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Cisplatin In Cancer Therapy: Pharmacology, Toxicity, And Nanotechnology Based Enhancements

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Abstract:
Cisplatin (cis-diamminedichloroplatinum(II)) is a platinum-based chemotherapy cornerstone used since the 1970s for testicular, ovarian, bladder, head & neck, lung and other solid tumours. Its clinical utility is limited by dose-limiting toxicities (notably nephrotoxicity, ototoxicity and neurotoxicity) and by the frequent development of tumour resistance. This review summarises cisplatin's chemistry and pharmacology, molecular mechanism of action, main toxicities and mechanisms of resistance, and recent strategies — including combination therapies and drug-delivery/nanotechnology approaches — aimed at improving therapeutic index and overcoming resistance.

1. Introduction and historical note:

Cisplatin, a neutral platinum (II) complex, was recognized for anticancer activity in the 1960s–70s and rapidly became a foundational cytotoxic agent after dramatic activity in testicular cancer was demonstrated. It remains widely used — often in combination regimens — despite the advent of targeted therapies and immunotherapy because of its broad-spectrum cytotoxicity and predictable synergy with radiation.

Cancer is one of the most important health problems in the world and 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 normal mechanism of 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 tumor [2].

According to 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) [274], [275]. 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 [276], targeted therapy [277], hormone therapy [278], gene therapy [279] and photodynamic therapy [280]. Surgery is the process of removing cancer by doing operation and it is generally used only when cancer is localized [281]. Radiation therapy uses high doses of radiation to shrink or kill cancer cells [282]. 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 [3], [4], [5].

2. Chemistry and pharmacokinetics:

Cisplatin (chemical formula: $Pt(NH_3)_2Cl_2$) is activated intracellularly: aquation (replacement of chloride ligands by water) generates electrophilic species that react with nucleophilic sites on DNA and proteins. It is administered intravenously; distribution is extensive, binding quickly to plasma proteins. Renal excretion is the primary elimination route, which underpins its renal toxicity risk.

1. Absorption

Cisplatin is not absorbed orally because it is unstable in the gastrointestinal tract.
Therefore, it is administered intravenously (IV infusion).
After IV administration, it rapidly distributes from plasma into tissues and binds to proteins.

2. Distribution

Plasma protein binding: Very high (≈ 90%), mainly to albumin and other sulfur-containing proteins.
Volume of distribution: Moderate; cisplatin distributes widely into:
kidneys (highest accumulation)
liver
ovaries and testes
inner ear (leading to ototoxicity)

3. Metabolism (Biotransformation)

Cisplatin undergoes non-enzymatic metabolic activation, not enzymatic metabolism.
In low-chloride intracellular environments, it undergoes aquation:
chloride ligands replaced by water
forms positively charged, reactive platinum complexes
These reactive species bind to:
DNA (forming crosslinks)
proteins
glutathione and other thiol-containing molecules
Because of extensive binding, most circulating platinum becomes irreversibly protein-bound, prolonging terminal half-life.

4. Excretion

Primary route: Renal (glomerular filtration + tubular secretion).
20–40% of the dose is excreted unchanged in urine within 24 hours.
The drug accumulates in renal proximal tubules, contributing to nephrotoxicity.
Clearance declines with renal impairment → dose adjustments are required.

5. Half-life

Cisplatin displays multi-compartment kinetics:

Phase	Half-life	Notes
α-phase	20–30 minutes	Initial rapid distribution
β-phase	1–4 hours	Intermediate elimination
γ (terminal) phase	Up to 5 days	Due to irreversible protein binding

The extremely long terminal half-life reflects slow release of platinum from tissues and proteins.

