An Updated Insight about Toxicological Effects of Cisplatin

Nehal Mohammed Mohammed Omar, Ibrahim Amin Maher, Adel Mohammed Salah El Din, Marwa Tharwat Abdel Fattah

Human Anatomy and Embryology Department, Faculty of Medicine - Zagazig University, Egypt **Corresponding author:** Nehal Mohammed Mohammed Omar
E-mail: drnehalomar29@gmail.com, NMMohammed@meicine.zu.edu.eg
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Abstract

One well-known chemotherapy medication is cisplatin, also known as cisplatinum or cis-diamminedichloroplatinum (II). Cancers of the bladder, head and neck, lungs, ovaries, and testicles are among those that have benefited from its usage. Cancers such as lymphomas, sarcomas, germ cell tumors, and carcinomas can all be effectively treated with it. Scientists believe it triggers cell death in cancer cells by interfering with DNA repair systems, damaging DNA, and its capacity to crosslink with DNA's purine bases. Nevertheless, alternative anti-cancer medications containing platinum, such as carboplatin and oxaliplatin, have been utilized due to drug resistance and a plethora of unwanted side effects, including severe kidney problems, allergic reactions, decreased immunity to infections, gastrointestinal disorders, hemorrhage, and hearing loss, particularly in younger patients. Additionally, cisplatin-based combination therapy with other medications have been extensively researched for the purpose of reducing toxicity and overcoming drug resistance. The physicochemical features of cisplatin and related platinum-based medications are highlighted in this detailed overview, which also examines its usefulness in the treatment of various human cancers, either alone or in combination with other drugs. Its molecular mechanisms of action and its unpleasant side effects are given specific consideration.

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Introduction

Cisplatin; cisplatinum, also called cis-diamminedichloroplatinum(II), 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 dimethylprimanide and N,N-dimethylformamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the trans-isomer [1,2]. 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 [3].

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 [4] 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-dichlorodiammineplatinum (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 has been especially interesting since it 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 [5]. This has led to interest in platinum (II) - and other metal-containing compounds as potential anticancer drugs [6].

Cisplatin is clinically proven to combat different types of cancers including sarcomas, cancers of soft tissue, bones, muscles, and blood vessels. Although such cancers have recently received better prognosis and therefore have become less life threatening [7], significant challenges remain with regard to their cure. Also, because of drug resistance and considerable side effects, combination therapy of cisplatin with other cancer drugs have been applied as novel therapeutic strategies for many human cancers. In this research, we aim 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.

. Lung cancer remains one of the most common types of fatal malignancies [8]. Small cell lung cancers (SCLCs) represent 15% of all lung cancers [9]. At present, platinum based treatments are key drugs for SCLC [10]. Cisplatin and carboplatin are two of the most common types of platinum based treatments used in SCLC chemotherapy [11]. In clinical trials, cisplatin is often selected due to its strong antitumor activity, but its adverse effects include renal toxicity [12], nausea and vomiting [13]. 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.

The standard of care for localized non-small-cell lung cancer (NSCLC) is surgery followed by, in case of stage II and III disease, adjuvant cisplatin-based chemotherapy. The Lung Adjuvant Cisplatin Evaluation program, a pooled analysis of the five largest trials, recently showed an absolute 5-year survival benefit of 5.3%with adjuvant chemotherapy as well as the NSCLC meta-analysis [14].

CD133, a surface glycoprotein linked to organ-specific stem cells, has been described as a marker of cancer-initiating cells in different tumor types. It has also been reported that a CD133+, epithelial-specific antigen-positive (CD133+ESA+) population is increased in primary non-small cell lung cancer (NSCLC) compared with normal lung tissue [15].

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 [16]. 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 [17]. 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. For example Cisplatin is used along with honey venom [18], withaferin [19], trichostatin A or 5-aza-2′-deoxycytidine [20], overcoming chemotherapy resistance of ovarian cancer cells by liposomal Cisplatin [21]

Head and neck squamous cell carcinoma (HNSCC) is a common malignant disease with more than 600,000 new cases registered worldwide every year [22]. 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 [23,24].

Cisplatin-Induced Oxidative Stress

Under normal physiological conditions, cells control reactive oxygen species levels by balancing the generation of reactive oxygen species with their elimination by scavenging system (reduced glutathione-GSH, superoxide dismutase-SOD, and catalase-CAT). But under oxidative stress conditions, excessive reactive oxygen species can damage cellular proteins, lipids and DNA, leading to fatal lesions in cells that contribute to carcinogenesis. Cancer cells exhibit greater reactive oxygen species stress than normal cells do, partly due to oncogenic stimulation, increased metabolic activity and mitochondrial malfunction. Oxidative stress is the one of most important mechanisms involved in cisplatin toxicity. The mitochondrion is the primary target for cisplatin induced oxidative stress, resulting in loss of mitochondrial protein sulfhydrl group, calcium uptake inhibition and reduction of mitochondrial membrane potential [25]

Exposure to oxidative stress can upset regular biological functions. Cisplatin also induces reactive oxygen species that trigger cell death besides DNA damage. Cell death occurs upon immediate activation of numerous signaling pathways, whereas the definite pathways depend on the (cancer) cell. The formation of reactive oxygen species depends on the concentration of cis-

diamminedichloro platinum(II) and the length of exposure [26]. The intracellular redox homeostasis is maintained by the thiol group (-SH) containing molecules. Under certain conditions a thiol group may lead to formation of thiyl radicals that in turn can interact with molecular oxygen, therefore generating reactive oxygen species [27].

