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Review on the Platinum Metal Based Anticancer Agent: Cis-Platin

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Abstract:
Cisplatin, a platinum-based compound, is one of the most widely used anticancer agents in clinical oncology. Its discovery marked a significant milestone in cancer therapy due to its ability to effectively target various types of malignancies, including testicular, ovarian, bladder, and lung cancers. This review explores the molecular mechanisms underlying cisplatin's antitumor activity, which primarily involves the formation of DNA-platinum adducts that disrupt DNA replication and transcription, triggering apoptosis in cancer cells. However, the therapeutic utility of cisplatin is often hampered by severe side effects, such as nephrotoxicity, ototoxicity, and peripheral neuropathy, as well as the development of drug resistance. The review also discusses advances in overcoming these challenges, including structural modifications of cisplatin, development of next-generation platinum-based drugs, and combination therapies. Furthermore, insights into targeted delivery systems, such as nanoparticles and liposomes, are highlighted for improving drug selectivity and minimizing toxicity. By addressing current limitations and evaluating innovative strategies, this review underscores the ongoing potential of platinum-based agents in cancer therapy and their role in shaping future oncological treatments.

Key words: Cisplatin, DNA damage, platinum-based agents, carboplatin, oxaliplatin, apoptosis.

1. Introduction:

Cisplatin, also known as cisplatinum or cis-diamminedichloroplatinum(II), is a widely recognized chemotherapeutic agent. It has been utilized in the treatment of various human cancers, including carcinomas, germ cell tumors, lymphomas, and sarcomas. The drug exerts its effects primarily by forming crosslinks with purine bases on DNA, disrupting cellular processes and inducing cell death[1]. However, cisplatin is associated with several significant side effects, such as kidney damage, hemorrhaging, and other severe complications[2]. To address these issues, other platinum-based drugs like carboplatin and oxaliplatin have been developed and employed in cancer therapy. Current research efforts focus on creating platinum analogs that retain cisplatin's efficacy while offering improved safety profiles and overcoming cross-resistance challenges[3]. Cisplatin is a landmark in the history of chemotherapy, being one of the first platinum-based drugs to demonstrate effective anti-cancer activity[4]. It has played a critical role in the treatment of various cancers, including carcinomas, germ cell tumors, lymphomas, and sarcomas, making it an essential subject for review. Despite its efficacy, cisplatin's side effects, such as nephrotoxicity and hematological complications, have necessitated the development of safer alternatives, which is a critical topic for exploration[5]. This review is written to highlight the significant contributions of cisplatin as a pioneering anti-cancer drug while addressing its limitations and the ongoing efforts to improve cancer treatment.

2. Details of Cis-platin

2.1. Chemical structure and discovery of Cis-platin:

Cisplatin's discovery as an anticancer agent can be traced back to the mid 1960s, when biophysicist Barnett Rosenberg at Michigan State University was investigating the effects of electric fields on the growth of Escherichia coli in culture. This work led to the recognition of cisplatin's biological significance[6]. They had hypothesized that, during cell division, the orientation of the mitotic spindle might be affected by the local electric fields which they hoped to perturb. Instead, they observed growth without cell division, the result being elongated, spaghetti-like bacterial filaments approaching 1cm in length. After much detective work, they realized that small amounts of platinum from the electrodes used to apply the electric fields had reacted with NH_4Cl in their buffer to produce various platinum ammine halide compounds. Two of these, *cis*-$[Pt(NH_3)_2Cl_2]$ and cis$[Pt(NH_3)_2Cl_4]$, were capable of inducing filamentous growth in the absence of any electric field. Hence, the birth of the first anti cancer drug opened a new field involving bioinorganic chemistry and cancer chemotherapy. The drug marketed as Platinol with the generic name cisplatin, received FDA approval in 1979 and is today one of the leading anticancer agents[7]. It is a coordination compound that consists of a platinum ion centrally bound to two ammine groups and two chloride ions. These ligands are arranged in a square planar geometry. Platinum in cisplatin typically exists in the +2 oxidation state. The ammine groups serve as carrier ligands, while the chloride ions function as leaving groups, which is critical for the compound's biological activity. The ability of these leaving groups to dissociate is essential for cisplatin's mechanism of action[8].

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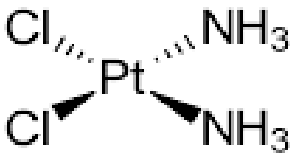

Figure 1: Chemical structure of Cisplatin

2.2. DNA binding of Cis-platin:

Cisplatin exerts its anticancer activity primarily by targeting DNA and disrupting critical cellular processes. It works by cross linking of DNA, thus stopping both DNA replication and transcription by halting the replication of genome and production of proteins. Cisplatin is capable of binding to its preferred nitrogenous bases which are adenine and guanine which are both purine bases out of all the nitrogenous bases present in the DNA(**Fig 2**) except for uracil which is present in RNA strand only. The activated form of cisplatin binds to DNA, forming covalent bonds primarily at the N7 position of purine bases such as guanine and adenine. The most common bindings are in between adjacent guanines (GpG) or guanine and adenine (ApG) within the same strand, between guanine bases on opposite DNA strands and Single binding to a guanine base without cross linking[9].

