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Cisplatin: Antitumor Pharmacodynamic Profiles, Clinical Utility and Nanoformulation Design

Yuhui Tian

The Affiliated High School of Peking University, Beijing, China
tianyuhui2028@i.pkuschool.edu.cn

Abstract. Cisplatin is a first-line platinum-based chemotherapeutic agent that is widely implemented for the clinical management of diverse solid tumors, ranging from testicular and ovarian carcinoma to bladder and lung cancers. Nevertheless, its therapeutic benefits are substantially hampered by dose-limiting adverse effects such as nephrotoxicity and irreversible ototoxicity, as well as frequent intrinsic and acquired tumor multidrug resistance that greatly reduces treatment response. This article first outlines the core physicochemical and pharmacological features of cisplatin and further elaborates on the molecular mechanisms underlying cisplatin-related toxic injuries and multifaceted tumor resistance, including impaired drug uptake via cation transporters, enhanced intracellular detoxification, abnormal DNA damage repair, and the immunosuppressive tumor microenvironment. Moreover, it systematically summarizes recent research advances in formulation optimization and diverse nanovehicle delivery strategies, ranging from platinum(IV) prodrugs, passive- and active-targeted nanocarriers to stimulus-responsive and synergistic co-delivery platforms that can simultaneously load cisplatin and functional adjuvants. Finally, this review explores major translational obstacles in practical clinical application and puts forward prospective future research directions for cisplatin-based antitumor therapy.

Keywords: cisplatin, formulation optimization, tumor drug resistance

1. Introduction

Malignant solid tumors represent one of the leading causes of disease-related mortality worldwide, imposing an enormous socioeconomic burden on global public-health systems. Systemic chemotherapy occupies an irreplaceable position in comprehensive anti-tumor treatment regimens, serving as the mainstay for neoadjuvant therapy, adjuvant therapy, and palliative systemic intervention for inoperable metastatic malignancies. Among diverse chemotherapeutic families, platinum-based agents stand out for their broad-spectrum anti-tumor activity. Since Barnett Rosenberg uncovered the anti-cancer property of cis-diamminedichloroplatinum(II), commonly known as cisplatin, in the 1960s, this small-molecule platinum compound has revolutionized the clinical management of multiple solid malignancies [1]. After obtaining United States Food and Drug Administration approval for testicular cancer in 1978, cisplatin-based therapeutic regimens were rapidly extended to ovarian carcinoma, bladder cancer, non-small-cell and small-cell lung

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cancer, head-and-neck squamous cell carcinoma, and other tumor types [1]. For testicular germ cell tumors, the classic BEP (bleomycin, etoposide, cisplatin) combination chemotherapy achieves cure rates higher than 90 %, and the five-year overall survival can exceed 95 %, representing one of the most successful curative chemotherapy paradigms for solid tumors [1]. Even with the rapid blossoming of targeted therapies, immune checkpoint blockade and adoptive cell therapies over the past decade, cisplatin still cannot be substituted in routine clinical oncology; a large proportion of solid-tumor therapeutic schemes still take cisplatin as the core backbone [2].

Nevertheless, the real-world clinical application of cisplatin is severely restricted by two intractable clinical barriers: dose-limiting organ toxicities and pervasive intrinsic as well as acquired multidrug resistance [3]. Clinically, cisplatin must be administrated by slow intravenous infusion diluted with normal saline over 0.5-2 h. High-chloride saline environment prevents premature intracellular aquation and hydrolysis of cisplatin, preserving the drug's pharmacological activity before entering tumor cells. Owing to its special physicochemical and pharmacokinetic characteristics, cisplatin displays uneven tissue distribution after systemic infusion. It accumulates preferentially within renal proximal tubular epithelial cells via organic cation transporter 2 (OCT2), which renders kidney the primary vulnerable organ for cisplatin-induced injury [4]. Apart from nephrotoxicity, cisplatin also enters inner-ear hair cells through cation transporters. These sensory hair cells possess very limited DNA-repair capacity, so repeated cycles of cisplatin treatment will trigger irreversible sensorineural ototoxicity manifested as high-frequency hearing loss and tinnitus, which occurs more frequently among younger patients [4]. Peripheral neuropathy, myelosuppression, gastrointestinal adverse reactions and rare cardiotoxicity or hepatotoxicity further complicate clinical safety management. To avoid life-threatening cumulative organ damage, clinical cumulative cisplatin dosage is strictly confined within 180-200 mg/m² [2]. Such rigid dose ceiling directly limits the maximal anti-tumor effect that can be achieved, even for cisplatin-sensitive tumors.

