Application of cisplatin and other platinum-containing drugs in cancer therapy: comprehensive review

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Abstract: A well-known chemotherapy medication is a cisplatin, also referred to as cis-diamminedichloroplatinum or cisplatinum(II). Cancers such as bone metastases, lymphomas, germ cell tumors, and carcinomas can all be treated with it. Its mode has been takenpertaining to its capability to cross-link with purine biological branches, obstructing DNA repair processes, generating DNA damage, and, as a result, cancerous cells undergo apoptosis. Nevertheless, due to drug resistance and a number of unfavorable side effects, including severe kidney problems, allergic reactions, lowered immunity to infections, gastrointestinal problems and others, have also been used. For overcoming drug resistance and reducing adverse effects, cisplatin-based combination therapies with other pharmaceuticals have also garnered considerable investigation. This in-depth analysis looks at the isotopes of the properties cisplatin and associated platinum-based drugs, as well as how they can be is employed to treat a range of health maligancies. Particular focus is placed on its unfavorable side effects and molecular mechanisms of action. The current paper provides a pharmacological assessment of the drug, outlining its clinical applications, toxic effects, and mechanisms of resistance. The ability of cisplatin to form DNA adducts by crosslinking with urine bases on DNA has been connected to its mode of action. As a result,

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cancer cells experience apoptosis, which stops DNA damage from being repaired. The drug does, however, display certainly improved DNA damage repair, decreased drug accusation inside cells, and cisplatin deactivation in the cytosol are all signs of resistance. The drug also has some negative adverse consequences, including vomiting, kidney damage, cardiotoxicity, liver toxicity, and neurodegeneration.

Keywords:

The platinum-based drug, cancer treatment, cisplatin, cardiotoxicity, anti-cancer medications, kidney damage, and Chemotherapy.

1. Introduction:

Cisplatin is a facilitation compound comprising a square planer and a metallic (platinum), also known as cis-diamminedichloroplatinum (II). It is a white, dark yellow, or yellow-orange crystalline powder at room temperature. Partially dissolved in water, dimethylprimanide, and N, N-dimethylformamide[1]. At normal pressure and temperature, cisplatin is stable, but with time, it may gradually transform into trans-isomers.

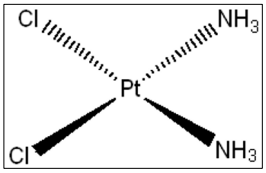

Fig.1. Molecular Structure of Cisplatin

Cisplatin has been particularly noteworthy because it has demonstrated antitumor efficacy in numerous cancers, such as cancers of the ovaries and testicles. Since its cytotoxic properties were discovered in the 1960s, systemic therapy for germ cell cancers has relied heavily on this drug. By the end of the 1970s, it had become an essential part of the regimen. One of the most efficient chemotherapy drugs used to treat cancer[2]. It was the inaugural platinum substance used to treat cancer to receive FDA approval in 1978. Due to this, molecules containing platinum (II) and other metals have attracted interest as potential anticancer medications[3]. According to clinical research. Although the prognosis for these malignancies has lately improved and they are now less deadly, there are still big obstacles to their solution[4][5]. Additionally, due to medication resistance and severe side effects, cisplatin combination therapy has been employed as a unique therapeutic strategy for specific types of human malignancies[6]. We set out to present a thorough analysis to evaluate the application of cisplatin and related platinum-based medications in the treatment of various human cancers, to examine their molecular mechanisms of action, to examine any potential adverse effects, and to describe the chemical composition of these medications. Because cisplatin is linked to several negative effects, its usage in cancer patients is strictly regulated[7][8]. When a patient's renal function is impaired, doctors are advised to reduce the doses of cisplatin because large doses can have adverse effects connected to nephrotoxicity[2]. Toxicities is a side effect that depends on dosage, which must be kept in mind. Neurobiological adverse effects, such some people's decreased hearing and perception individuals, have been observed in nerve conduction investigations conducted before and after cisplatin treatment. Prophylactic antiemetic and corticosteroids combined usually avoid other side effects including nausea and vomiting[9][10]. Doctors and researchers are advised

to use caution while prescribing the medicine as the degree of the side effects varies from patient to patient. According to current research, using other medications in addition to cisplatin therapy is useful in decreasing toxicity in addition to overcoming drug resistance[11].