6. Factors Affecting Pharmacokinetics

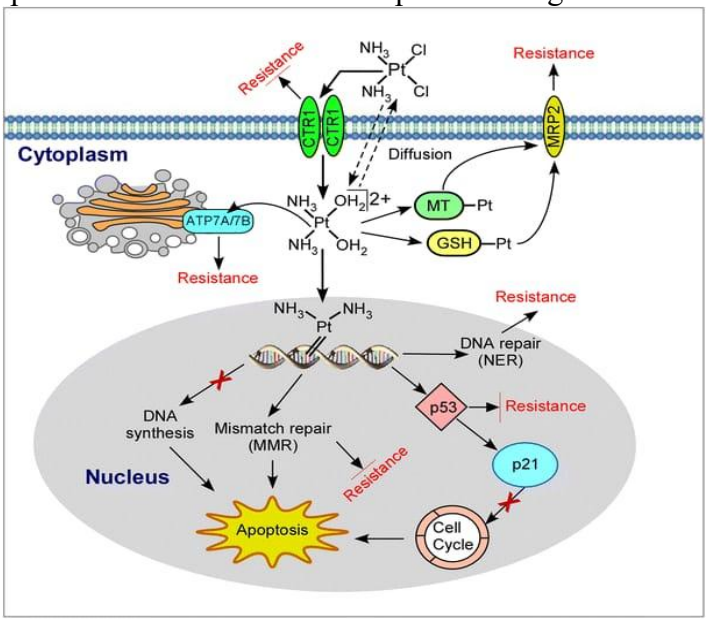
Renal function: Decreased GFR increases toxicity and prolongs elimination.
Hydration status: Adequate IV hydration enhances clearance and reduces nephrotoxicity.
Co-administered nephrotoxic drugs: Aminoglycosides, NSAIDs may worsen renal clearance.
Age: Elderly patients show reduced **clearance.**
Genetic factors: Variants in transporters (e.g., OCT2, CTR1) influence uptake and toxicity.

7. Clinical Implications

Because of renal excretion, dose adjustments are essential in renal impairment.
High protein binding means drug–drug interactions are minimal, but toxicity is prolonged.
Hydration protocols (1–2 L saline pre- and post-dose) are critical to reduce kidney damage.
Monitoring of serum creatinine, electrolytes (Mg^{2+}, K^{+}), and urine output is required.

3. Mechanism of anticancer action:

The principal cytotoxic event is formation of platinum–DNA adducts (intra- and interstrand crosslinks), which distort DNA, inhibit replication and transcription, and trigger DNA damage response pathways leading to apoptosis if damage is irreparable. Cisplatin also induces mitochondrial dysfunction, reactive oxygen species (ROS) generation and can modulate immune responses in the tumour microenvironment. 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-kinase1;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

4. Treatment of cisplatin:

Cisplatin is used as a first-line chemotherapeutic agent for several solid tumors. Treatment usually follows specific regimens depending on cancer type.

Major Clinical Uses

Testicular cancer – BEP regimen (Bleomycin + Etoposide + Cisplatin)

Ovarian cancer – Cisplatin + Paclitaxel

Bladder cancer – GC regimen (Gemcitabine + Cisplatin)

Head & neck cancers – Cisplatin + radiotherapy

Lung cancer (NSCLC & SCLC) – Cisplatin + Etoposide / Pemetrexed

Dose (general ranges)

50–100 mg/m² every 3–4 weeks

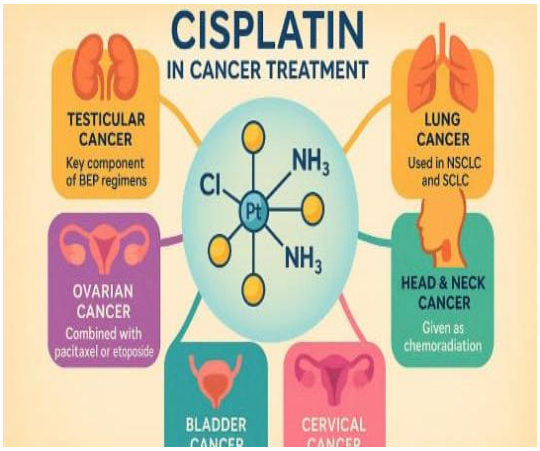
or

20–40 mg/m² weekly (e.g., during radiotherapy)

Supportive measures during treatment

Vigorous IV hydration

Antiemetics (to prevent nausea)
Regular monitoring of:
Kidney function
Electrolytes (Mg^{2+}, K^{+})
Hearing and nerves



5. Clinical indications and dosing principles:
Cisplatin is used alone or in combination regimens for testicular, ovarian, bladder, head & neck, cervical, non-small cell lung, and other cancers. Doses and schedules vary by regimen (common single doses range from 50–100 mg/m² per cycle), and hydration/diuresis protocols are routinely applied to reduce nephrotoxicity. The drug is frequently combined with agents such as 5-FU, paclitaxel, gemcitabine, or etoposide depending on tumour type and line of therapy.

6. Major toxicities and management:
Nephrotoxicity: The dose-limiting toxicity. Cisplatin accumulates in proximal tubular cells causing DNA damage, oxidative stress, mitochondrial injury and inflammation — producing acute kidney injury and possible chronic impairment. Aggressive pre- and post-hydration (saline), mannitol diuresis in some protocols, and monitoring of renal function are standard preventive measures.
Ototoxicity: Sensorineural hearing loss, particularly high-frequency, more common in children and with cumulative dosing. Baseline audiometry and follow-up are recommended.
Peripheral neuropathy: A dose-dependent sensory neuropathy can be persistent.
Other effects: Nausea/vomiting (antemetic prophylaxis required), myelosuppression (less than some agents), electrolyte disturbances (hypomagnesemia), and hypersensitivity reactions on re-exposure.