Besides toxicity, drug resistance constitutes another major obstacle. More than 60 % of patients receiving cisplatin-based neoadjuvant chemotherapy will eventually develop varying degrees of cisplatin resistance [5]. Tumors can exhibit primary intrinsic resistance from the very beginning of treatment, or acquire secondary resistance after repeated drug exposure. Cisplatin resistance is not generated by a single isolated event; instead, it arises from the interplay of pre-target, on-target, post-target and off-target resistance mechanisms [6]. These mechanisms comprise reduced drug uptake caused by CTR1 transporter down-regulation, intracellular drug detoxification mediated by glutathione and metallothionein, enhanced drug efflux driven by ABC-family transporters, overactivated DNA-damage-repair pathways, dysregulated apoptotic signaling, ferroptosis resistance, as well as the remodeling of the immunosuppressive tumor immune microenvironment [4]. Notably, the tumor immune microenvironment, populated by TAMs, MDSCs, CAFs and regulatory immune cells, can independently foster cisplatin refractoriness, which means merely elevating local platinum concentration cannot eliminate resistant tumor subpopulations [2]. Clinical oncologists have tried to overcome this dilemma by combining cisplatin with other cytotoxic chemotherapeutics, molecular-targeted agents or immune-checkpoint inhibitors. Though some combinatorial regimens yield improved objective response rates, they also bring extra overlapping toxicities, and a considerable fraction of patients still fail to achieve durable therapeutic benefit.

Nanotechnology-based drug-delivery systems have emerged as a promising alternative strategy to break the above-mentioned therapeutic bottlenecks [6]. A rich variety of nano-platforms have been designed for cisplatin formulation optimization, including platinum(IV) prodrugs, passive-targeted liposomes and polymeric micelles, ligand-modified active-targeted nanocarriers,

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tumor-microenvironment-stimulus-responsive intelligent nanoparticles, and multi-payload synergistic co-delivery nanovehicles [6]. These nanomedicines are expected to boost tumor-specific drug accumulation via the EPR effect or receptor-mediated endocytosis, lower systemic off-target toxicities, and simultaneously deliver cisplatin together with DNA-repair inhibitors, glutathione depleting agents, ferroptosis inducers or immunomodulators to counteract multiple interwoven resistance pathways at the same time [6].

Unfortunately, numerous unresolved translational hurdles still prevent these pre-clinical nanoplatforms from stepping into routine clinical practice. Most reported cisplatin nanoformulations are only validated in cell-culture models and small-animal tumor models. Many studies focus merely on one or two individual resistance pathways, while ignoring the complex crosstalk between intracellular molecular alterations and the tumor immune microenvironment [6]. For co-delivery systems, it remains challenging to precisely tune the mass ratio of different cargos inside nanocarriers and harmonize their pharmacokinetic and pharmacodynamic profiles. Improper carrier design may trigger premature drug leakage or defective intracellular payload release, which will abolish the anticipated synergistic anti-tumor potency. Moreover, batch-to-batch reproducibility during large-scale manufacturing, long-term formulation stability, tumor heterogeneity-associated targeting efficiency decay and potential immunogenic risks further impede clinical transformation [6]. Up to now, only a handful of cisplatin-loaded liposomal formulations have advanced into phase II or phase III clinical trials, and very few have obtained wide clinical approval.

2. Physicochemical properties and pharmacokinetics of cisplatin

2.1. Structural and physicochemical characteristics

Cisplatin is a typical platinum alkylating agent. The molecule has a square planar configuration, with a central platinum ion coordinated to two chlorine atoms and two primary amino groups. Cisplatin also has a molecular weight of 301.1 g/mol and is highly hydrophilic, with an octanol-water partition coefficient of only -2.19 in log Kow. However, its water solubility is not very high, with a solubility of about 2.53 g/L in water at 25 °C. Other basic physical and chemical parameters are its density 3.74 g/cm³, melting point about 270 °C [4].

Additionally, In terms of appearance, cisplatin at room temperature is a white to yellow-orange crystalline powder. In conventional storage environments, cisplatin is chemically stable, but if stored for too long, molecules will slowly undergo isomerization, forming ineffective trans-platinum, which directly reduce the drug efficacy [4].

2.2. Absorption, distribution, metabolism, and excretion

Clinically, cisplatin is administered slowly by intravenous infusion, with an infusion time controlled in about 0.5–2 hours. The drug solution is diluted with saline before administration. A relatively high concentration of chloride ions in the system can inhibit premature hydrolysis and inactivation of cisplatin, which prevents the drug from losing efficacy before entering cells. When using the commonly used 1-hour infusion regimen clinically, the dosage is 80–100 mg/m², with a peak plasma drug concentration of about 4.8 μg/mL after administration [4].

