International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 896-899 www.ijprajournal.com ISSN: 2249-7781

Cisplatin: The First Metal-Based Antineoplastic Drug

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Submitted: 25-03-2024 Accepted: 05-04-2024

HIGHLIGHTS:

- The history of cisplatin motivates researchers to explain negative observations.
- Knowledge of synthesis and purification of cisplatin is useful for medical purposes.
- Knowledge of mechanism action and resistance may improve the delivery of anticancer drugs.
- Uses and side effects are useful for cancer patients to understand precautions.
- Combination therapies and development strategies help to build more effective drugs.
- Understanding of nanoconjugated platinum drugs helps to deliver drugs more easily.

ABSTRACT:
Cisplatin was initially discovered to prevent the growth of Escherichia coli and was further recognized for its anti-neoplastic and cytotoxic effects on cancer cells. Administered intravenously to humans, It is used as first-line chemotherapy treatment, cisplatinum or cis-diamminedichloroplatinum(II) (CDDP) is a platinum-based chemotherapy drug used to treat various types of cancers, including sarcomas, some carcinomas (e.g. small cell lung cancer, and ovarian cancer), lymphomas and germ cell tumours. It was the first member of its class, which now also includes carboplatin and oxaliplatin. 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. The drug is also characterized by various toxic side effects including nausea, nephrotoxicity, Cardiotoxicity, hepatotoxicity and neurotoxicity. However, side effects and drug resistance are the two inherent challenges of cisplatin which limit its application and effectiveness. Reduction of drug accumulation inside cancer cells, inactivation of drug by reacting with glutathione and metallothioneins and faster repairing of DNA lesions are responsible for cisplatin resistance. To minimize cisplatin side effects and resistance, combination therapies are used and have proven more effective in defect cancers.

Keywords: Cisplatin, Cardiotoxicity, Nephrotoxicity, Hepatotoxicity, Chemotherapy.

I. INTRODUCTION:

Cancer is one of the most important health problems in the world and the second cause of death in the United States. In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the United States [1]. Cancer is defined as the uncontrolled growth of abnormal cells anywhere in the body. It is accepted that cancer can develop when the normal mechanism of the body stops working. Old cells do not die and instead grow out of control, forming new abnormal cells. These extra cells may form a mass of tissue, called a tumour [2]. According to the World Health Organization (WHO), cancer may arise due to interaction between a person's genetic factors and 3 categories of external agents, including physical carcinogens (ultraviolet and ionizing radiation), chemical carcinogens (asbestos, components of tobacco smoke, aflatoxin, and arsenic) and biological carcinogens (infections from certain viruses, bacteria, or parasites). Depending on the type and stage of cancer, patients are treated with either traditional therapies (such as surgery, chemotherapy, and radiation therapy) or newer forms of treatment (such as immunotherapy, targeted therapy, hormone therapy, gene therapy and photodynamic therapy. Surgery is the process of removing cancer by doing an operation and it is generally used only when cancer is localized. Radiation therapy uses high doses of radiation to shrink or kill cancer cells On the other hand, chemotherapy is an effective and widespread way of cancer treatment in which one or more chemotherapeutic or alkylating agents are used.

Cisplatin is one of the best and first metal-based chemotherapeutic drugs. It is reported that ! 2 billion U.S. dollars of platinum-based anticancer drugs are sold worldwide and nearly about 50% of all patients are treated with cisplatin. Cisplatin was discovered in 1845 by Michele Peyrone but its biological property was hidden until 1965 when a biophysicist, Dr. Barnett Rosenberg discovered its

