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Review on Pharmacology of Cisplatin: Clinical Use, Toxicity and Mechanism of Resistance of Cisplatin

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Cisplatin is a chemotherapeutic drug that has been used in the treatment of various types of human cancers such as ovarian, lung, head and neck, testicular and bladder. Cisplatin has demonstrated efficacy against various types of cancers such as germ cell tumors, sarcomas, carcinomas as well as lymphomas. The current study presents a pharmacological review on the drug including its mechanism of action, resistance mechanism, and toxicity as well as its clinical applications. The mechanism of action of cisplatin has been associated with ability to crosslink with the urine bases on the DNA to form DNA adducts, preventing repair of the DNA leading to DNA damage and subsequently induces apoptosis within cancer cells. However, the drug exhibits certain level of resistance including increased repair of the damaged DNA, reduction in the accumulation of the drug intracellular and cytosolic inactivation of cisplatin. The drug is also characterized by various toxic side effects including nausea, nephrotoxicity, Cardiotoxicity, hepatotoxicity and neurotoxicity. Due various side effects as well as drug resistance, other anti-cancer drugs that contain platinum such as carboplatin and oxaliplatin among others have been used in combination with cisplatin in chemotherapeutic treatment of cancer. Strong evidence from research has demonstrated higher efficacy of combination of chemotherapies of cisplatin together with other drugs in overcoming drug resistance and in reducing toxic effects as well. Future studies that explore combinational techniques that target various mechanisms such as reduction in the uptake of cisplatin as well as inflammation could enhance efficacy of cisplatin.

Keywords: Cardiotoxicity, Chemotherapy, Nephrotoxicity, Hepatotoxicity and cisplatin.

Cisplatin is a chemotherapy medication used to treat patients with bladder, ovarian, head and neck, lung, testicular, cervical, esophageal, breast and brain cancers often given as an injection. Cisplatin, referred to by chemical name as cis-diamminedichloroplatinum (II), is anticancer, neutral and DNA destroying agent that is square planar platinum (II) complex and contains 2 ligands of chloride in a cis configuration orientation [1]. Cisplatin has been cited as being among the most used cytotoxic anticancer medication due to its broader efficacy in the treatment of various types of cancers[1; 2].The mode of administration of cisplatin is intravenous as a short term infusion with normal saline for the treatment of solid malignancies. Cancer refers to the abnormal cell division with potential to invade adjacent cells. Genotypic expression of some important properties in the cell is obligatory for Carcinogenesis[3].Cancer also refers to the malignant neoplasm which occurs when the cellular proliferation in the normal body tissues is no longer under normal control[4]. Evidence from past studies have singled out testicular cancer as the type of cancer that cisplatin is most effective

at treating. One important property of cisplatin is that it is not stable in Dimethyl Sulfoxide (DMSO) thus researchers and medical practitioners have to pay careful attention on how long it remains in the solvent. DMSO is a colorless solvent that dissolves nonpolar and polar compounds.

The administration of cisplatin among cancer patients is highly controlled due to the fact that it is associated with various side effects. High doses of cisplatin is linked to nephrotoxicity, hence practitioners are advised to reduce doses when a patient renal function is reduced. It is therefore important to note that nephrotoxicity is a dose limiting side effect[1]. Evidence from nerve conduction studies done before and after cisplatin treatment also reveals that there are neurological effects such as impaired hearing and perception in some patients. Other side effects such as nausea as well as vomiting are mostly prevented by prophylactic antiemetic together with corticosteroids. The severity of the side effects differs from one patient to the other and practitioners and researchers are encouraged to be careful when administering the drug. Recent studies have suggested that combination of cisplatin therapies with other drugs are effective in not only overcoming drug resistant, but also in reducing toxicity [3].

Significance Statement

Cisplatin helps in the treatment of various types of cancers in the body like such as ovarian, lung, head and neck, testicular and bladder[5]. Cisplatin is efficient in use against various types of cancers such as germ cell tumors, sarcomas, carcinomas as well as lymphomas. The principle of action of Cisplatin in combating cancer involves exerting its cytotoxicity upon cancer cells through the formation of DNA adducts that include mono-, inter, and intrastrand cisplatin DNA cross-links that arrest the cell cycle at S, G1 or G2-M thus induces apoptosis.