After intravenous administration, cisplatin will spread to various tissues throughout the body, with most significant accumulation in the kidneys and liver. Most internal organs, reproductive tissues, and muscle levels of the drug are also high, but cisplatin has difficulty entering brain tissue, resulting in very low levels of drug accumulation in the brain. Usually, over 90% of cisplatin enters

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the bloodstream and binds in an irreversible way with plasma proteins such as albumin, γ-globulin, and transferrin. The resulting platinum-protein complex can remain in the human body for a long time, with a half-life exceeding 5 days, causing persistent accumulation of platinum in the body [4].

Inside the kidney, glutathione S-transferase can mediate the binding of cisplatin to glutathione; this complex is further metabolized by γ-glutamyltransferase, cysteine S-conjugated β-lyase, ultimately producing highly nephrotoxic metabolites [4].

When cisplatin successfully enters the tumor cells, it undergoes hydrolysis in the cytoplasmic environment: coordinated chloride ions are replaced by water molecules, finally forming highly reactive charged intermediates.

Cisplatin can be released quite slowly from tissues, which has been clinically confirmed: platinum residues can still be detected in patients' serum for 20 years after chemotherapy, indicating that platinum remains in the body for a long time. To be more specific, the terminal elimination half-life of total platinum can reach 5 days or even longer. However, the half-life of free, unbound platinum is only 1.32 hours.

Platinum is mainly excreted through urine, and its excretion process is divided into two types, with half-lives of 160 days and 720 days, respectively. These two half-lives reflect the gradual release of platinum from rapidly and slowly renewing tissues precisely [4]. Table 1 summarizes the key physicochemical and pharmacokinetic parameters of cisplatin, including its molecular weight, solubility, plasma peak concentration, protein binding rate and elimination half-life.

Table 1. Key physicochemical and pharmacokinetic parameters of cisplatin [6]

Property	Value	Number format
Molar mass (g/mol)	301.1	
Plasma Cmax (μg/mL)	4.82	[7]
Elimination half-life (h)	24	[8]
Elimination clearance (L/h)	0.68	[9]
Volume of distribution (L)	20	[10]
Water solubility (mg/L)	2530	[11]
logP	-2.21	[12]
Oral bioavailability	Not absorbed	[13]
Plasma protein binding (%)	>90	[14]
Excretion (%)	>90% urine, 25% during first 24 h	[15]
Unbound Pt Plasma Cmax (μg/mL)	0.87	[16]
Unbound Pt elimination half-life (h)	1.32	[17]
Unbound Pt volume of distribution (L)	70	[18]
Bound Pt elimination half-life (h)	50	[19]

2.3. Pharmacokinetic limitations and their impact on clinical efficacy and toxicity

The therapeutic index of cisplatin is extremely narrow. Clinically, the cumulative dose of cisplatin is strictly limited to 180–200 mg/m², as higher cumulative doses can significantly increase the incidence of severe dose-limiting toxicities, especially nephrotoxicity and ototoxicity [3]. Additionally, the kidneys are the primary organs for the excretion of cisplatin and also the main target organs for toxicity. The susceptibility of renal tubules is due to the selective accumulation of

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the drug: Organic cation transporter 2 (OCT2/SLC22A2) is specifically expressed on the basolateral membrane of the proximal renal tubules, leading to intracellular cisplatin levels that are five times higher than those in the circulating serum. Moreover, the uptake mediated by OCT2 is crucial for nephrotoxicity, as shown by the protective effect observed in mice with OCT1/2 gene knockout [4]. Population pharmacokinetic studies have determined that body surface area (BSA) is an important covariate affecting the clearance rate and volume of distribution of cisplatin. More precisely, creatinine clearance rate (CrCl) influences the clearance rate of cisplatin, while age and BSA affect the volume of distribution. Serum protein levels regulate the conversion of free platinum to bound platinum [4]. These pharmacokinetic parameters are highly related to endpoints of nephrotoxicity, including maximum serum creatinine level, blood urea nitrogen (BUN), and minimum creatinine clearance rate [4].

