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An integrative review of Cisplatin: the first metal anti-tumor drug.

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ABSTRACT

Cisplatin and other platinum derivatives like carboplatin and oxaliplatin are widely used chemotherapeutic agents used in the treatment of solid tumors including head and neck, ovarian and testicular germ cell tumors. Cisplatin is also used successfully in the treatment of paediatric malignancies, such as medulloblastoma and osteogenic sarcoma. In most recent treatment schedules, the drug is used in combination with other cytotoxic agents such as otoposide, doxorubicine, paclitaxel, 5-fluorouracil, gemcitabine, vinblastine, bleomycin and others. It is one of on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in health system. This comprehensive review highlights the physicochemical properties of cisplatin and related platinum based drugs, uses of platinum, either alone or in combination with other drugs for the treatment of various human cancers and also discuss about various Potential protective strategies against cisplatin-induced cytotoxicities. A special attention is given to it's molecular mechanisms of action, historical background, undesirable side effects & future prospective.

Keywords: Cisplatin, cytotoxicity, cis-diamminedichloroplatinum.

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INTRODUCTION

Platinum based drug Cisplatin also called as 'The Penicillin of cancer' is the first potent drug used in the chemotherapy of cancer. Food and Drug Administration (FDA) in 1978, approved cisplatin as leading anti- cancer drug for several types of cancer, such as bladder cancer, ovarian cancer, cervical cancer non-small cell lung cancer, squamous cell carcinoma of the head & neck and testicular cancer.[1] Even with the advancement of new therapies in the past decades, the use of cisplatin remains strong.[2–4] Cisplatin is one of the most remarkable successes in 'the war on cancer.' Although the profound effects of cisplatin in different types of the cancer, the patients experience severe side effects such as vomiting and nausea, myelosuppression, neurotoxicity, ototoxicity and nephrotoxicity that limit its use.[5]

Historical perspective of cisplatin discovery

This compound was first synthesized in 1840 by Peyrone and known for a long time as Peyrone Chloride.[6] However, its antineoplastic activity remained unnoticed for 120 years. The physicist Barnett Rosenberg accidently observed that cisplatin inhibited the proliferation of Escherichia coli cells and provoked filamentous growth of bacterial cells.[7] Since its biological properties were first tested on tumors in 1971. The involvement of inorganic metal based compounds was very limited until the discovery of potent anti-cancer activity in certain platinum compounds by Rosenberg and Van Camp in 1969.[8] The world of clinical oncology was initially not too enthusiastic about the potential usefulness of the first platinum based drug; this was perhaps not surprising as medical scientists tend to regard all heavy metal compounds as non-selective poisons. However, the platinum discovery heralded the arrival of metal co-ordination compounds as a new class of potential antitumor drugs and some researchers such as late Sir Alex Haddow at the Institute of Cancer Research, London, persevered with platinum in the belief that such a new group would emerge from Rosenberg's discovery. After some toxicological problems the first platinum drug, cisplatin, has now become a useful first line treatment for several tumours and has been approved by the U.K. and U.S.A. governments.[9, 10]

Chemistry of Cisplatin

Unlike most cancer therapy drugs, which are usually complex organic compounds, cisplatin is a simple inorganic molecule containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position, see figure-1.[11]

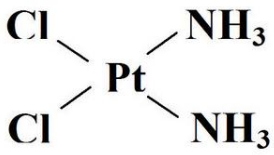

Figure 1: Chemical Structure of Cisplatin.

It is a white powder with the molecular formula $PtCl_2H_6N_2$.[11] it is a metallic (platinum) coordination compound with a square planar geometry that is a white or deep yellow to yellow-orange crystalline powder at room temperature. It is slightly soluble in water and soluble in dimethylprimanide and N, N-dimethylformamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the trans-isomer.[10, 11] It is a small, uncharged platinum complex with two chloride ligands. The compound is rather stable and inert as long as it is in a high chloride environment, such as in the blood stream (150 mM). When entering the cell, where chloride concentrations are as low as 5 mM, the ligands of cisplatin are sequentially exchanged by water molecules forming so-called highly reactive positively charged aqua complexes, which can be either monohydrated [Pt(NH)Cl(OH)] or dihydrated [Pt(NH)(OH)]. Both positively charged hydrated forms of cisplatin are electrostatically attracted by negatively charged macromolecules in the cell, such as DNA, and thereby, facilitating the reaction with nucleophilic centers like the N7 atom of Due to the presence of two potentially reactive sites, cisplatin is a bifunctional drug enabling the formation of covalent crosslinks between two molecules. guanine.[9] Cisplatin has a molecular weight of 301.1 gm/mol, a density of 3.74 g/cm3, a melting point of 270° C, a log Kow of -2.19 and a water solubility of 2.53 g/L at 25° C.[11]