This review will focus on cisplatin, one of the most commonly used chemotherapeutic drugs to date. Its primary action is by the interaction with DNA in order to for DNA adducts. Inducing the cell apoptosis to discuss its side effects and the possible mechanisms for its resistance.

Mechanism of Action

The mechanism of action of cisplatin is mediated by the interaction of cisplatin with DNA in order to for DNA adducts. The principle of action involves exerting its cytotoxicity upon cancer cells through the formation of DNA adducts that include mono-, inter, and intrastrand cisplatin DNA cross-links that arrest the cell cycle at S, G1 or G2-M thus induces apoptosis[3]. This is because cisplatin results into the arrest of cells at G2, S or G1-phases of the cell cycle in an effort to repair the damage. The primary DNA adducts is the intrastrand crosslink adducts responsible for activation of apoptosis. This results into failure of the failure of the adequate repair resulting into aberrant mitosis of the cells followed by apoptosis. Siddik defines apoptosis as a series of death of cancer cells that is programed by the formation of DNA adducts[6]. The resulting impairment of replication of the cancer cells DNA is responsible for the death of fastest proliferating cells which are carcinogenic[5]. Apoptosis therefore involve various pathways that converge on a single nonreversible phase in which nucleases and proteases digest the doomed cell.

Evidences from previous studies on apoptosis have singled out many factors within the cell that determines the survival of the cell. As stated by Hu *et al*, these factors are Bcl-2 family of proteins, p53-tumor suppressor and intracellular signal-transduction pathways that are often facilitated by protein kinases and phosphatidylinositol 3-kinase [1; 2; 6]It is therefore important to note that the understanding of the mechanism that drives the regulation of cell cycle and apoptosis gives new insights that can be targeted with the objective of enhancing the therapeutic activity of cisplatin. As outlined in the mechanism above, cisplatin mechanism of actions can be improved by preventing arrest of the cell cycle or through inhibition of protein kinase. According to Galluzzi *et al*, when the drug is administered, immediate displacement of one or two chloride atoms occurs; this gives an aqua-complex known as aquation[5; 7]. The condition within the cell encourages the dissociation of chloride because the lower intracellular concentration of chloride [7].The hydrolyzed product is an important electrophile that can react with nucleophile such as sulfhydryl groups on proteins and nitrogen donor atoms on the nucleic acids. The binding of cisplatin to the N7 reactive center on residues of purine results into destruction of the deoxyribonucleic acid (DNA) in cancer cells [8]. This process is very

important in cell division because DNA play a key role in transcription and replication. Since DNA is damaged, there is subsequent blockage of cell division which finally results into apoptotic cell death[8]. According to Elise *et al*, evidence has shown that the most notable changes to the DNA that results into its death as a result of cisplatin administration is 1, 2-intrastrand cross-link purine bases. This represent approximately 90% of DNA adducts[8]. However as stated by Yoshikawa *et al* other adducts such as inter-strand, 1, 3-intrastrand adducts and other nonfunctional adducts have been closely linked to toxicity of the drug[8].

However, current research on the mechanism connecting destruction of the DNA and pathway leading to death of the cell is not very clear[9]. As stated by Torres, apoptosis is a critical process in the maintenance of the physiological processes with regard to response to stimuli. At the molecular levels, apoptosis is accomplished through caspases activation[9]. Caspases refers to a group of intracellular cysteine proteases that cleave substrates at aspartic acid residues[1; 10]. Once caspases have been activated, they target and invade both the nuclear and the cytoplasmic factors that are responsible for the maintenance of architecture of the cell and participate in the repair of the DNA, replication and transcription. This process is also enhanced by the fact that regulation of apoptotic pathways is enhanced in the presence of anti-apoptotic as well as apoptotic proteins. However, as Bagnobianchi states, certain cancer cells often don't respond to treatment by cisplatin in varying degrees[10]. This is partly attributed to failure of cell death resulting from apoptosis and caspases pathways failure. Certain compounds referred to as inhibitor of apoptosis proteins (IAPs) is a group of intracellular apoptosis proteins that are responsible for blocking cell death through inhibition of caspases activation downstream [10]. Generally, IPAs are the key obstacles of cancer medications such as cisplatin because they protect cancer cells from different extrinsic and intrinsic pathways that are triggered by cisplatin medication [11].