3. Core antitumor mechanisms of cisplatin

3.1. DNA crosslinking and replication blockade

The antitumor potency of cisplatin is principally derived from its capacity to induce irreversible DNA damage, which blocks tumor genomic replication and transcriptional progression. There are two main ways in which cisplatin enters cells: one is through active transport mediated by copper transporter 1, and the other is passive diffusion. After the drug enters the cell, the chloride ions that are bound to it are replaced by water molecules, resulting in highly electrophilic active intermediates. These active species can form covalent bonds with the N7 position of purine bases in DNA. The main product of this process is 1,2-intralinker; among these situations, the d(GpG) crosslinking product accounts for approximately 65% of all complexes, while the d(ApG) product accounts for about 25%. The proportion of 1,3-intralinker d(GpXpG) is relatively low, at only 5–10%. In addition, a small amount of interlinker crosslinks are also formed [1].

Such covalent DNA adducts distort the double-helix structure via local bending and unwinding, thereby severely hindering the progression of replicative DNA polymerases. Even a single intrastrand crosslink reduces polymerase elongation efficiency to approximately 10% [Cisplatin in the era of PARP inhibitors and immunotherapy]. Given their reliance on persistent genomic replication for uncontrolled proliferation, malignant cells are selectively vulnerable to cisplatin-induced DNA damage. However, cells can employ translesion synthesis (TLS) polymerases to bypass cisplatin adducts, albeit with low fidelity, introduce mutation that contribute to acquired chemoresistance. Characteristic mutational signatures (SBS31 and SBS35) associated with platinum therapy include C>T, C>A, and T>A substitutions [Cisplatin in the era of PARP inhibitors and immunotherapy].

3.2. Induction of Apoptosis and programmed cell death

Programmed cell death is a genetically controlled, active "cell-suicide" process, and apoptosis is its main form. Unlike necrosis—passive cell death caused by physical damage or poison that makes cells burst and triggers inflammation—apoptosis makes cells shrink, condense their DNA, and form small membrane-wrapped apoptotic bodies. These bodies are engulfed by surrounding cells without releasing cell contents, so no inflammation occurs.

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3.2.1. Intrinsic apoptotic pathway

Cisplatin-induced DNA damage activates p53, which transcriptionally upregulates pro-apoptotic genes, including PUMA (p53 upregulated modulator of apoptosis), Bax, Noxa, and PIDD (p53-induced protein with a death domain). Bax translocates to mitochondria, promoting cytochrome c release into the cytosol. Once at the outer mitochondrial membrane, Bax oligomerizes to form membrane pores that trigger mitochondrial outer membrane permeabilization (MOMP), allowing cytochrome c stored in the mitochondrial intermembrane space to leak out. Cytochrome c binds APAF-1 to form the apoptosome, activating procaspase-9, which can turn on executioner caspases (caspase-3 and -7), leading to DNA fragmentation and cell dismantling. These activated executioner caspases cleave key nuclear and cytoskeletal cellular substrates; they trigger chromatin breakdown and produce characteristic fragmented DNA, and also drive cell morphological changes such as cell shrinkage and membrane blebbing typical of apoptosis [1].

3.2.2. Extrinsic apoptotic pathway

Cisplatin increases cell-surface expression of Fas (cell-surface death receptor). The interaction between Fas and Fas ligand (FasL) recruits Fas-associated death-domain protein (FADD) and pro-cysteine-aspartic protease-8 (procaspase-8), which subsequently activate downstream pro-cysteine-aspartic protease-3 (caspase-3). Cisplatin can also trigger endoplasmic reticulum stress as well as nucleus-independent apoptotic signaling to reach the goal of suppressing cancer pain [1].

3.2.3. Mitogen-activated protein kinase signaling

Cisplatin activates multiple MAPK (mitogen-activated protein kinase) pathways—ERK (extracellular signal-regulated kinase) phosphorylates p53, stabilizing the p53 protein by preventing its rapid degradation, upregulating p21 and GADD45 and GADD45 (growth-arrest and DNA-damage-inducible gene 45); JNK (c-Jun N-terminal kinase) binds and activates p73 to enhance pro-apoptotic transcription; p38 MAPK, through p18, stimulates PUMA (p53-up-regulated modulator of apoptosis) and NOXA (damage-responsive protein) transcription [1].

3.2.4. Alternative regulated cell death modalities

Beyond canonical apoptosis, cisplatin elicits multiple regulated cell death modalities, including ferroptosis driven by GSH (glutathione) exhaustion and lipid peroxidation, RIP1 (receptor-interacting protein kinase 1)/RIP3 (receptor-interacting protein kinase 3)/MLKL (mixed-lineage kinase domain-like protein)-dependent necroptosis, and NLRP3 (NOD-like receptor pyrin domain-containing protein 3) inflammasome-mediated pyroptosis. These alternative death pathways dualistically mediate antitumor efficacy and normal tissue toxicity [3].