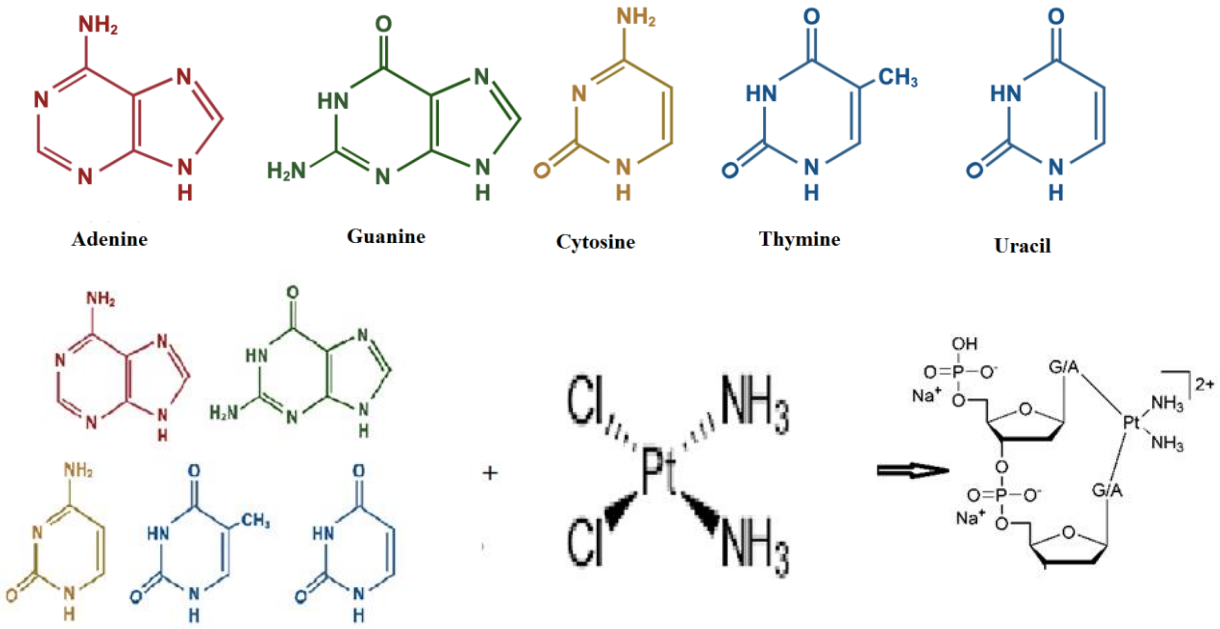

Figure 2 : Cis platin binding with different nitrogenous bases purine and pyrimidine

Cisplatin induced DNA adducts cause significant structural distortion in the DNA double helix also. These distortions interfere with essential processes, such as DNA replication and transcription. These defects cause the bending and unwinding of the double helix and loss of function[10]. This DNA damage activates cellular DNA damage recognition and repair pathways nucleotide excision repair (NER). Several proteins can recognize the DNA bending induced by specific cisplatin adducts. Cisplatin activates the tumor suppressor protein p53, which regulates the expression of pro-apoptotic genes. It induced DNA damage disrupts mitochondrial function, leading to the release of cytochrome c and activation of caspase-dependent apoptosis. Again, it increases reactive oxygen species (ROS), contributing to oxidative stress and cell death. The three most important families of DNA repair proteins are nucleotide excision repair (NER), mismatch repair (MMR), and DNA dependent protein kinase (DNA-PK) proteins. They play crucial roles in maintaining genomic integrity by repairing different types of DNA damage[11].

The NER repairs bulky DNA lesions, such as those caused by UV-induced thymine dimers and DNA adducts formed by cisplatin. The major steps of NER are

(a) Damage Recognition: Proteins like XPC (xeroderma pigmentosum C) recognize Recognition of the DNA lesion of Cisplatin.

(b) Helix unwinding: TFIIH complex helicases (XPB and XPD) unwind the damaged DNA region.

(c) Dual Incision: Incision is made on both the sides of the lesion so that the part of the DNA with the lesion is removed leaving behind an empty space.

(d) Repair Synthesis: DNA polymerases fill the gap, and DNA ligase seals it to restore the DNA to its original form.

