin is one of the most effective anticancer drugs currently in use. Following the finding of its antitumor activity over three decades ago, strong research has been carried out to reveal the details of its cytotoxic activity and to design analogs with reduced side effects. Recently, computational studies have been conducted to complement experimental works. The hydrolysis process of cisplatin which activates the drug was the goal of past research.

Cisplatin–DNA interactions are the next theoretical studies, since DNA is the primary target of the drug. At present, to study the thermodynamics and kinetics of not only cisplatin–DNA complexes, but also of other complexes such as Pt(II)-based cisplatin analogs, other transition metal complexes, and DNA binding organic molecules, both quantum mechanical and molecular mechanical methods are being used. Future research is aiming at elucidating the role of repair enzymes in modulating the cytotoxic activity of DNA binding agents.

6. Toxicological Effects of Cisplatin

Cisplatin interacts with DNA, and forms covalent adduct with purine DNA bases and this platinum compound, interaction is the root cause for cytotoxic effect of cisplatin. Cisplatin treatment has been associated with several toxic side effects including nephrotoxicity, hepatotoxicity and Cardiotoxicity. Many cardiac events have been reported in many case reports including electro-cardiographicchanges,

arrhythmias, myocarditis, cardiomyopathy and congestive heart failure. Decrease in antioxidant defense system is reported due to oxidative stress through the generation of reactive oxygen species, including antioxidant enzymes and non enzymatic molecules, reduced glutathione, are major alterations in the cisplatin toxicity.

1. Hepatotoxicity

High dosage of Cisplatin may lead to hepatotoxicity. Oxidative stress is the main reason for cisplatin-induced toxicity possibly due to depletion of reduced glutathione GSH, also many studies reported that there were a significant elevation in the hepatic malonaldehyde (MDA) and reduction in the level of antioxidant enzymes in rats treated with cisplatin. Elevation of the hepatic enzymes level in serum and bilirubin are the indicators for impaired liver functions. Recent studies have focused on methods for protection of cisplatin-induced Hepatotoxicity using various agents, such as selenium and vitamin E.

2.Cardiotoxicity

Leakage of lactate dehydrogenase (LDH) and creatine kinase (CK) from cardiac myocytes is due to cardiotoxicity could be a secondary event following cisplatin-induced lipid peroxidation of cardiac membranes. Degeneration and necrosis of cardiac muscle fiber cells with fibrous tissue reaction and vacuolated cytoplasm of many muscle cells and blood vessels are inflated with blood are the histological changes of cisplatin induced toxicology

3.Nephrotoxicity

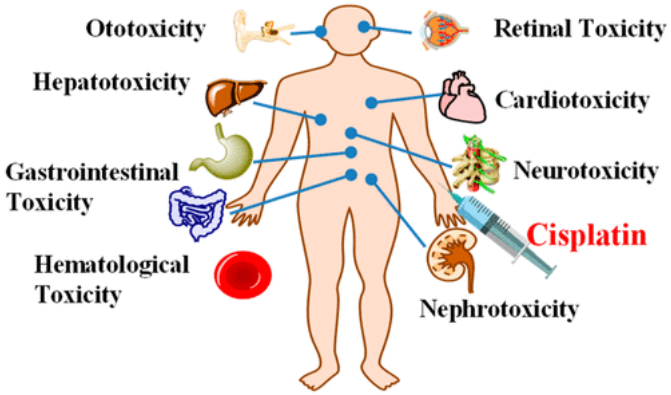
The kidney accumulates cisplatin to a greater degree than other organs and is the major route for its excretion. The cisplatin concentration in proximal tubular epithelial cells is about 5 times the serum concentration. The disproportionate accumulation of cisplatin in kidney tissue contributes to cisplatin-induced nephrotoxicity.

Biosynthesis of amino acid lysine and methionine yields a quaternary ammonium compound called Carnitine, which is required for the transport of fatty acids from the cytosol into the mitochondria during the breakdown of lipids to generate metabolic energy. Kidney damage is caused by the inhibition of Carnitine synthesis and also by the Carnitine reabsorption by the proximal tubule of nephron, which is due to declined production of Carnitine.

Cisplatin is cleared by the kidney by both glomerular filtration and tubular secretion Cisplatin concentrations within the kidney exceed those in blood suggesting an active accumulation of drug by renal parenchymal cells.

4. Other Organ Toxicity

Other cisplatin-induced organ toxicities such as ototoxicity, gastrotoxicity, myelosuppression, allergic reactions and some reproductive toxic effects have also been reported.



7. Concluding Remarks

Cisplatin is one of the most effective anticancer agents widely used in the treatment of solid tumors. It has been extensively used for the cure of different types of neoplasms including head and neck, lung, ovarian, leukemia, breast, brain, kidney and testicular cancers. In general, cisplatin and other platinum-based compounds are considered as cytotoxic drugs which kill cancer cells by damaging DNA, inhibiting DNA synthesis and mitosis, and inducing apoptotic cell death.

Several molecular mechanisms of action including induction of oxidative stress as characterized by reactive oxygen species production and lipid peroxidation, induction of p53 signaling and cell cycle arrest, down-regulation of proto-oncogenes and anti-apoptotic proteins, and activation of both intrinsic and extrinsic pathways of apoptosis. However, cisplatin chemotherapy is also associated with substantial side effects that include hepatotoxic, nephrotoxic, cardiotoxic, neurotoxic and/or hematotoxic damage. Also, some patients may relapse from cisplatin treatment with their cancers being refractory to cisplatin regimen.

Hence, combination therapies of cisplatin with other drugs are common practice in the treatment of human cancers. Findings of several studies have suggested that other compounds combined with cisplatin constitute the best therapeutic approach to overcome drug resistance and reduce the undesirable side effects. Moving forward, combinatorial strategies which target multiple mechanisms, such as reducing cisplatin uptake and reducing inflammation, may offer the best chance for clinically meaningful prevention.

The development of platinum-based anticancer compounds has long been focused on the synthesis and evaluation of complexes. These pursuits have produced carboplatin and oxaliplatin, two widely employed anticancer drugs. The prevalence of inherent and acquired resistance to platinum treatment, however, requires the development of new complexes that operate *via* different mechanisms.

Although initially thought to be ineffective, the recent discovery of phenanthriplatin has revealed that monofunctional compounds can indeed be potent anticancer agents. They distort DNA significantly less than cisplatin, but their efficacy tracks with transcription inhibition, corroborating the fact that DNA is their major target. The spectrum of activity of these compounds is highly differentiated from that of classical platinum complexes, giving rise to the hope that they might form a class of clinically relevant drug candidates.

In a more general sense, these results also validate the exploration of other metal complexes that can only interact with DNA in a monofunctional manner as anticancer drug candidates.

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