3.3. Oxidative stress and inflammatory modulation as adjuvant mechanisms

The way in which cisplatin controls the dosage and duration of treatment induces the production of reactive oxygen species (ROS) within cells; these ROS mainly consist of superoxide anions and hydroxyl radicals. Mitochondria are the primary source of ROS, as cisplatin targets mitochondrial DNA (mtDNA) preferentially. However, due to the lack of an efficient repair system for mitochondrial DNA, this process can lead to mitochondrial dysfunction, impaired calcium uptake, membrane depolarization, and reduced ATP synthesis [1].

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The cancer genes within tumor cells are activated, and combined with the reprogramming of cellular metabolism, the total level of oxidative stress is significantly higher than that in normal cells. It is this characteristic that makes the tumor cells more susceptible to additional oxidative damage. Cisplatin can bind to intracellular glutathione, continuously depleting the cell's glutathione reserves, thereby further exacerbating oxidative damage in the cells [6].

Regarding inflammation, cisplatin regulates the tumor immune microenvironment by promoting M1 polarization of tumor-associated macrophages (TAMs), enhancing the infiltration and activation of cytotoxic T lymphocytes (CTLs), and inducing the differentiation of myeloid-derived suppressor cells (MDSCs) into dendritic cells (DCs). Cisplatin can also trigger immunogenic cell death mechanisms (ICD), releasing damage-associated molecular patterns (DAMPs). These DAMPs recruit and activate DCs, and through the cGAS-STING pathway, they stimulate the production of type I interferons, thereby achieving a suppressing effect on tumors [6]. Notably, cisplatin-triggered immunogenic cell death is dose-dependent; excessively high drug concentrations may directly kill immune cells and suppress antitumor immunity.

3.4. Inhibition of tumor invasion, metastasis, and angiogenesis

Cisplatin restricts tumor cell invasion and metastasis through multimolecular regulatory pathways. It reverses epithelial-mesenchymal transition (EMT) by increasing E-cadherin expression and inhibiting mesenchymal markers such as perforin, snail, and slug. Meanwhile, cisplatin also downregulates hypoxia-inducible factor-1α (HIF-1α) and its downstream target vascular endothelial growth factor (VEGF), suppressing tumor-associated angiogenesis. Additionally, cisplatin can trigger apoptosis of vascular endothelial cells, promote vascular normalization, and further inhibit tumor progression. Although cisplatin is highly effective, multiple studies still indicate that cisplatin may cause compensatory upregulation of angiogenesis factor in certain pathological contexts [1].

3.5. Enhanced radio sensitivity

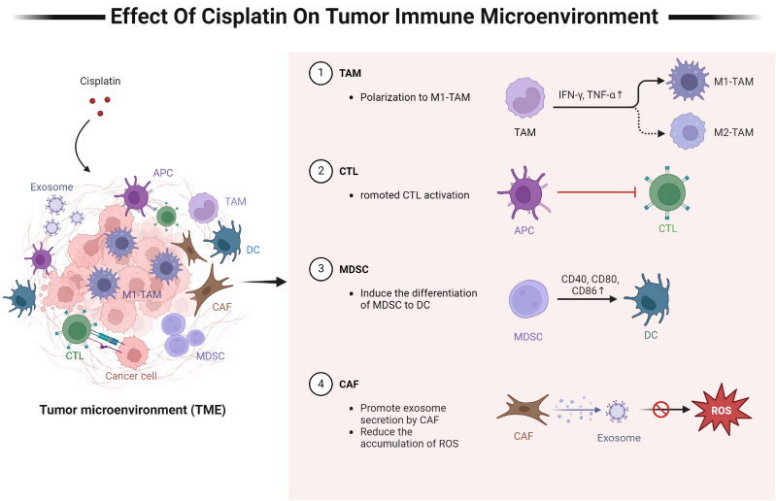


Figure 1. Overview of cisplatinmediated regulation of tumourassociated macrophages, cytotoxic Tlymphocytes, myeloidderived suppressor cells and cancerassociated fibroblasts within the tumour immune microenvironment [3]

Cisplatin usually functions as a potent radiosensitizer; it interferes with the cell's DNA damage repair mechanisms, thereby amplifying the genomic damage caused by radiation. Moreover, the

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complex formed between cisplatin and DNA disrupts the repair process of radiation-induced DNA damage, lead to the accumulation of lethal double-strand break. Inhibiting the nucleotide excision repair (NER) mechanism, especially by interfering with the function of ERCC1–XPF, can work synergistically with ionizing radiation, resulting in better therapeutic effects [1]. The regulatory effects of cisplatin on the tumour immune microenvironment are summarized in Figure 1.