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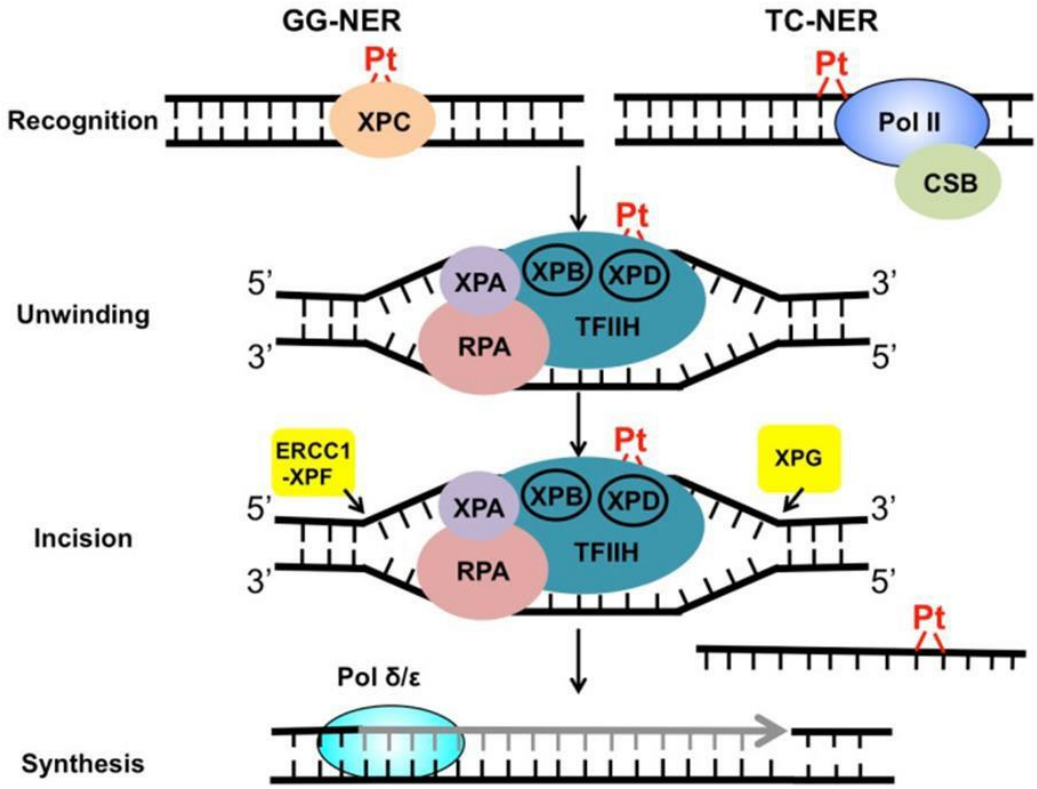

Figure 3 : Cis platin induced DNA damage and binding

Mismatch Repair (MMR) Proteins recognize and bind to cisplatin induced adducts, signaling apoptosis when repair fails. Defects in MMR proteins (e.g., MLH1 or MSH2 loss) often lead to cisplatin resistance in cancer cells. It is associated with the process like recognition of single and small insertion detection loops, coordination downstream process, and removal of the enormous DNA segment. On the other hand, DNA-PK proteins play an indirect role in repairing DNA breaks generated as secondary damage following replication fork collapse due to cisplatin adducts. It binds to DNA ends and recruits DNA-PKcs which activates repair proteins and aligns broken DNA ends and finally artemis, DNA ligase IV, XRCC4, and XLF complete the repair. Treatment with cisplatin often induces a robust DNA damage response (DDR), resulting in cell cycle arrest and, when the damage is irreparable results apoptosis[12].

2.3. Activation of Apoptosis in Response to Cisplatin-Induced DNA Damage:

The activation of apoptosis following DNA damage caused by cisplatin is orchestrated through a series of molecular events. These involve damage detection by kinase enzymes, stabilization of tumor suppressor protein p53, and downstream transcriptional activation of apoptotic genes. DNA damage, such as intra-strand cross-links caused by cisplatin, is recognized by sensor proteins, which recruit and activate the kinase enzymes ATM (Ataxia Telangiectasia Mutated) and ATR (Ataxia Telangiectasia Rad3-related)[13]. When p53 protein is produced, it is immediately bound to mouse double minute (MDM2) which feeds the entire protein into the proteasome where it gets destroyed into small fragments. This regulation keeps p53 levels low in the absence of stress or DNA damage. Again, Phosphorylation disrupts the interaction between p53 and MDM2, preventing its ubiquitination and subsequent degradation. The stabilized p53 acts as a transcription factor to activate pro-apoptotic genes, leading to mitochondrial dysfunction, caspase activation, and apoptosis. The efficiency of this process depends on the affinity of gene promoter regions for transcriptional machinery, which determines the level of apoptotic protein synthesis. These pathways ensure the elimination of damaged cells, preventing tumor progression and maintaining genomic stability. In order to increase the expression of downstream genes, four p53s comes to the promoter region and binds to it and increases the production of the expression of genes. Also, when DNA damage is detected, DNA repair mechanisms are activated and as a result cell cycle inhibitors are also produced because naturally if a cell is damaged, the body will readily try to get rid of it by introducing cell cycle inhibitors and stop the cancerous cell from amplifying itself[14]. If p53 levels remain high for a long time even after repeated cisplatin dosage, that means new. Intra-strand cross-links are continuously being formed without actually reaching the targeted cell. The DNA damage remains for a long time and the cell would just not get repaired. Therefore, the last option that remains is suicide of the cell called 'apoptosis' of the cell by automatically triggering proapoptotic factors[15].