Mechanism of Resistance and Studies

The main goal of cancer treatment through administration of chemotherapy is to commit tumor cells to apoptosis due to exposure to antitumor agents[12; 13]. While cisplatin is recognized for its efficacy in treatment of a broader range of cancer types, evidence from research show that many patients with these cancers eventually relapse and become resistant to chemotherapy [14] Although apoptosis is highly induced by the inorganic drug cisplatin Koberle *et al* there is development of resistance when there is failure of tumor cells to undergo apoptosis at the right clinical concentrations of the drug[15]. Other researchers have also indicated that cisplatin has low effectiveness against certain common types of cancers such as pancreatic, colorectal as well as advanced hormone refractory prostate cancers[15]. In this respect, the presence or acquisition of resistance to cisplatin presents a serious barrier to successful therapy thus significantly reduces the curative efficacy of cisplatin. Difficulty and complexity of the chemotherapy is severely increased by cross-resistance of cisplatin-resistant cancer cells [16]Resistance can therefore be acquired through chronic drugs exposure or can be present just as an intrinsic phenomenon.

The level of resistance exhibited as a result of cisplatin is not easy to define; however, clinical studies have inferred at least twofold resistance. There are various mechanisms that are involved in the cisplatin resistance. The first is the reduction in the accumulation of the drug intracellular[17]. Reduced accumulation of drug is a significant mechanism that results into resistance and reductions in accumulation of drugs by a factor of between 20% to70% could cause resistance of cisplatin by a factor of 3 to 40 fold respectively[18]. However asKoberle *et al* states, reduction in the accumulation of drug is not directly proportional to the level of resistance[19]. Moreover Nikounezhad *et al* acknowledges that the profile of resistance mechanism of a specific tumor cell may not include defects in accumulation of drugs [19]. This varies from one patient to another and in certain cancer cells; reduced cisplatin accumulation is a major contributing factor to resistance contributing to over 70-90% of the total resistance

The other mechanism that could perpetuate resistance of the cisplatin to tumor cells is the increased repair of the damaged DNA[19]. In the previous section, we outlined the importance of the formation and persistence of DNA adducts as an essential inducing mechanisms for apoptosis that is responsible for cell death. It therefore follows

that an increased repair of the DNA adducts will attenuate the apoptotic process. Evidence from past studies have supported this mechanism of resistance as outlined in a study by Amable who reported that increased rate of repair is linked to the inhibition of drug induced cytotoxicity in several tumor cells[20]. Nucleotide Excision Repair (NER) is considered the main pathway for platinum adduct removal as well as repair of the DNA. The importance of NER is evident by the research findings showing that cellular defect causes cisplatin hypersensitivity and hence when NER integrity is restored there is reestablishment of sensitivity to normal levels[20]. This implies that when repair of DNA adducts is enhanced, this causes higher resistance and hence difficulty in management through platinum analogue process of drugs development.

Finally, the third resistance mechanism of cisplatin is the cytosolic inactivation of cisplatin. The inactivation o of cisplatin affects its efficacy since it impairs its ability to react with the DNA[8; 21]. The effects is that less production of DNA adducts is achieved and hence there is less damage to the DNA leading to increased survival of the cancer cells. The major form or primary form of cisplatin inactivation is the conjugation of cisplatin with glutathione leading to cellular export by MRP transporters[22]. Higher inactivation results from thiol-containing molecules. For instance, glutathione-S-transferases (GSTs) catalyze the conjugation of glutathione (GSH) to cisplatin. The drug is therefore inactivated by the formation of platinum-glutathione conjugates since cisplatin solubility is increased[19]. This results into higher rate of excretion of the drug from the cells. As stated by Brozovic *et al* intracellular, glutathione play the role of antioxidant thus maintains the redox environment by keeping reduced sulfhydryl groups[23]. This process results into the depletion of GSH within the cells that are resistant to cisplatin thus increases toxicity of cisplatin. In a study that examined ovarian cancer cells, increased levels of GSH was evident among the platinum resistant cells lines. Another mechanism of cisplatin activation includes metallothionein binding proteins[23].