7. Mechanisms of resistance:
Resistance to cisplatin is multifactorial and may be intrinsic or acquired. Key mechanisms include:

1. Reduced intracellular drug accumulation — downregulation of uptake transporters (e.g., CTR1) and/or upregulation of efflux pumps (e.g., ATP7A/B).
2. Detoxification/inactivation — increased intracellular thiols (glutathione) and metallothioneins that sequester platinum.
3. Enhanced DNA repair — upregulation of nucleotide excision repair (NER), homologous recombination (HR) and other repair pathways that remove platinum–DNA adducts.
4. Altered apoptosis signaling / survival pathway activation — changes in p53, BCL-2 family, PI3K/AKT, and other pathways.
5. Metabolic and epigenetic rewiring — changes in metabolism (e.g., shift to OXPHOS) and epigenetic modifications that support survival.

8. Challenges and Future Directions:
1. Better biomarkers: Multi-omics studies highlight potential biomarkers (e.g., m6A methylation, metabolic signatures) for predicting cisplatin resistance and response.
2. Renoprotection: While antioxidants, natural products, SGLT2 inhibitors, and organoid-based screening are promising, more clinical trials are needed to validate safety and efficacy in cancer patients.
3. Nanotechnology translation: Though liposomal and magnetoliposome approaches are promising in preclinical models, scaling these to safe and effective clinical-grade systems remains a challenge.
4. Personalized therapy: Integrating patient-specific data (genetics, transporter expression, DNA repair capacity) could help tailor cisplatin dosing or choose alternative regimens.

5. Toxicity in special populations: Long-term
nephrotoxicity (especially in pediatric cancer survivors) needs more systematic tracking and intervention protocols.

9. Strategies to overcome resistance and improve therapeutic index:
Combination therapies: Pairing cisplatin with DNA repair inhibitors (e.g., PARP inhibitors), targeted agents, or immunotherapy can produce synthetic lethality or restore sensitivity in some settings. Recent clinical and preclinical data support combinations (e.g., PARP + platinum) in BRCA-mutant and some BRCA-like tumours.

Drug delivery and nanotechnology: Liposomal and nanoparticle formulations, tumour-targeted carriers, and prodrug strategies aim to increase tumour delivery while reducing off-target accumulation (kidney/inner ear). Nano-approaches also enable co-delivery of modulators that reverse resistance. Emerging reviews show promising preclinical results and several translational efforts.

Renoprotective strategies: Agents and interventions that reduce renal uptake or attenuate oxidative/inflammatory injury (e.g., amifostine in selected protocols, experimental antioxidants, transporter modulators) are under study; hydration remains primary standard of care.

Biomarker-guided therapy: Predictive biomarkers (e.g., DNA repair deficiency, transporter expression, specific mutational profiles) are being evaluated to select patients likelier to benefit or to guide combination approaches. Evidence is evolving.

10. Recent advances and research directions (2022–2025 highlights):
Increased mechanistic understanding of nephrotoxicity and identification of signalling pathways that may be druggable to protect kidney cells.
Growth in epigenetic and metabolic studies revealing new resistance axes (and candidate targets) in lung, ovarian and other tumours.
Rapid expansion of nanomedicine strategies specifically designed to overcome the four canonical resistance mechanisms with encouraging preclinical results and early translational programmes.

11. Practical considerations for clinicians and researchers:
Maintain careful dose calculations and renal monitoring; aggressive hydration protocols should be enforced.

Consider tumour histology, prior platinum exposure, molecular markers (BRCA/HRD status) and performance status when selecting cisplatin vs carboplatin or alternative agents.

In research, integrate biomarkers of DNA repair and transporter expression into trial design; explore combinations that target identified resistance mechanisms.

12. Conclusions:

Cisplatin remains a powerful anticancer agent with well-characterised mechanisms of action and toxicity. The major clinical challenges—nephrotoxicity and tumour resistance—are active areas of basic and translational research. Advances in combination strategies, targeted inhibitors of repair pathways, and delivery systems (notably nanotherapeutics) offer realistic routes to improve efficacy and safety. Continued biomarker-driven clinical trials are essential to personalize platinum-based therapy and to extend the therapeutic lifetime of cisplatin.

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