Use of Cisplatin in cancer treatment

cisplatin has become one of the most used drugs in the treatment of solid tumors of epithelial origin. Although cisplatin has been a mainstay for testicular cancer therapy. It is also commonly used to treat ovarian, cervical, bladder, and non-small cell lung carcinoma as well as head and neck cancers. Cisplatin is also successfully used in the treatment of paediatric malignancies, such as medulloblastoma and osteogenic sarcoma.[12] In most recent treatment schedules, the drug is used in combination with other cytotoxic agents such as otoposide, paclitaxel, doxorubicine, 5-fluorouracil, gemcitabine, vinblastine, bleomycin and other.[13-15]

Synthesis & Production of cisplatin

Preparation of cisplatin was reported in the 1840s.[6,10] The synthesis of cisplatin starts from potassium tetrachloroplatinate. The tetraiodide is formed by reaction with an excess of potassium iodide. Reaction with ammonia forms $K_2[PtI_2(NH_3)_2]$ which is isolated as a yellow compound. When silver nitrate in water is added insoluble silver iodide precipitates and $K_2[Pt(OH_2)_2(NH_3)_2]$ remains in solution. Addition of potassium chloride will form the final product which precipitates.[16] See Figure 2,

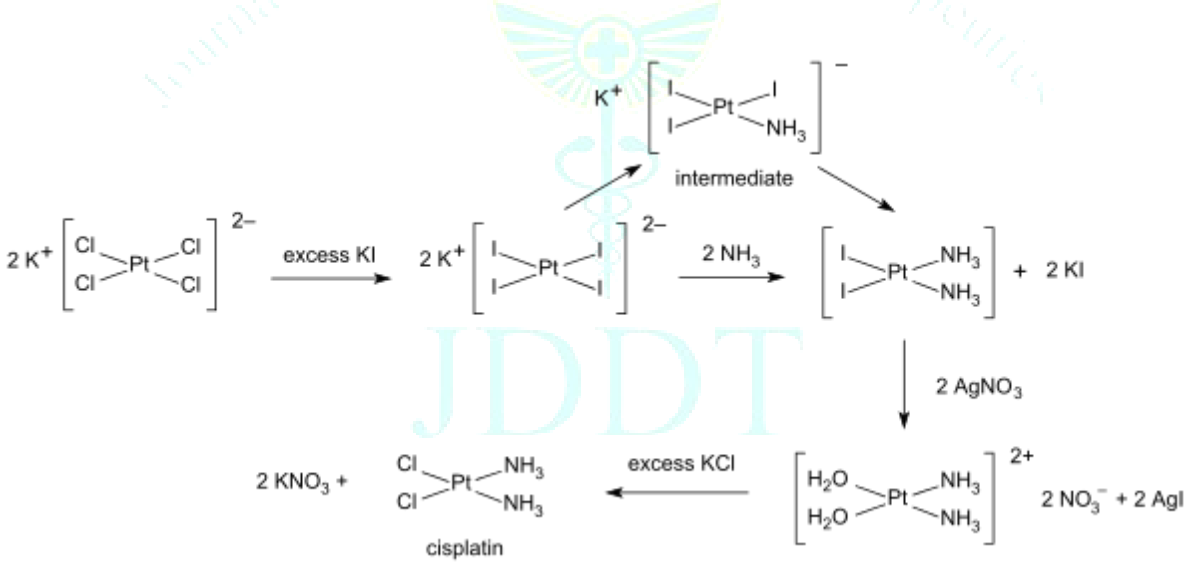

Figure 2: Synthesis of Cisplatin.

In 2009, cisplatin was produced by eleven manufacturers worldwide, including four in India, three in Central and South America, two in Europe, one each in China and Mexico, and none in the United States.[17] It was available from 35 suppliers; including 23 U.S. suppliers and seven drug products with cisplatin as the active ingredient were produced by five pharmaceutical companies.[18, 19]

Mechanisms of cytotoxic action

The exact molecular mechanism of the cytotoxicity induced by cisplatin is still unknown, but it is generally accepted that the primary target for the drug is nuclear DNA. 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.[20, 21] There are several reports on the interaction of cisplatin with RNA, proteins involved in antioxidant systems, cell signalling, cell metabolism and mitochondrial DNA. Those reactions may induce apoptosis, necrosis or autophagy, as cell death pathways.[22-24]