2. Mechanism of cisplatin:

The relationship between cisplatin and genetic material from DNA adducts mediates the drug's mode of action[12]. The theory of action holds that the DNA adducts formed by cisplatin, such as mono-, inter-, and intrastrand cisplatin DNA crosslinks, cause cancer cells to undergo apoptosis and cause the cell cycle to stop at S, G1, or G2-M, are what cause cancer cells to die. This is due to the fact that cisplatin stops the cell cycle at the G2, S, or G1 phasesto make good the harm. Intrastrand adducts are the main DNA adducts crosslinks, which trigger apoptosis[13]. This results in inadequate repair, which forces the cells to go through aberrant mitosis before they perish. Apoptosis is described by siddik as a sequence of cancer cells dying as directed by the synthesis of DNA adducts. The fastest proliferating cancerous cells are killed off as a result of blocking the replication of DNA in cancer cells. As a result, apoptosis involves some events that culminate in the dying cell being digested by nucleases and proteases in a unified, irreparable phase. The cell is activated when cisplatin enters it[12]. In the cytoplasm, water molecules replace the chloride molecules on cisplatin. Many nucleophiles can react with this hydrolysis product, two examples of which are the proteins' thiolate groups and nucleic acids' nitrogen donor atoms[14][15]. Cisplatin can harm DNA in cancer cells by attaching to the N7 reactive center on a purine residue, which prevents cell division and results in apoptotic cell death. Purine nucleotide 1,2-intrastrand cross-links with cisplatin are the most obvious DNA alterations[16]. Consequently, indeed, the great sensitivity. The principal target for cisplatin cytotoxicity has been emphasized in scientific papers from a variety of institutions as being the resistance to cisplatin displayed by both prokaryotic and eukaryotic cells deficient in DNA repair[17]. The use of cisplatin to treat human tumors has been linked to a number of molecular processes resulting in apoptosis[18].

