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REVIEW ON REPORTED ACTIVITIES OF CISPLATIN AS ANTICANCER AGENT

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Abstract: Cisplatin is a platinum chemotherapeutic used in a variety of malignancies. The antineoplastic activity occurs from DNA cross-links and adducts, in addition to the generation of superoxide radicals. Nephrotoxicity is the most well-known and potentially most clinically significant toxicity. Unfortunately, the mechanism for cisplatin nephrotoxicity has not been completely elucidated; however, many theories have been developed. Other toxicities include gastrointestinal, myelosuppression, ototoxicity and neurotoxicity. Saline diuresis is currently the most accepted way to prevent cisplatin nephrotoxicity. Research has focused on pharmaceuticals and enzyme/molecular alterations as alternatives to long-term diuresis. No agents have currently been identified that can protect from all toxicities.

***Keywords*-cisplatin, natural products, combination therapy, mode of action**

I. INTRODUCTION

Cisplatin is a platinum chemotherapeutic used in a variety of malignancies. The antineoplastic activity occurs from DNA cross-links and adducts, in addition to the generation of superoxide radicals. Nephrotoxicity is the most well-known and potentially most clinically significant toxicity. Unfortunately, the mechanism for cisplatin nephrotoxicity has not been completely elucidated; however, many theories have been developed. Other toxicities include gastrointestinal, myelosuppression, ototoxicity and neurotoxicity. Saline diuresis is currently the most accepted way to prevent cisplatin nephrotoxicity. Research has focused on pharmaceuticals and enzyme/molecular alterations as alternatives to long-term diuresis. No agents have currently been identified that can protect from all toxicities. Cisplatin has shown activity against osteosarcoma, transitional cell carcinoma, squamous cell carcinoma (SCC), melanoma, mesothelioma, carcinomatosis and germinal cell tumours in the dog. In the cat, cisplatin cannot be utilized because of fulminant pulmonary oedema that occurs at standard doses. Intralesional cisplatin has been utilized in horses for the treatment of SCC and sarcoids.[1] Cisplatin and other platinum-based drugs, such as carboplatin, ormaplatin, and oxaliplatin, have been widely used to treat a multitude of human cancers. However, a considerable proportion of patients often relapse due to drug resistance and/or toxicity to multiple organs including the liver, kidneys, gastrointestinal tract, and the

cardiovascular, hematologic, and nervous systems. In this study, we sought to provide a comprehensive review of the current state of the science highlighting the use of cisplatin in cancer therapy, with a special emphasis on its molecular mechanisms of action, and treatment modalities including the combination therapy with natural products. Hence, we searched the literature using various scientific databases., such as MEDLINE, PubMed, Google Scholar, and relevant sources, to collect and review relevant publications on cisplatin, natural products, combination therapy, uses in cancer treatment, modes of action, and therapeutic strategies. Our search results revealed that new strategic approaches for cancer treatment, including the combination therapy of cisplatin and natural products, have been evaluated with some degree of success. Scientific evidence from both in vitro and in vivo studies demonstrates that many medicinal plants contain bioactive compounds that are promising candidates for the treatment of human diseases, and therefore represent an excellent source for drug discovery. In preclinical studies, it has been demonstrated that natural products not only enhance the therapeutic activity of cisplatin but also attenuate its chemotherapy-induced toxicity. Many experimental studies have also reported that natural products exert their therapeutic action by triggering apoptosis through modulation of mitogen-activated protein kinase (MAPK) and p53 signal transduction pathways and enhancement of cisplatin chemosensitivity. Furthermore, natural products protect against cisplatin-induced organ toxicity by modulating several gene transcription factors and inducing cell death through apoptosis and/or necrosis. In addition, formulations of cisplatin with polymeric, lipid, inorganic, and carbon-based nano-drug delivery systems have been found to delay drug release, prolong half-life, and reduce systemic toxicity while other formulations, such as nanocapsules, nanogels, and hydrogels, have been reported to enhance cell penetration, target cancer cells, and inhibit tumor progression.[2]

Cisplatin is a highly effective antitumor agent whose clinical application is limited by the inherent nephrotoxicity. The current measures of nephroprotection used in patients receiving cisplatin are not satisfactory, and studies have focused on the investigation of new possible protective strategies. Many pathways involved in cisplatin nephrotoxicity have been delineated and proposed as targets for nephroprotection, and many new potentially protective agents have been reported. The multiple pathways which lead to renal damage and renal cell death have points of convergence and share some common modulators. The most frequent event among all the described pathways is the oxidative stress that acts as both a trigger and a result. The most exploited pathways, the proposed protective strategies, the achievements obtained so far as well as conflicting data are summarized and discussed in this review, providing a general view of the knowledge accumulated with past and recent research on this subject.[3]