Factors limiting the therapeutic efficacy of cisplatin

In spite of the clinical success of cisplatin, repetitive treatment often has to be discontinued at a certain stage. The two limiting factors for a successful application of cisplatin are acquired or intrinsic drug resistance of the tumor and severe side effects in normal tissues, mainly in the kidney, in the inner ear and in the peripheral nerves.[25, 26]

Cisplatin resistance

The molecular mechanism of cisplatin resistance has been studied extensively, which may involve decreased uptake or increased efflux of cisplatin, neutralization of cisplatin by glutathione and other sulfur-containing molecules, increased DNA repair, and defective apoptotic signaling in response to DNA damage.[27, 28]

Cisplatin side effects

Cisplatin treatment has been associated with several toxic side effects including nephrotoxicity, hepatotoxicity and Cardiotoxicity.[29, 30] Many cardiac events have been reported in many case reports including electro-cardiographicchanges, arrhythmias, myocarditis, cardiomyopathy and congestive heart failure.[31] 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.[32]

Nephrotoxicity

Nephrotoxicity (kidney damage) is a major concern. Nephrotoxicity is a dose-limiting side effect.[33] Cisplatin causes tubular cell death by either necrosis or apoptosis depending upon the concentration and duration of exposure of drug.[34] The dose is reduced when the patient's creatinine clearance (a measure of renal function) is reduced. Adequate hydration and diuresis is used to prevent renal damage. The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species and in animal models can be ameliorated by free radical scavenging agents (e.g., amifostine). Recent literature indicates that reactive oxygen species (ROS) play important roles in the progression of kidney damage.[35, 36] Oxidative stress caused by alterations in redox homeostasis can directly exert renal parenchymal damage and may intensify renal microvascular and functional dysregulation.[37] Then, increased oxidative stress in the kidney leads to deterioration of the renal function, inflammation, and apoptosis.[38]

Neurotoxicity (nerve damage)

Despite favorable anti-tumor properties, platinum drugs can cause serious neurotoxicity. Common neurological side effects of cisplatin include visual perception and hearing disorder, which can occur soon after treatment begins. While triggering apoptosis through interfering with DNA replication remains the primary mechanism of cisplatin, this has not been found to contribute to neurological side effects.[39, 40] Recent studies have shown that cisplatin noncompetitively inhibits an archetypal, membrane-bound mechanosensitive sodium-hydrogen ion transporter known as NHE-1. It is primarily found on cells of the peripheral nervous system, which are aggregated in large numbers near the ocular and aural stimuli-receiving centers. This noncompetitive interaction has been linked to hydroelectrolytic imbalances and cytoskeleton alterations, both of which have been confirmed in vitro and in vivo.[41]

GIT toxicity

Nausea, vomiting and anorexia are common side effect of cisplatin treatment. An antiemetic regimen is normally incorporated. Treatment has been improved by the addition of 5-HT-3 receptor antagonists, which now constitute a basis of every antiemetic regime together with steroids.[42] Changes in diet such as eating several small meals or limiting activity may help lessen some of these effects.

Ototoxicity (hearing loss)

Ototoxicity is one dose limiting side effect of cisplatin. there is at present no effective treatment to prevent this side effect, which may be severe. Audiometric analysis may be necessary to assess the severity of ototoxicity. Other drugs (such as the aminoglycoside antibiotic class) may also cause ototoxicity, and the administration of this class of antibiotics in patients receiving cisplatin is generally avoided. The ototoxicity of both the aminoglycosides and cisplatin may be related to their ability to bind to melanin in the stria vascularis of the inner ear or the generation of reactive oxygen species.[43]

Electrolyte disturbance

Cisplatin can cause hypomagnesaemia, hypokalaemia and hypocalcaemia. The hypocalcaemia seems to occur in those with low serum magnesium secondary to cisplatin, so it is not primarily due to the cisplatin.[41]

Hemolytic anemia

Anaemia can be developed after several courses of cisplatin. It is suggested that an antibody reacting with a cisplatin-red-cell membrane is responsible for hemolysis.[44, 45]

Other Organ Toxicity

Other cisplatin-induced organ toxicities such as myelosuppression, allergic reactions and some reproductive toxic effects have also been reported.[46]