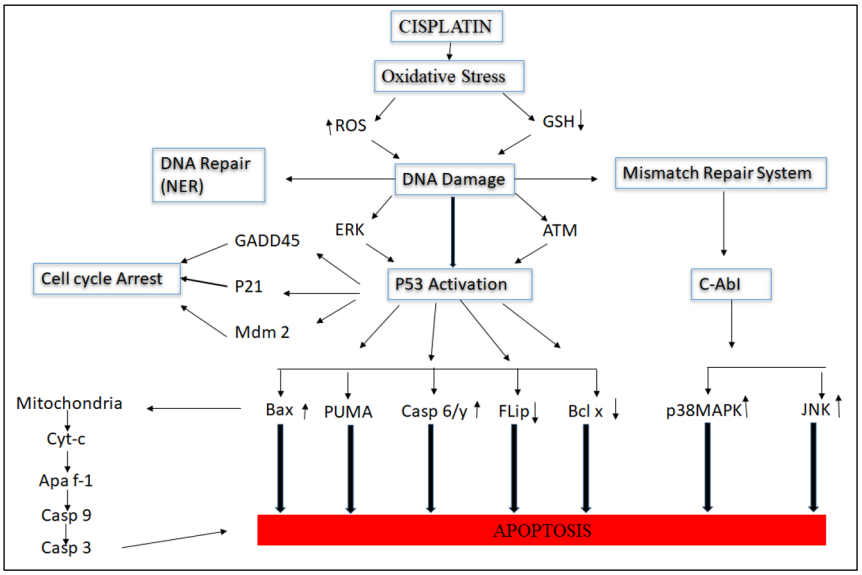

Fig.2. Mechanism of cisplatin in cancer treatment

3. Other use of medications containing platinum, such as cisplatin:

Cisplatin's drug development began with early seminal work, and since then, numerous aptamers exist and developed and tested for features that could raise its therapeutic index[19][20]. In clinical studies, 13 of these analogs have been tested, but only one has outperformed cisplatin and received universal approval[21]. Cisplatin is a fantastic illustration from a molecular standpoint of how a modest chemical structural changes can affect a huge impact on targets morphogenesis cell[22][23]. The four ligands that makeup cisplatin, carboplatin, and oxaliplatin are doubly charged platinum ions[21]. Molecular carboxylates also on right prevent the platinum ion from leaving groups that allow it to establish connections with DNA bases, whereas the amine ligands on the left bind with the platinum ion more strongly[24][25]. In vitro, it produces the same reaction products at the same concentrations as cisplatin, although it is less reactive and it is DNA binding kinetics are slower contrary to potential alternate pathways, cisplatin, and carboplatin are more sensitive. According to several research, cisplatin and carboplatin both exhibit cytotoxic action in MCF-7 cells while causing various morphological alternations [26][27][28]. The biggest advantages of carboplatin over cisplatin are the absence of nephrotoxic side effects and the consequent reduction in adverse effects. One of the carboplatin's key drawbacks is that it has a myeloid suppressive effect, which significantly reduces the body's synthesis of blood cells and platelets, sometimes to as low as 10% of normal levels[29].

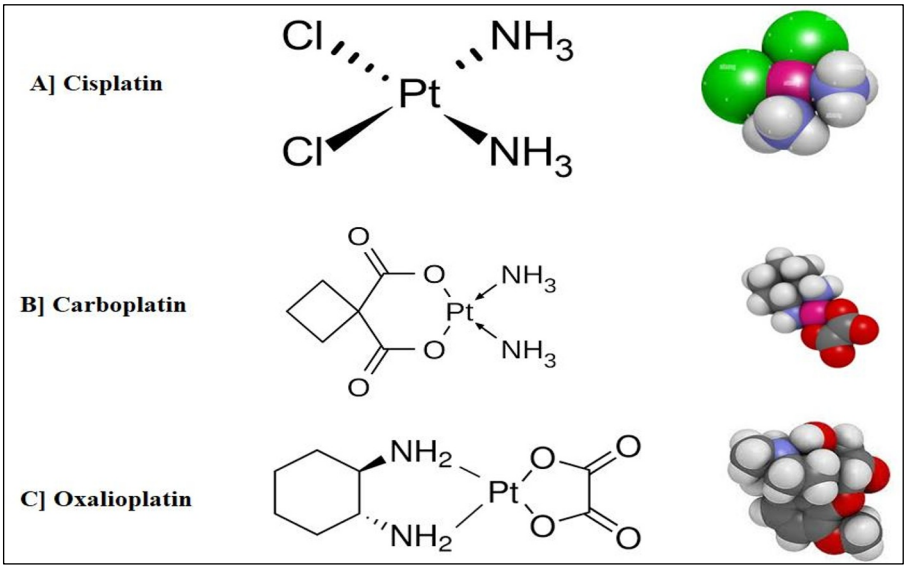

Fig.3. Chemical and molecular structure of platinum drugs

4. Uses of cisplatin in the treatment of cancer:

4.1. Lung cancer:

Among the most prevalent and deadly cancers is still thought to be lung cancer. Small cell lung tumors make up 15 percent of the entire cases of pulmonary cancer. Platinum-based therapy are currently the most commonly prescribed treatments for SCLC[30][31]. Cisplatin is often used in clinical trials due to its powerful anticancer properties; however, it can cause kidney damage, nausea, and vomiting[32]. As a result, substantial infusions are required in chemotherapy that is solely focused on cisplatin, and urine volumes must be