4. Clinical application, dosing regimens, and adverse effects

4.1. Major clinical indications and combination chemotherapy regimens

Cisplatin is the core chemotherapy drug for treating various solid tumors. In 1978, the U.S. Food and Drug Administration officially approved cisplatin for the treatment of testicular cancer. Since then, the cisplatin-based BEP combination chemotherapy regimen has greatly improved treatment outcomes for testicular cancer, with cure rates exceeding 90% and five-year survival rates exceeding 95% [1]. Here are some typical cancers that can be treated with cisplatin.

First, for ovarian cancer, tumor cytoreductive surgery is generally performed first, followed by a platinum-based combined paclitaxel regimen for chemotherapy. The vast majority of ovarian cancer patients (about 90%) show significant efficacy when initially receiving platinum drug therapy, but over 70% experience relapse due to tumor resistance. To improve resistance, cisplatin is often combined with chemotherapy drugs such as paclitaxel and docetaxel, or combined with erlotinib for treatment [1].

Second, in lung cancer, cisplatin combined with etoposide is the first-line chemotherapy regimen for small cell lung cancer. For stage II and III non-small cell lung cancer, cisplatin-based adjuvant chemotherapy is often chosen clinically. LACE meta-analysis results show that this treatment strategy can improve patients' 5-year survival rate by 5.3% [3].

Additionally, for locally advanced head and neck squamous cell carcinoma, the standard regimen is simultaneous cisplatin radiotherapy. Cisplatin alone has limited efficacy; clinically, it is often combined with methotrexate, vincristine, doxorubicin, gemcitabine, and other drugs for comprehensive treatment [3].

Since the late 1980s, cisplatin combination regimens have become the standard adjuvant chemotherapy for bladder cancer, but the objective response rate is only about 35%, and overall efficacy remains limited [3]. The molecular target and downstream biological effects of cisplatin are summarized in Table 2.

4.2. Administration routes, dose principles and clinical practice

Cisplatin is given intravenously over 0.5–2 hours in normal saline. Common clinical dosing strategies vary by tumor type and treatment cycle, including daily administration of 20 mg/m² for 5 consecutive days, weekly infusion of 25–50 mg/m² over 3–6 weeks, or high-dose intermittent therapy of 50–100 mg/m² every 3–4 weeks. Hyperthermic intraperitoneal chemotherapy (HIPEC) is used for peritoneal metastases, offering high local drug concentrations with reduced systemic absorption [4-20].

To avoid severe toxicity, the conventional cumulative dose is limited to approximately 180–200 mg/m², and hydration with saline must be performed. Additionally, body surface area (BSA) and creatinine clearance rate (CrCl) are important covariates that affect the clearance of cisplatin. In general, magnesium supplements are used to reduce nephhrotoxicity [1]. To detect toxicity promptly, close monitoring of renal function (serum creatinine, blood urea nitrogen, estimated glomerular

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filtration rate), serum electrolytes (magnesium, potassium), hematological parameters, and hearing tests is necessary during treatment [1]. The common toxicities induced by cisplatin, along with their underlying mechanisms, clinical manifestations and prevalence, are summarized in Table 2.

Table 2. Common toxicities triggered by cisplatin: underlying causes, clinical manifestations and approximate prevalence [4]

Toxicity	Cause	Manifestation	Approximate Prevalence (%)	References
Gastrointestinal toxicity	Gastrointestinal damage activates VC	Nausea/ vomiting	Low-dose: 40/16 High-dose:69/30	[21]
Nephrotoxicity	Cisplatin-specific transporters (i.e., OCT2)result in high renal levels of cisplatin	Acute kidney injury	33	[22-24]
Neurotoxicity	Cisplatin accumulation innervous system causesdamage in peripheral sensory nerves	Neuropathy	42	[25, 26]
Ototoxicity	Cisplatin accumulation innervous system causesdamage in outer hair cellsof the organ of Corti	Loss of hearing, tinnitus. ear pain	36	[26, 27]
Cardiotoxicity	Cisplatin-induced degeneration and necrosis of cardiac muscle fiber cells	Arrhythmias, congestive heart failure, myocardial ischemia, myocarditis	Rare (<5%)	[28, 29]
Hepatotoxicity	Cisplatin-specific transporters (i.e., OCT1) result in high hepatic levels of cisplatin	Serum enzyme (i.e., AST) elevations	Rare (<5%)	[30]

Notes: AST, aspartate aminotransferase; VC, vomiting center

4.3. Primary dose-limiting toxicity and injury mechanisms

Even under standard dosing schemes, cisplatin harms healthy organs and sets strict upper limits for clinical dosage. Nephrotoxicity stands out as its most-studied adverse effect. Organic cation transporter 2 (OCT2) accumulates cisplatin inside renal proximal tubular cells, generating far higher intracellular drug concentrations than seen in circulating blood [4]. Within these cells, cisplatin induces DNA breaks and excess reactive oxygen species, triggering multiple forms of programmed cell death and gradually impairing renal tubular function. Some patients experience permanent drops in glomerular filtration after repeated treatment cycles.