Excessive reactive oxygen species can induce apoptosis through both the extrinsic and intrinsic pathways [28]. In the extrinsic pathway of apoptosis, reactive oxygen species are generated by Fas ligand as an upstream event for Fas activation via phosphorylation, which is necessary for subsequent recruitment of Fas-associated protein with death domain and caspase 8 as well as apoptosis induction [29]. In the intrinsic pathway, reactive oxygen species function to facilitate cytochrome c release by activating pore-stabilizing proteins (Bcl-2 and Bcl-xL) as well as inhibiting pore-destabilizing proteins (Bcl-2-associated X protein, Bcl-2 homologous antagonist/killer) [30]. An even higher reactive oxygen species level can result in both apoptosis and necrosis in cancer cells [31]. Reactive oxygen species can also induce cell death through autophagy, which is a self-catabolic process involving sequestration of cytoplasmic contents (exhausted organelles and protein aggregates), for degradation in lyposomes [32]

Cisplatin-Induced Cell Apoptosis

Apoptosis is a controlled type of cell death which is energy-dependent leading to cell shrinkage, chromatin condensation, membrane budding, phosphatidylserine externalization, and activation of a family of cysteine proteases called caspases [33,34]. Caspase activation is the key step in the beginning of apoptosis, and several stimuli activate caspases, including those that activate plasma membrane death receptors (caspase 8) and cause mitochondrial dysfunction (caspase 9). Caspases are either initiators or executioners of apoptosis. Initiator caspases include caspases 8 and 9, and activation of these caspases results in activation of downstream or executioner caspases such as caspases 3 and 7 [35]. Executioner caspases are accountable for many of the biochemical characteristics of apoptosis, including cleavage and activation of poly (ADP-ribose) polymerase and of the inhibitor of caspase activator domain protein, which leads to DNA fragmentation.

Cisplatin primarily induces cell death by apoptosis and a defect in apoptotic signaling could also confer cisplatin resistance. There are two major pathways of apoptotic cell death [36,37]. The extrinsic pathway is initiated when ligands bind to the tumor necrosis factor-α (TNFα) receptor super family followed by oligomerization and recruitment of procaspase-8 via adaptor molecules to form the death-inducing signaling complex (DISC). The intrinsic pathway is initiated by cellular stress, such as DNA damage, resulting in release of cytochrome-c from the mitochondria causing activation of procaspase-9 through the interaction with apoptosis promoting activating factor-1 (APAF-1) and formation of an active apoptosome complex. Bcl-2 family proteins regulate DNA damage-induced apoptosis by regulating the release of mitochondrial cytochrome c in response to DNA damage. Cisplatin-induced genotoxic stress activates multiple signal transduction pathways, which can contribute to apoptosis or chemo resistance.

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 [38]. Cisplatin treatment has been associated with several toxic side effects including nephrotoxicity [39], hepatotoxicity and Cardiotoxicity [40]. Many cardiac events have been reported in many case reports including electro-cardiographic changes, arrhythmias, myocarditis, cardiomyopathy and congestive heart failure [38]. 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 [41].

Hepatotoxicity

High dosage of Cisplatin may lead to hepatotoxicity [42].Oxidative stress is the main reason for cisplatin-induced toxicity possibly due to depletion of reduced glutathione GSH [43], 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 [43,44,45]. The most sensitive biomarkers directly concerned in causing the cellular damage and toxicity are transaminases, because they are cytoplasmic in location and are released into the circulation after cellular damage. Elevation of the hepatic enzymes level in serum and bilirubin are the indicators for impaired liver functions [46]. Cisplatin hepatotoxicity was shown to be exacerbated by increased expression of cytochrome P450-2E1 enzyme [47]. Observed histopathological changes will be necrosis and degeneration of hepatocytes with inflammatory cells infiltration around portal area with sinusoidal dilatation [41,48]. Recent studies have focused on methods for protection of cisplatin-induced Hepatotoxicity using various agents, such as selenium [49] and vitamin E [50,51].

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 [40]

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 [52]. The disproportionate accumulation of cisplatin in kidney tissue contributes to cisplatin-induced nephrotoxicity [53].

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 [54,55]. Cisplatin concentrations within the kidney exceed those in blood suggesting an active accumulation of drug by renal parenchymal cells. Studies in recent years have identified two different membrane transporters capable of transporting cisplatin into cells: Ctr1 and OCT2 [55]. Later, cisplatin is biotransformed in the kidney into cysteinyl glycine conjugates and other high thiols by some localized enzymes.

Other Organ Toxicity

Other cisplatin-induced organ toxicities such as ototoxicity, gastrotoxicity, myelosuppression, allergic reactions and some reproductive toxic effects have also been reported [56,57].

No Conflict of interest.

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