regulated to avoid renal damage. Cisplatin could perhaps be replaced by carboplatin, according to some research because forceful hydration is frequently problematic in clinical practice. There appears to be no loss of clinical effectiveness. Among the most typical forms of cancer is lung cancer. Over two million new cases are believed to be diagnosed each year, and there are over 1.7 million projected deaths from it globally[33]. Patients with lung cancer are currently treated broadly with platinum-based chemotherapy regimens. Cisplatin, carboplatin, oxaliplatin, and nedaplatin are the four platinum-containing compounds that have grown in popularity as anticancer drugs. In contrast to other anticancer drugs, cisplatin has a wider range of cancer-treating applications, including lung, head, neck, and cervical malignancies. Additionally, it may boost the proportion of survivors. Also known as cis-di ammine-dichloro-platinum(CDDP)[34]. Cisplatin's interaction with DNA results in interstrand and intramolecular cross-linking, which prevents RNA transcription and DNA replication, ultimately causing DNA breakage and inducing apoptosis. Lung cancer five-year health outcomes continue to be too low to be satisfactory, cisplatin resistance is the main factor in therapeutic failure. Tiredness, malaise, vomiting, nephrotoxicity, and hearing loss are typical cisplatin side effects that can also cause patient vulnerability and therapy inability[35]. Therefore, for maximum harm to cancer cells and a long-lasting therapeutic impact, a therapeutic agent that can overcome chemoresistance and reduce the adverse effects of cisplatin is preferable impact in many methods that increase their toxicity to cells for the treatment of tumorous cells[36][37]. To assess the toxicity of GE-Pt NPs[38]. Recently, both the NSCLC meta-analysis moreover, analysed the five largest studies' results from the cisplatin assessment study showed a 5.3 percent on average absolute 5-year survival improvement from adjuvant therapy[39].

4.2. Brain cancer:

Glioblastoma multiforme (GBM), the most commonly diagnosed metastatic disease tumor, is inevitably fatal[40]. Temozolomide followed by multiple cycles of surgery, radiation, and temozolomide is the current standard of care for GBM patients. Although the combination treatment regimen maintained a survival advantage after 5 years, the total median survival had increased by only 2.5 months[41]. Cisplatin therapy can be used to treat recurrent juvenile brain tumors, as well as leukemia, anal cancer, and stomach cancer. Cisplatin, a chemotherapeutic treatment also used to treat brain cancer, neurotoxicity, and tuberculosis was utilized as a model medicine to test[42][43]. Chest, genital, cervix, pulmonary, urinary, abdominal, head, and neck, esophageal. And other cancers can be treated with cisplatin [44][45]. After that, cells were given 24 hours in a DMEM medium containing 10% FBS and penicillin-streptomycin solution to adhere to and proliferate over the Gibco. The media was then taken out, and inserts were relocated to a fresh 24-well plate. Cisplatin stock solutions were produced in 0.9% w/v NaCl solution[46][47]. To get different cisplatin concentrations, this was diluted with DMEM solution. It was then applied to the BBB transwell inserts and incubated for three days. Based on the outcomes of the MTT cell viability assay and the migration assay, this cisplatin concentration range was selected. As controls, transwell-GelMA-50 with GelMA-astrocyte and endothelial cell layers were employed[48]. To exclude the influence of NaCl, the highest NaCl level feasible was employed as a control. In three separate experiment fields, migrating cells in each well were counted daily under a fluorescent microscope[49].