Toxicity of Cisplatin

We outlined in the previous sections the interaction between cisplatin and the DNA to form covalent adduct with purine DNA base. While this interaction is the foundation for efficacy of cisplatin in the treatment of cancer, these platinum compounds, interaction is the rout cause for cytotoxic effect of cisplatin[24]. Cisplatin treatment has been linked to various toxic side effects including nausea, nephrotoxicity, Cardiotoxicity, hepatotoxicity and neurotoxicity[3]. Many toxic events have been reported in various studies that include arrhythmias, congestive heart failure, electro-cardiographicchanges as well as myocarditis. The generation of reactive oxygen species is very important cause of oxidative stress which eventually results into the reduction in the antioxidant capacity and defense system[3; 25]. Other changes that take place include generation of non-enzymatic molecules and antioxidant enzymes, reduction of glutathione and play an important role in causing major alterations in the cisplatin toxicity. Toxicological effects of cisplatin are diverse and have been an area of concern for many oncologists, practitioners and researchers.

Nausea and Vomiting are considered as the most common types of cisplatin toxicity during chemotherapy. One study that examined toxicity of cisplatin after a 120mg/m2 dose found that those patients who did not receive antiemetic medication prior to cisplatin medication developed an average of 11 emetic episodes [26] . Due to the increased episodes of emesis, scientists have developed 5-hydroxytryptamine (5-HT3) receptor antagonists. Evidence from studies has also shown that these agents have played a major role in reducing nausea and vomiting side effects of cisplatin medication[27]. Tests on the effectiveness of 5-HT3 indicated that it plays an important role in delayed nausea and vomiting and reduces across multiple days and most often after repeat chemotherapy cycles. Other studies have also cited less management of nausea compared to the control of emesis while incomplete control of nausea persist in approximately fifty percent of the patients. Evidences from study of 1,900 patients undergoing therapy show that there is higher risk of vomiting and nausea with cisplatin treatment compared to carboplatin therapy[19; 28].

Nephrotoxicity is another major toxicity caused by cisplatin treatment. Kidney plays an important role as the main route of cisplatin excretion. Evidence from past studies has suggested that kidney has tendency of accumulating cisplatin to higher levels compared to any other organ in

the body including the liver[19; 29]. The accumulation and concentration of cisplatin within the proximal tubular epithelial cells is approximately five times that of the serum concentration. Cisplatin induced nephrotoxicity is a result of disproportionate retention of cisplatin within the tissues of the kidney. Another mechanism of nephrotoxicity is linked to the inhibition of Carnitine production coupled by increased reabsorption by proximal tubule of nephron[30]. Carnitine, a compound that is essential for the transport of fatty acids from cytosol into the mitochondria during energy metabolism is produced through biosynthesis processes involving lysine and methionine. The processes of removal of cisplatin from the kidney include both tubular secretion as well as glomerular filtration. However, when concentration of cisplatin within the blood is lower than those in the kidney, it is an indication of toxicity. Evidence from recent studies has identified two main membrane transporters namely: OCT2 and Ctrl1 to be transporting cisplatin into cells[31]. Once in the kidney, cisplatin undergoes biotransformation to cysteinyl glycine conjugates and other higher thiols that is believed to cause toxicity.

It is also believed that the mechanism of cisplatin-induced nephrotoxicity is the same as the tumor cytotoxicity. Both mechanisms involve the formation of highly reactive equated platinum species that cross-link DNA and is highly dependent on the availability and the concentration of ambient chloride concentrations[28]. Early clinical trials showed nephrotoxicity to be dose limiting for cisplatin since impacts observed were reversible azotemia to irreversible kidney failure that required dialysis. Evidences from previous studies have shown that proximal tubular damages at an early stage of toxicity results into reduction in the reabsorption of water and sodium[22; 23; 32]. This is followed by the damage of distal tubular reabsorption, impairment in the renal flow of blood as well as the glomerular filtration which increases secretion of proteins, enzymes as well as other electrolytes including potassium and magnesium.