Cisplatin is one of the most potent anticancer agents, displaying significant clinical activity against a variety of solid tumors. For more than two decades, the most effective systemic chemotherapy for non-small cell lung cancer (NSCLC), the leading cause of cancer morbidity and mortality among men and women in the western world, was cisplatin-based combination treatment. Unfortunately, the outcome of cisplatin therapy on NSCLC seems to have reached a plateau. Therefore, the biological mechanisms of cisplatin action need to be understood in order to overcome the treatment plateau on NSCLC. Moreover, the development of resistance is a hurdle in the use of this drug. The molecular mechanisms that underlie this chemoresistance are largely unknown. Possible mechanisms of acquired resistance to cisplatin include reduced intracellular accumulation

of cisplatin, enhanced drug inactivation by metallothionine and glutathione, increased repair activity of DNA damage, and altered expression of oncogenes and regulatory proteins. In addition, it is generally accepted that cytotoxicity of cisplatin is mediated through induction of apoptosis and arrest of cell cycle resulting from its interaction with DNA, such as the formation of cisplatin-DNA adducts, which activates multiple signaling pathways, including those involving p53, Bcl-2 family, caspases, cyclins, CDKs, pRb, PKC, MAPK and PI3K/Akt. Increased expression of anti-apoptotic genes and mutations in the intrinsic apoptotic pathway may contribute to the inability of cells to detect DNA damage or to induce apoptosis. Towards an understanding of the molecular basis of the cellular response to cisplatin-based chemotherapy in NSCLC, in this review we provide some insights into the pathways involved in cisplatin damage from entering the cells to execution of apoptosis or survival of NSCLC cells. We believe that as more and more molecular mechanisms of response to cisplatin-based therapy are unraveled, this knowledge should provide a basis for further studies to improve our understanding of molecular events associated with lung NSCLC as well as to devise novel and effective therapeutic approaches to overcome the treatment plateau or reverse drug resistance in this disease.[4]

Cisplatin is one of the most widely used chemotherapeutic agents for various solid tumors in the clinic due to its high efficacy and broad spectrum. The antineoplastic activity of cisplatin is mainly due to its ability to cross-link with DNA, thus blocking transcription and replication. Unfortunately, the clinical use of cisplatin is limited by its severe, dose-dependent toxic side effects. There are approximately 40 specific toxicities of cisplatin, among which nephrotoxicity is the most common one. Other common side effects include ototoxicity, neurotoxicity, gastrointestinal toxicity, hematological toxicity, cardiotoxicity, and hepatotoxicity. These side effects together reduce the life quality of patients and require lowering the dosage of the drug, even stopping administration, thus weakening the treatment effect. Few effective measures exist clinically against these side effects because the exact mechanisms of various side effects from cisplatin remain still unclear. Therefore, substantial effort has been made to explore the complicated biochemical processes involved in the toxicology of cisplatin, aiming to identify effective ways to reduce or eradicate its toxicity. This review summarizes and reviews the updated advances in the toxicological research of cisplatin. We anticipate to provide insights into the understanding of the mechanisms underlying the side effects of cisplatin and designing comprehensive therapeutic strategies involving cisplatin.[5]

Cisplatin is one of the chemotherapeutic agents used the most for testicular, ovarian and several other cancers. In order to overcome cisplatin resistance, other platinum (Pt) compounds have been developed and, in the last ten years, Pt-derivatives with reporting activity have also been synthesized. The first generation of reporting Pt-compounds was based on linking a fluorescent molecule (e.g. cyanine) to cisplatin, but more recent studies have focused on strategies to synthesize intrinsically fluorescent derivatives. Accordingly, bile acid Pt-compounds have shown fluorescence intensity that is stable at room temperature for a long time; this fluorescence is maintained after binding to oligonucleotides or DNA. Because of this, the binding mode of these compounds to DNA can be easily analyzed both by flow injection and fluorescence techniques, showing that although these compounds target the nuclei, they form adducts with the DNA that are different from those due to cisplatin. In line with this, these bile acid derivatives have shown increased cytotoxicity and ability to overcome resistance as compared to cisplatin in several cell lines. This review summarizes the information

available on reporting Pt-compounds and focuses on these novel, intrinsically fluorescent bile acid Pt derivatives, their biochemical characteristics and biological activity.[6]

Neurotoxicity remains the major dose-limiting toxicity of cisplatin. Peripheral sensory neuropathy, the primary type of cisplatin neurotoxicity, has been reported in 30–100% of patients with clinical symptoms typically developing after cumulative cisplatin doses of $300 mg/m^2. Several clinical studies have established an important dose-response, dose intensity-response and cumulative total dose-response relationship for cisplatin in the treatment of head and neck, testicular, melanoma, and ovarian cancers. In patients with these tumor types, the occurrence of moderate or severe neuropathy presents an important therapeutic dilemma. Several types of agents–including micleophilic sulfur thiols, neurotrophic factors, phosphonic acid antibiotics and free oxygen radical scavengers–have been investigated for amelioration of cisplatin-related neurotoxicity. Of these, amifostine is likely to be the first neuroprotective agent widely used to enhance the clinical effectiveness of cisplatin. Recently reported results from a multicenter phase III trial of women with advance ovarian cancer receiving combination chemotheraphy with cisplatin plus cyclophosphamide showed that amifostine pretreatment was associated with moderate but significant reductions in cisplatin-associated peripheral neuropathy, tinnitus and nephrotoxicity, while achieving equivalent pathological response rates and median survival. Preclinical data suggest that several additional agents, especially the neurotropic factors nerve growth factor, insulin-like growth factor-I and neurotrophin-3, merit further investigation. Nerve growth factor is the only agent reported to prevent, rather than partially protect, cisplatin-induced neuropathy in an experimental model.[7]