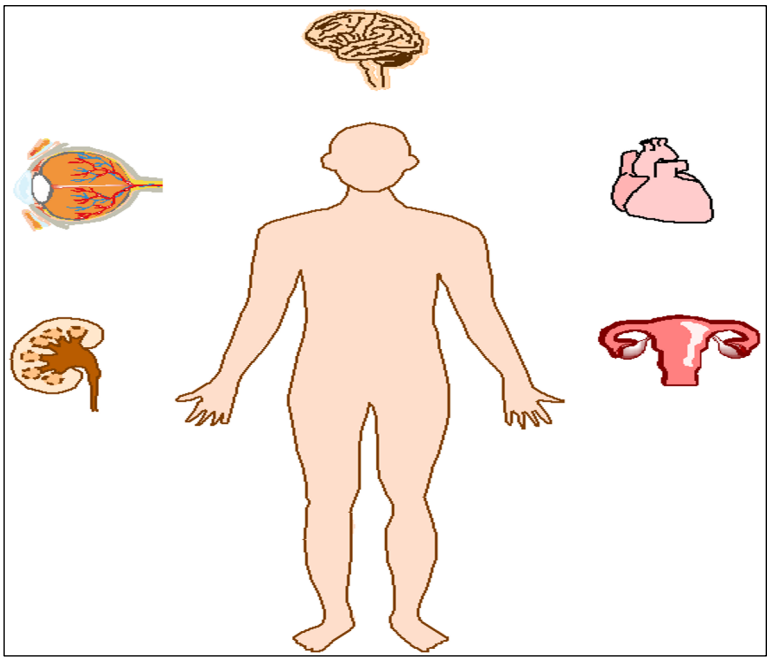

Fig. 4. Systematic diagram of cisplatin in the treatment of other cancer

4.3. Ovarian cancer:

Every year ovarian cancer affects more than 2laclks women worldwide. The majority of women don't receive a diagnosis till the ovaries have become infected, which has a poor outlook[50]. For ovarian cancer, the average rate of five-year survival is just slightly above 50%. Cytoreductive surgery is the cornerstone of first-line treatment, then chemotherapeutic. This has only ever been carried out intravenously in the past but there is growing interest in intraperitoneal chemotherapy delivery that makes use of the peritoneal barriers' therapeutic benefits. Even though three sizable randomised controlled trials contrasting patients receiving at least some of their chemotherapy via the intramuscular injection method and intravenous chemotherapy had better outcomes. In addition to gynecologic cancers, cancer of the ovaries has the highest mortality rate[51]. Cancer of the ovaries is not properly diagnosed owing to the absence of precise tests for detection and particular symptoms and signs which indicate an early disease, which frequently arises in patients after it becomes advanced to late stages. The standard remedy for advanced ovarian cancer is chemotherapy with platinum and taxane, followed by surgical resection[52]. Despite the fact that this initial therapy is effective, recurring takes place in up to 75% of all patients with ovarian cancer. Repeated ovarian cancer victims ultimately develop treatment resistance and die from the disease. Most ovarian malignancies (90%) begin in the ovaries for unknown reasons, with the remaining 10% having inherited roots. Despite the development of resistance and significant side effects, cisplatin derivatives remain the primary treatment for ovarian cancer. Cisplatin is also utilized in combination with other medications to treat sensitive and resistant ovarian cancer cell lines, as well as other chemical agents. For instance, liposomal to overcome the ovarian cancer cell's resistance to the treatment, cisplatin is combined with honey venom[53]. The tumor response to the drug cisplatin most effective carcinoma of the ovary therapy for the past 4 decades, and it can be used to predict a woman's prognosis. An extremely dismal prognosis applies to patients whose malignancies are inherently platinum-resistant at the time of beginning treatment[54]. Although the majority of ovarian cancer patients react the majority will switch to the front

platinum combo chemotherapy and eventually acquire cisplatin-resistant illness and pass away from the condition[55].

5. Cisplatin used with additional cancer medicines in combination therapy:

The foundation of many cancer treatments is a chemotherapy regimen containing cisplatin. Even though most terminally ill people respond well to platinum, most would create cisplatin-resistant tumors illness[56]. As a result, it has been observed that many people who revert after undergoing treatment with cisplatin possess drug resistance[57]. Some of the hypothesized enhanced liver enzymatic hydrolysis and purification, an increase in DNA repair and replication, and altered cellular absorption and efflux of cisplatin are some examples of the mechanisms of cisplatin resistance and anti-apoptotic activity[58][59]. Cisplatin is frequently used in conjunction with other drugs to treat cancers.

Table 1. Use of various drugs in types of cancer

Type of cancer	Combination of drugs	Reference
Neck carcinoma, head, breast melanoma, lung, and ovarian carcinoma	Paclitaxel	[60][9]
Non-small lung carcinoma	UFT, Bevacizumab, Vindesine	[61][62]
Biliary cancer	Gemcitabine	[63]
Ovarian cancer	Honeybee venom, Oxaliplatin, thymoquinone, and quercetin	[64]
Cervical cancer	Tetra arsenic oxide	[65]