Higher cisplatin dose can also result into hepatotoxicity. This may be caused by the oxidative stress which results from a reduction of glutathione. A lot of studies have also reported significant elevation in hepatic malonaldehyde and decrease in the quantities of the antioxidant enzymes[32; 33]. According to other studies transaminases enzymes have been identified as the highly sensitive biomarkers that affects cells directly and causes its death. This is attributed to the fact that they are located within the cells and are released after the cells have been damaged. Higher levels of hepatic enzymes within the blood serum as well as bilirubin are indications for the impaired functions of the liver[34]. This has been studied and evidence show that hepatotoxicity could be caused by the administration of cisplatin in chemotherapy. Another study reported that cisplatin hepatotoxicity was shown to be exacerbated by elevated expression of cytochrome P450-2E1 enzyme. The evidence of histopathological changes will be varied including degeneration of hepatocytes and necrosis with infiltration of inflammatory cells within the portal area with sinusoidal dilatation[24]. Due to increasing knowledge and understanding of the complexity and severity of cisplatin-induced hepatotoxicity several anti-toxicity agents have been proposed for protection of the patients including vitamin E and selenium. However, toxicity that results into the damage of the liver is still a great challenge to the effectiveness of cisplatin as anti-cancer agent[35].

Neurotoxicity is the third and most serious cisplatin toxicity. According to a recent review on the pharmacological impact of cisplatin, neuropathy was cited as the current major dose-limiting cisplatin toxicity. The most affected parts of the neuron system are the peripheral sensory nerves. Peripheral neuropathy among patients undergoing cisplatin chemotherapy treatment is exhibited by automatic neuropathy, loss of haring, seizures, Lhermitte's sign as well as encephalopathy[36]. Recent evidence has shown that this type of toxicity is dose dependent and is common among the patients with higher cumulative dose that is over 300mg/m2. However, statistics have shown that in between 30-50% of the patients, neuropathy is never reversible. Neurotoxicity is the accumulation of cisplatin within the neuron system[37]. DNA adducts are present in various organs of the body including the peripheral nerves. However, researchers have linked the dorsal tissues with higher accumulation of platinum DNA adducts particularly within the dorsal root ganglia of autopsied patients. This observation is consistent with earlier findings showing sensory neuropathy among patients undergoing

chemotherapy treatment using cisplatin[38]. The damage in the outer hair cells of the Corti organ is a major cause of higher impairment of hearing often referred to as ototoxicity.

Researchers have also correlated the percentage of histopathologic impairments as well as neurotoxicity to the concentration of cisplatin within the nervous tissue. However, other studies found additive neuropathy with the administration of cisplatin with other neurotoxic agents such as paclitaxel as well as doce-taxel[33; 34]. In order to prevent cisplatin-induced neurotoxicity, various types of agents have been explored to protect customers. Anti-cisplatin neurotoxicity agents currently being used are neurotropic factors, sulfur thiols, free oxygen radical scavengers as well as phosphoric acid antibiotics. According to research, neurotoxicity is less common with carboplatin treatment compared to cisplatin treatment[31; 32]. Another research estimated the rate of neurotoxicity to be in approximately 3% individuals who have been treated with cisplatin and does not worsen in more than three quarters of the patients who already have cisplatin toxicity[24].

Cardiotoxicity has also been linked to cisplatin treatment. The leakages of lactate dehydrogenase (LDH) as well as creatine kinase from the cardiac myocytes result from Cardiotoxicity[39]. This could be secondary processes that results from cisplatin-induced lipid peroxidation or cardiac membranes. According to past studies, cisplatin-induced toxicology has resulted into various histological changes depending on the physiological health of cancer patients. They include: vacuolated cytoplasm of several muscle cells, inflated blood vessels as well as degeneration and necrosis of cardiac muscle fiber cells accompanied with fibrous tissue reactions[38]. While evidence from clinical studies show that Cardiotoxicity is not a common cisplatin-induced toxicity, when it so severe and could completely impair the overall cardiovascular system of a patient.