Cisplatin is a potent platinum-based anticancer drug approved by the Food Drug Administration (FDA) in 1978. Despite its advantages against solid tumors, cisplatin confers toxicity to various tissues that limit its clinical uses. In cisplatin-induced hepatotoxicity, few mechanisms have been identified, which started as excess generation of reactive oxygen species that leads to oxidative stress, inflammation, DNA damage and apoptosis in the liver. Various natural products, plant extracts and oil rich in flavonoids, terpenoids, polyphenols, and phenolic acids were able to minimize oxidative stress by restoring the level of antioxidant enzymes and acting as an anti-inflammatory agent. Likewise, treatment with honey and royal jelly was demonstrated to decrease serum transaminases and scavenge free radicals in the liver after cisplatin administration. Medicinal properties of these natural products have a promising potential as a complementary therapy to counteract cisplatin-induced hepatotoxicity. This review concentrated on the protective role of several natural products, which has been proven in the laboratory findings to combat cisplatin-induced hepatotoxicity.[8]

The clinical success of cisplatin (*cis* -diamminedichloroplatinum(II)) in antitumor chemotherapy has encouraged an all-out search for analogues with lower toxicity, improved therapeutic index and increased activity. Literally thousands of analogues, obtained by replacement of the ammine- and chloro-ligands by other amines and anionic ligands, respectively, have been systematically screened for activity in experimental tumor models. Some of these analogues have been selected for clinical evaluation, but only very few of them appear to be promising antitumor agents. More recently, cisplatin analogues have been designed and synthesized on the basis of, inter alia, the following considerations: 1) platinum complexes with carrier

molecules as ligands should prove useful for achieving increasing drug concentration in tumor tissues; 2) platinum complexes with chemotherapeutic agents as ligands could afford polyfunctional drugs with synergistic action; 3) complexes containing more than one platinum atom might be more effective than complexes containing only one platinum atom; 4) platinum complexes could be used as sensitizers in radiation therapy. In this paper, we shall give a brief account of the "traditional" analogues, and then critically discuss what we believe could be the new trends in the design of cisplatin analogues.[9]

Cisplatin is a major antineoplastic drug for the treatment of solid tumors, but it has dose-dependent renal toxicity.We reviewed clinical and experimental literature on cisplatin nephrotoxicity to identify new information on the mechanism of injury and potential approaches to prevention and/or treatment. Unbound cisplatin is freely filtered at the glomerulus and taken up into renal tubular cells mainly by a transport-mediated process. The drug is at least partially metabolized into toxic species. Cisplatin has multiple intracellular effects, including regulating genes, causing direct cytotoxicity with reactive oxygen species, activating mitogen-activated protein kinases, inducing apoptosis, and stimulating inflammation and fibrogenesis. These events cause tubular damage and tubular dysfunction with sodium, potassium, and magnesium wasting. Most patients have a reversible decrease in glomerular filtration, but some have an irreversible decrease in glomerular filtration. Volume expansion and saline diuresis remain the most effective preventive strategies. Understanding the mechanisms of injury has led to multiple approaches to prevention. Furthermore, the experimental approaches in these studies with cisplatin are potentially applicable to other drugs causing renal dysfunction. [10]

Since the discovery of its anticancer activity in 1970s, cisplatin and its analogs have become widely used in clinical practice, being administered to 40-80% of patients undergoing chemotherapy for solid tumors. The fascinating story of this drug continues to evolve presently, which includes advances in our understanding of complexity of molecular mechanisms involved in its anticancer activity and drug toxicity. While genomic DNA has been generally recognized as the most critical pharmacological target of cisplatin, the results reported across multiple disciplines suggest that other targets and molecular interactions are likely involved in the anticancer mode of action, drug toxicity and resistance of cancer cells to this remarkable anticancer drug. This article reviews interactions of cisplatin with non-DNA targets, including RNAs, proteins, phospholipids and carbohydrates in the context of its pharmacological activity and drug toxicity. Some of these non-DNA targets and associated mechanisms likely act in a highly concerted manner towards the biological outcome in cisplatin-treated tumors; therefore, the understanding of complexity of cisplatin interactome may open new avenues for modulation of its clinical efficacy or for designing more efficient platinum-based anticancer drugs to reproduce the success of cisplatin in the treatment of highly curable testicular germ cell tumors in its therapeutic applications to other cancers.[11]

Cisplatin, cisplatinum, or *cis*-diamminedichloroplatinum (II), 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 have been 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 paid to its molecular mechanisms of action, and its undesirable side effects.[12]

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