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inhibiting cell division property. It is used for a wide range of solid cancers such as testicular, ovarian, bladder, lung, cervical, head and neck cancer, gastric cancer and some other cancers. Studies confirmed that cisplatin exerts its anticancer activity by attacking more than one place. It generally binds with genomic DNA (gDNA) or mitochondrial DNA (mtDNA) to create DNA lesions, block the production of DNA, mRNA and proteins, arrest DNA replication, and activate several transduction pathways which finally leads to necrosis or apoptosis. However, cisplatin does not show its highest potential because of side effects and drug resistance. Resistance to cisplatin depends on multiple factors such as reduced drug accumulation, inactivation of the drug by binding with different proteins, an increase of DNA repairing, and alteration of different proteins that signal apoptosis. The major toxicities that arise from cisplatin therapy are nephrotoxicity, ototoxicity, hepatotoxicity, gastrointestinal, and neurotoxicity. Furthermore, relapsing is also a very important drawback of cisplatin. The clinical limitations of cisplatin motivate researchers to create thousands of cisplatin analogues. However only two (carboplatin and oxaliplatin) have been approved worldwide and a few have entered clinical trials. However, most platinum compounds do not show a substantial advantage over cisplatin.

This article is a complete overview of cisplatin which includes a brief history of cisplatin, synthesis and clinical applications of cisplatin. Special attention is paid to the mechanism of action and drug resistance.

Invention of 1st metal based chemotherapeutic agent

The compound is-[Pt(NH3)2Cl2] was first prepared by Michele Peyrone in 1845 [21] and hence it was called Peyrone's salt for a long time. The structure of Peyrone's salt was properly deduced by Alfred Werner in 1893 [22]. But the mysterious property of inhibition of cell division was accidentally discovered by Barnett Rosenberg [23], a biophysicist in the study of the effects of the electric field on bacterial growth where he used platinum as an electrode and ammonium chloride as a buffer. During his...

Synthesis of cisplatin:

The most efficient method for the synthesis of cisplatin was given by Dhara which was published in 1970 entitled "A rapid method for the synthesis of cis- [PtCl2(NH3)2]''. Dhara method (Scheme 1) is a multi-step process in which aqueous K2[PtCl4] is treated with excess KI in the first step to form K2[PtI4]. Ammonium Hydroxide is added in this dark brown solution of K2[PtI4] which results in a yellow precipitate of cis-[Pt(NH3)2I2]. It is then collected and dried. To remove iodide ligands from.

Action mechanism of cisplatin:

The detailed molecular mechanism of cisplatin anticancer activity goes beyond this review and remains elsewhere. Here a brief overview of the mechanism of cisplatin activity is explained.

Cisplatin is administered intravenously to the patients as a sterile saline solution. In the bloodstream, the concentration of chloride is relatively high (approximately 100 mM) and hence cisplatin remains unchanged and neutral. This unchanged cisplatin keeps flowing over the.

Cisplatin binds with DNA

DNA is the main target for cisplatin to show anticancer activity. The mono or dihydratedplatin entered into the nucleus is vulnerable enough to react with bases of DNA. The potential binding sites on each base of DNA. It is reported for in vitro studies that the N7 position of the imidazole ring of guanine is preferable to attack adenine or any other bases present in DNA (i.e. cytosine and thymine). Though adenine N7 is less reactive.

Toxicity of Cisplatin:

Cisplatin treatment has been linked to various toxic side effects including nausea, nephrotoxicity, Cardiotoxicity, hepatotoxicity and neurotoxicity. Many toxic events have been reported in various studies including arrhythmias, congestive heart failure, changes as well and myocarditis.

Nausea and Vomiting are considered the most common types of cisplatin toxicity during chemotherapy. One study that examined the toxicity of cisplatin a"er a 120mg/m2 dose found that those patients who did not receive antiemetic medication before cisplatin medication developed an average of 11 emetic episodes. Due to the increased episodes of emesis, scientists have developed 5- 5-hydroxytryptamine (5-HT3) receptor antagonists. Evidence from studies has also shown that these agents have played a major role in reducing the nausea and vomiting side effects of cisplatin medication.

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Nephrotoxicity is another major toxicity caused by cisplatin treatment. The kidney plays an important role as the main route of cisplatin excretion. Evidence from past studies has suggested that the kidney tends to accumulate cisplatin at higher levels compared to any other organ in the body including the liver. 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.