Clinical Use of Cisplatin

Cisplatin is considered as one of the most effective anticancer drugs used widely for the treatment of solid tumors. One of the most prominent and effective clinical applications of cisplatin is on the treatment of lung cancer. According to studies, lung cancer is considered one of the most common and complex types of malignancies. For instance, small cell lung cancers (SCLCs) constitute approximately 15% of all lung cancers[40]. Research has shown that platinum based therapy treatments for cancers are key drugs for the treatment of small cell lung cancers. The use of carboplatin as well as cisplatin represents the two major chemotherapeutic drugs for treatment of SCLCs. However, cisplatin is often selected in clinical trials due to the fact that it exhibits the strongest antitumor property compared to carboplatin treatments[39]. However, due to the risk of renal toxicity, precautions are taken with keen monitoring of urine volumes and a large dose is often a must in cisplatin based chemotherapy. While the standard care of a localized non-small cell lung cancer is mainly surgery, in case of stage 2 or 3 cancer disease, administration of adjuvant cisplatin-based chemotherapy is recommended.

Cisplatin is also applied clinically in the treatment of ovarian cancer. According to studies, ovarian cancer has been associated with the highest mortality rates among gynecological cancers. While many patients are diagnosed at late stages because many hospitals do not have effective screening strategies as well as lack of manifestations of symptoms at the early stage of the disease, surgical excision is often recommended as the conventional treatment[3; 40]. This is however followed by platinum chemotherapy. Evidence from studies show that the use of cisplatin chemotherapy is effective in the early stages of the disease, however patients who suffer recurrent of the disease often develop resistance to chemotherapy and eventually succumb. Despite having severe side effects as well as risk of developing resistance, drugs derived from cisplatin have been applied as the mainline treatment of the ovarian cancer[37; 38]. Cisplatin is often used as a combination with other drugs and chemical agents to treat ovarian cancer in sensitive and resistant cell lines.

The third clinical application of Cisplatin is in the treatment of Carcinoma. Head and neck cancer also referred to as Head and Neck Squamous Cell Carcinoma (HNSCC) is a common malignant disease[3]. HNSCC is often associated with higher mortality rates despite availability of higher standards of treatments such as radiation, surgery and chemotherapy. The five-year survival rate is estimated at 50% and has not changed for almost

a decade despite developing new findings about the disease[40]. It is therefore important to note that absolute use of cisplatin in the treatment of the disease is not effective. In this regard, cisplatin is often combined with other agents such as doxorubicin, methotrexate, gemcitabine and or vinblastine especially in patients with metastatic urothelial carcinoma[41]. Nevertheless, use of cisplatin in the treatment of carcinoma is still popular chemotherapy agent in many hospitals due to its efficacy in certain cancer cells.

Fourth, cisplatin is also used as chemotherapy drug for the treatment of breast cancer. Apart from ovarian cancer, breast cancer is another leading cause of death among women across the world[40]. While surgical procedures are applied in the treatment of other cancer, for breast cancer, chemotherapy is the only option for the treatment of malignant breast cancer as well as mandatory processes to increase the lifespan of breast cancer patients[40]. Chemotherapy with cisplatin containing agents have been applied in the treatment of various malignant of the breast cancer because many chemotherapeutic agents target cells that are fast dividing hence damages tissues due to their cytotoxicity properties[38; 40]. However, with cisplatin, cytotoxicity is reduced and the presence of cytotoxic effects is likely as a result of replication inhibition particularly by cisplatin-DNA adducts and induction of apoptosis. Due to this property, cisplatin is also applied in the treatment of brain cancer.

CONCLUSION

In conclusion researchers have often stressed the importance of Cisplatin therapy as the basis for the treatment of different cancers. While most cancer cells are highly responsive to platinum chemotherapy, evidence has shown that many patients often relapse due to cisplatin resistance. This is dangerous because many patients who relapse from cisplatin treatment have always shown resistant to the drug. The mechanism of resistance has been outlined in the previous section of the current study and includes enhanced biotransformation, liver detoxification, cellular accumulation of cisplatin, elevated DNA repair as well as increased antipoetic processes. The efficacy of cisplatin in overcoming resistance and efficient treatment of broader types of cancers is therefore achieved through combination of cisplatin with certain agents in the treatment of ovarian, lung, carcinoma, gastric, biliary, melanoma, breast, prostate, pancreatic, colon, cervical as well as urothelial bladder cancer. Evidences from previous studies have demonstrated that when other compounds are combined with cisplatin chemotherapy, there is reduction not only in the drug resistance but also in reduction of undesirable side effects. Finally, combinational techniques that target various mechanisms such as reduction in the uptake of cisplatin as well as inflammation could offer the best opportunity for meaningful clinical application of cisplatin.

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