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2.4. Administration and development of Cis platin:

Cisplatin is administered intravenously as part of a carefully monitored regimen, ensuring its effective delivery and minimizing toxic side effects. It is typically given as an intravenous (IV) infusion in saline or glucose solution to maintain stability and solubility. Hydration protocols are crucial to reduce nephrotoxicity. Pre- and post-treatment hydration with saline is used to promote urine flow and flush the kidneys. The dosage depends on the cancer type, stage, and combination with other therapies[16]. A typical dose ranges from 50-100 mg/m² per cycle, administered every 3-4 weeks. The main side effects of cisplatin are found in nephrotoxicity, neurotoxicity, ototoxicity, nausea, and vomiting symptoms. Various modifications of cisplatin have been investigated to obtain a drug with a better toxicity profile and a wider therapeutic spectrum than cisplatin. New platinum drugs have been developed to reduce toxic side effects and overcome cancer cell resistance[17]. The second-generation platinum drug carboplatin was introduced into cancer treatment in 1989 in the treatment of ovarian cancer. Replacing the chloride groups of cisplatin with the cyclobutane carboxylate ligand of carboplatin (pictured below) provides good water solubility and better stability and results in fewer side effects. Oxaliplatin has a different carrier, diaminocyclohexane (DACH), which has less cross resistance and a more favorable toxicity profile. Platinum (IV) complexes are less reactive in mediator substitution reactions than their platinum (II) analogues, their toxicity is reduced and a smaller part of the drug is deactivated on the way to the target cell[18]. Platinum (IV) complexes are in the spotlight and have been tested in various cancer cell lines. Recently synthesized platinum (IV) complexes have been tested for their cytotoxic activity against various cell lines, and some of them have shown activity similar to cisplatin against human ovarian, breast, and colon cancer cell lines[19]. Platinum drugs resistance can also be circumvented by improved delivery of the drug to tumor tissue. This can be achieved by linking platinum-based drug to a water soluble, biocompatible co-polymer[20].

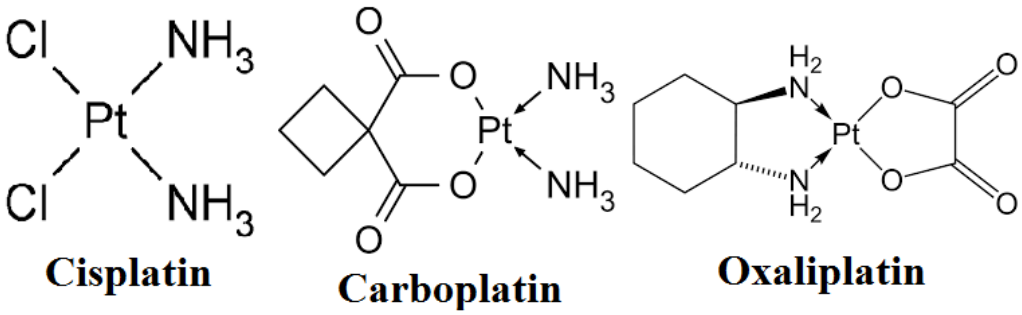

Figure 4 : Different platinum based Anticancer drug.

3. Conclusion:

Platinum based drugs such as cisplatin, carboplatin, and oxaliplatin have become key components in modern chemotherapy due to their efficacy in treating a wide range of cancers. These drugs function primarily by forming DNA adducts, which disrupt DNA replication and transcription, ultimately inducing apoptosis (programmed cell death) in cancer cells. Despite their shared mechanisms of action, these drugs differ in their clinical applications, toxicity profiles, and effectiveness. Cisplatin is the prototype of platinum-based drugs and has shown significant success in treating testicular, ovarian, bladder, and lung cancers. However, its clinical use is often limited by severe side effects, including nephrotoxicity (kidney damage), ototoxicity (hearing loss), and neurotoxicity. Advances in supportive care have helped mitigate some of these toxicities, but they remain a concern.

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Conflict of Interest

The author declares no conflict of interest.

Declaration

This manuscript has not been published in another publication and is not under simultaneous consideration by any other journal.

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