4.3.1. Sensorineural hearing

Sensorineural hearing loss is another largely irreversible complication. Inner-ear hair cells also take up cisplatin via cation transporters, yet they possess limited DNA-repair capacity. Cumulative DNA damage induced by cisplatin cannot be efficiently eliminated in these cells. Repeated chemotherapy

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cycles can destroy these sensory cells, causing high-frequency hearing loss, which occurs more frequently in younger patients [4].

4.3.2. Other symptoms

Clinicians also commonly observe gastrointestinal reactions, bone marrow suppression, and peripheral neuropathy. Nausea and vomiting arise from mucosal oxidative stress and inflammatory signalling. Myelosuppression lowers peripheral blood cell counts and raises infection risk. Cumulative drug exposure can trigger peripheral nerve damage, producing hand-foot numbness and tingling; sensory symptoms may not fully resolve after therapy ends [3].

4.4. Clinical issues and mechanisms of tumor multidrug resistance

Drug resistance remains one major clinical barrier limiting cisplatin outcomes. Many tumours respond well at first, but gradually escape chemotherapy pressure; roughly over 60 % of patients receiving neoadjuvant cisplatin-based regimens develop some level of resistance [5].

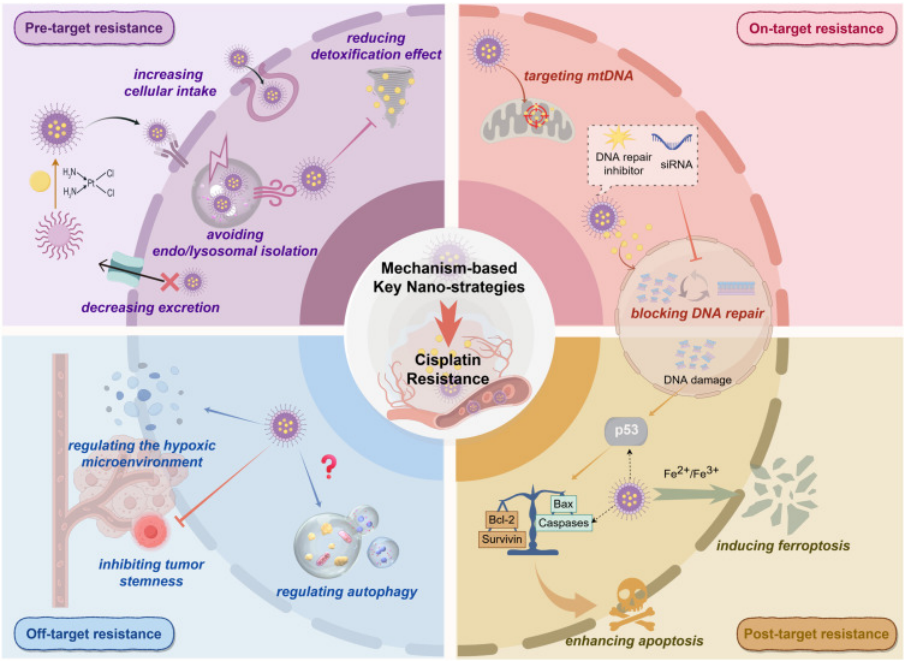


Figure 2. Mechanism-based nanomedicine strategies to overcome four categories of cisplatin resistance [4]

Researchers generally sort resistance mechanisms into four groups: pre-target, on-target, post-target, and off-target resistance. Pre-target resistance happens before cisplatin reaches DNA: tumour cells downregulate uptake transporters such as CTR1, boost glutathione, metallothionein-mediated drug detoxification, or pump platinum out through ABC efflux transporters [4]. The four categories of cisplatin resistance and corresponding nanomedicine strategies are summarized in Figure 2.

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5. Formulation optimization and administration-system improvement for cisplatin

5.1. Clinical issues and mechanisms of tumor multidrug resistance

Early improvements focused on excipient selection and infusion conditions. Physiological saline infusion uses high-chloride surroundings to slow premature cisplatin aquation in circulation [8]. Thiol-containing additives were once tested to neutralize reactive platinum species. However, they also weakened antitumor activity and never entered routine clinical use [4].