Resistance of cisplatin:

The most serious drawback of cisplatin therapy is its resistance toward cancer cells. Resistance to cisplatin depends on the type of cancer. For example, testicular cancer, ovarian cancer, head and neck cancer and small cell lung cancer are very sensitive to cisplatin, while non-small cell lung cancer and colorectal cancer are very resistant to cisplatin. There are two forms of resistance exist: intrinsic resistance and acquired resistance.

Use of cisplatin for the treatment of lung cancer:

One of the most common fatal malignancies is lung cancer. Two types of lung cancers are generally known in literature: Small-cell lung cancers (SCLC) and non-small cell lung cancers (NSCLC). These two types of cancer can be differentiated by the way of grow and spread. SCLCs are the most aggressive and readily growing of all lung cancers. Chemotherapy is the most effective treatment for SCLC because these tumours are generally widespread in the body when they are diagnosed.

Cisplatin and Breast Cancer:

Breast cancer is one of the leading causes of women's mortality worldwide. Chemotherapy is the only option for treating malignant breast cancer and conditions to increase the lifespan of the patient (Decatris, Sundar et al., 2004). 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 for the treatment of a variety of malignancies, including breast, testicular, ovarian, cervical, prostate, head and neck, bladder, lung and refractory non-Hodgkin's lymphomas (Tsimberidou, Braiteh et al., 2009; Dhar, Kolishetti et al., 2011). The cytotoxic effect is likely a result of inhibition of replication by cisplatin-DNA adducts and induction of apoptosis (Siddik, 2003).

Cisplatin and neuroblastoma:

Cancer occurring in the sympathetic nervous system in infants and children is known as neuroblastoma [77]. Chemotherapeutic drugs such as cisplatin, carboplatin, vincristine, and etoposide are the primary drugs for chemotherapy of neuroblastoma. Reoccurrence of the disease along with drug refusal malignant cells interfere with the advancement of curing patients with neuroblastoma [78]. It is presumed that resistance stems from epigenetic and several genetic modifications resulting in protein expression and abnormal RNA [79].

Cisplatin and Brain Cancer:

Glioblastoma multiform (GBM) is the most common primary malignant brain tumour, and with rare exceptions, is invariably fatal (Stupp, Mason et al., 2005). The current standard of care for patients with GBMs consists of surgery and radiotherapy in combination with temozolomide, followed by repetitive cycles of temozolomide (Stupp, Hegi et al., 2009). 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 tumours (Khan, D'Souza et al., 1982), as well as in other cancers such as gastric cancer (Koizumi, Narahara et al., 2008), anal cancer (Ajani, Winter et al., 2008), and leukaemia.

Combination Therapy of Cisplatin with Other Cancer Drugs:

Cisplatin combination chemotherapy is the basis of treatment for 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 (Gottesman, Fojo et al., 2002). To overcome resistance, cisplatin is commonly used in combination with some other drugs in treating ovarian cancer, biliary tract cancer, lung cancer

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(diffuse malignant pleural mesothelioma), gastric cancer, carcinoma of salivary gland origin, breast, colon, lung, prostate, melanoma and pancreatic cancer cell lines, squamous cell carcinoma of the male genital tract, urothelial bladder cancer, and cervical cancer.

Side effects of cisplatin:

Though cisplatin is very successful in the treatment of testicular and ovarian cancer, it induces a large number of toxic side effects. These side effects may be seen due to an overdose of cisplatin. The proper dosages of cisplatin used in different types of cancer. The major side effects of cisplatin are nephrotoxicity, ototoxicity, hepatotoxicity, gastrointestinal toxicity, etc.

II. CONCLUSION:

Cisplatin is one of the most used anticancer drugs without any doubt for the treatment of solid cancer such as prostate cancer, ovarian cancer, head and neck cancer, bladder and lung cancer and some other cancers. The oversensitivity of cisplatin toward testicular cancer is due to the overexpression of some proteins and the low ability of interstrand-crosslink repairing. It is a cytotoxic drug that causes apoptosis by damaging DNA, activation of several signal transductions, and then inhibiting.

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