Potential protective strategies against cisplatin-induced cytotoxicities

For years, various approaches have been attempted to curtail cisplatin side effects. Several pharmacological compounds are currently being tested to enhance protection during cisplatin treatment. One strategy is to synthesize and screen for novel cisplatin analogues that have lower toxicity in normal tissues. In this direction, several cisplatin analogues, such as carboplatin and oxaliplatin, have been identified with less severe side effects.[47] Unfortunately, both of them have severe and dose-limiting side effects as well. Carboplatin and especially oxaliplatin have prominent neurotoxic effects, but do not induce considerable ototoxicity or nephrotoxicity.[48] In contrast to oxaliplatin, carboplatin additionally displays prominent toxicity in the hematopoietic system. The mechanisms of the noted differences in side effects are still not fully understood. Another approach that has been used with some success is to hydrate the patients during cisplatin treatment.[49, 50] OCT2 inhibitors such as cimetidine have been shown to protect against cisplatin induced renal toxicity in mice without interfering with the antineoplastic actions of cisplatin.[51, 52] More recently, Kim HJ, et al. (2015),[53] reported that administration of glutamine, a substrate for glutathione synthesis, reduced cisplatin associated pathological changes in HK-2 cells and in rats via reduced expression of OCT2. Whereas these findings are promising, one possible drawback of pharmacological inhibition of OCT2 may be inhibition of cisplatin uptake by cancer cells, which are the target of cisplatin treatment, and hence, this may reduce the antineoplastic action of cisplatin. El Awady et al (2011),[54] investigated that administration of silymarin, a potent

antioxidant, in a rat model of cisplatin-induced cardiac toxicity, antagonized the depletion of glutathione and superoxide dismutase and consequently reduced the concentration of cardiac damage marker enzymes induced by cisplatin, towards normal level, resulting in cardiac protection. Also, treatment with the hydrogen sulfide (H2S) donor sodium hydrosulfide (NaHS) and garlic-derived diallyl disulfide (a natural source of H2S) has been reported to enhance the activity of renal antioxidant enzymes and reduced oxidative stress thereby attenuating cisplatin-induced renal toxicity in rats.[55, 56] Furthermore, combination treatment of tumor-bearing mice and rats with vitamin C and cisplatin significantly increased endogenous antioxidant levels, decreased tissue lipid peroxidation and well protected the kidney, liver and testes against cisplatin-induced toxicity compared to cisplatin treatment alone.[57] NaHS administration activated endogenous antioxidant defense system and protected proximal tubular cells from apoptosis in a rat model of cisplatin-induced renal toxicity.[58] Recently, H2S related therapy has been proven successful in treating other forms of cellular stress due to myocardial ischemia-reperfusion injury and acute kidney injury.[59, 60] Moreover, Strutynska NA, et al. (2013),[61] observed that H2S treatment prevented opening of the MPTPs in a rat model of spontaneous hypertension, suggesting its application in cisplatin-induced toxicity. Other protective pharmacological agents that may not interfere with the anticancer action of cisplatin could be used if they are tested and proven to ameliorate cisplatin-induced toxicity. Despite these efforts, the side effects of cisplatin, particularly nephrotoxicity, remain a major factor that limits the use and efficacy of cisplatin in cancer therapy.

Future perspectives

Over the last several decades, many researchers, have been developing new formulations of cisplatin in an effort to reduce its side effects. The best way to do this is through the use of nanoparticles to better target cisplatin to cancer cells. Better targeting cancer drugs are important so they don't attack non-cancerous tissue. One such nanoparticle formulation being commercially developed is Lipoplatin. This formulation encloses cisplatin in a shell called a liposome, which is similar in structure to the walls of human cells. As a result, it floats in the bloodstream for longer and gets trapped selectively in tumours but not normal tissue. And it doesn't stop there. Novel nanoparticle formulations of cisplatin using exotic materials are also being developed, although these are much further away from being ready for human testing. To date, cisplatin has been attached to carbon nanotubes, gold nanoparticles and even spaghetti ball-like polymers called dendrimers.

CONCLUSIONS

Cisplatin is currently one of the most widely-used chemotherapeutic agents against various malignancies. This drug has revolutionised the treatment of many types of cancer, especially testicular, and remains as critically important now as when it was first discovered. Its clinical application is limited, however, by inherent renal and cardiac toxicities and other side effects, of which the underlying mechanisms are only partly understood. Therefore, combinatorial strategies such as cisplatin plus H2S-related therapy or cisplatin with taurine, which target ROS generation, inflammatory and apoptotic pathways in cisplatin-induced toxicity may offer the best chance of clinically meaningful prevention. However, there are very few clinical trials reporting on combinatorial therapies to prevent these side effects, and hence require additional research. More importantly, there is the need to test pharmacological (and genetic) approaches to cytoprotection in experimental or natural tumor-bearing animals to enhance their application to cisplatin treatment in oncology. Identification of novel interventions aimed at minimizing cisplatin-induced cytotoxicities while enhancing its antineoplastic efficacy would open new avenues to enhance cisplatin-based cancer therapy.

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None

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