5.1. Use of cisplatin in medicine:

Cisplatin, one of the most effective anticancer drugs, is often prescribed to treat solid tumors. One of cisplatin's most well-known and effective clinical uses is used to treat cancer[66]. Studies show that one of the prevalent and challenging types of cancer is carcinoma. The use of platinum-based medicines is critical for the treatment of comparatively tiny lung cancer, according to studies[67]. Carboplatin and cisplatin are the two major chemotherapeutic drugs used to treat SCLCs. However it has the strongest anticancer potential when compared to carboplatin therapy, cisplatin is commonly used in clinical trials[68][69]. Furthermore, because of the possibility of renal damage, measures are taken with thorough monitoring of urine volumes, and cisplatin-based chemotherapy typically calls for a substantial dose. Since surgery is the main form of therapy to confined cancers that are not small cells, cisplatin-based additional chemotherapy has been suggested for stage 2 and 3 carcinomas. Considering serious adverse reactions and the possibility of resistance, cisplatin-based medications are the basis of medical therapy for ovarian cancer in cell lines with varying susceptibility and durability[70].

5.2. Toxicity of cisplatin:

The sections before this one discussed as a result of its interactions with DNA, cisplatin produces a pyrimidine DNA covalent adduct nucleotide[71]. Although this association between the platinum compounds is the reason why cisplatin is beneficial in the fight against cancer is what causes cisplatin to be cytotoxic[72]. Numerous harmful side effects of cisplatin therapy have been associated with it, including nausea, nephrotoxicity, cardiotoxicity, hepatotoxicity, and neurotoxicity[73][74]. Numerous hazardous events, such as arrhythmias, congestive shown in numerous studies. Oxidative stress gradually reduces

antioxidant capacity and the immune system because reactive oxygen species are produced[75]. Other changes that occur include the production of non-enzymatic compounds, the decrease of glutathione, and significant changes in cisplatin toxicity. Numerous oncologists, medical professionals, and researchers have expressed worry about the varied toxicological effects of cisplatin[76].

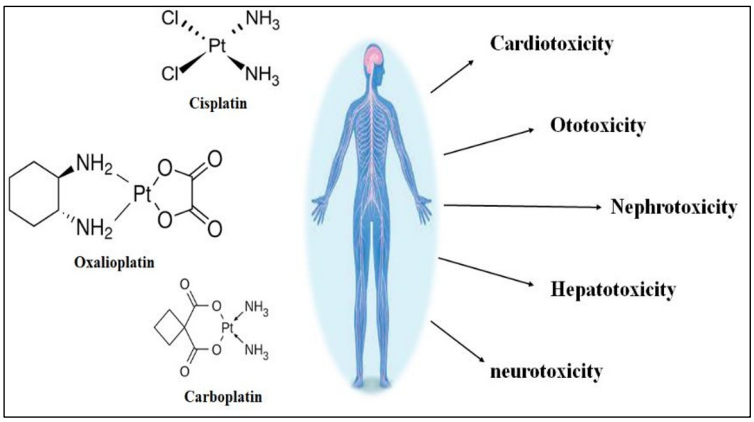

Fig.5. Toxicity of cancer in cisplatin drugs

Conclusion:

The importance of cisplatin therapy has frequently been emphasized by researchers as the cornerstone of the treatment of numerous malignancies. Research demonstrates that several people regularly revert attributable to intolerance to chemotherapeutics even if the majority of cancer cells respond relatively effectively to platinum chemotherapy. This is dangerous since resistance over time. The resistance mechanisms were described in the current study's preliminary part, but include higher metabolic activation, liver decontamination, cell development of cisplatin, accelerated DNA repair, as well as increased antipoetic activities[77]. Evidence from past studies has revealed something when more substance were introduced to the chemotherapy medication cisplatin, both treatment resistance and undesirable side effects are reduced[78][79]. Finally, the combinational approaches of inflammation and reduction in absorption of cisplatin increases which are the main focus to provide successful application of cisplatin in medicine. Among the most potent anticancer medications, cisplatin is frequently used to treat solid tumors [80][81]. Because they damage DNA, in cancer cells. Cisplatin and other platinum-based drugs cause apoptotic cell death by stopping DNA synthesis and mitosis treatments are sometimes referred to be cytotoxic drugs. The molecular mechanism of anti-apoptotic protein and proto-oncogenes are upregulated during the oxidative damage, and inductive reasoning pathways, simultaneous stimulation of apoptosis's extrinsic and intrinsic pathway[82].

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