Platinum(IV) prodrugs represent another classic modification. They stay inert in blood and only get activated under reductive conditions inside tumour cells. Still, poor solubility and inconsistent in-vivo activation limit most Pt(IV) candidates to preclinical investigation [4].

5.2. Passive targeted nano-delivery systems

The mechanism by which passive targeted nanoparticles work is based on the high permeability and retention effect (EPR effect) that is characteristic of solid tumors. The blood vessel permeability within tumor tissue increases abnormally, allowing nanoparticles with appropriate size to further seep out of the blood vessels and accumulate in the tumor area. Liposomes and polymeric micelles are typical examples of passive target nanocarriers. Take the cisplatin formulation encapsulated in liposomes as an example: these nanocarriers prolong the duration of the drug's circulation within the body and reduce the peak concentration of free platinum ions in the plasma, thereby minimizing the nephrotoxic effect caused by cisplatin. Most of these nanoparticles enter tumor cells through endocytosis. This process does not rely on the CTR1 transport protein. Thus, it can circumvent the drug uptake obstacles caused by abnormal CTR1 pathways in some resistant tumors, thereby increasing the efficiency with which tumor cells absorb the drug [4].

Nevertheless, there are several significant differences in the EPR effect between different types of tumors and individual patients. To be more specific, in some cases, there is dense tumor stroma, which often prevents nanoparticles from penetrating deeply into the tumor, resulting in the ineffective functioning of the EPR effect of these nanoparticles [4].

5.3. Active targeted modification delivery system

To address the instability associated with passive targeting, researchers have attached ligand-binding receptors for tumor cells to the surface of nanoparticles. Additionally, the hyaluronic acid can target CD44; this receptor is over-expressed in many solid tumors and cancer stem cells. Other test ligands include RGD peptide, single-chain antibody fragment that targets the epidermal growth factor receptor (EGFR), and LHRH analog—all of which can also target CD44. The interaction between ligands and receptors promotes receptor-mediated endocytosis, finally enhancing the targeted selectivity for tumors.

However, some practical challenges remain: protein adsorption in blood may mask the surface ligands, and the production of modified nanoparticles involve greater complexity, which can significantly reduce endocytosis and further diminish the targeted selectivity for tumors [4].

5.4. Environmental-responsive intelligent formulation

Since 2020, stimulus-responsive nanocarriers have attracted extensive research attention. These particles remain stable in the bloodstream; they release cisplatin only when tumor-specific microenvironment signals are detected. This greatly improves the precision of drug delivery and

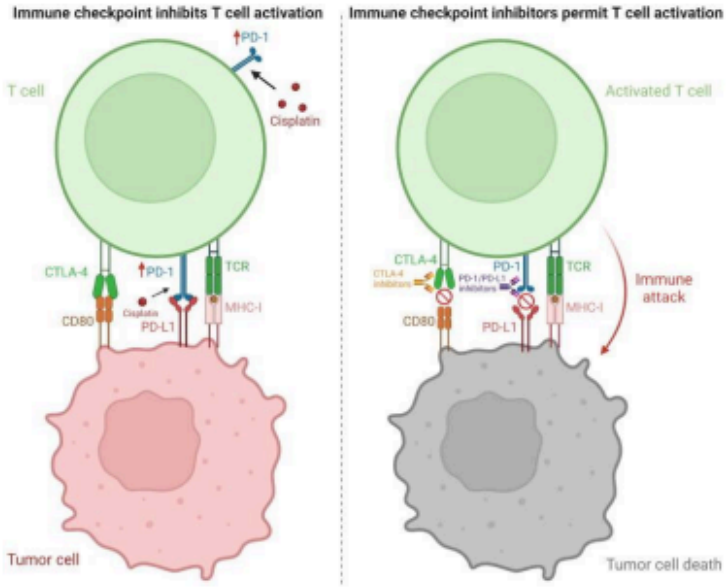
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reduces the risk of cisplatin damaging normal organs [4]. Common triggers include the weakly acidic environment outside tumor cells, high levels of glutathione within cells, and near-infrared light from the external environment. Formulations using triphenylphosphine groups that target mitochondria can deliver the platinum to mitochondrial DNA, to avoid resistance mechanisms based on nuclear repair [4].

However, most intelligent platforms are still limited in the level of laboratory research. Adjusting appropriate response thresholds and dealing with the variability of the patient's tumor microenvironment remain significant challenges that need to be addressed [4].

5.5. Co-delivery synergistic formulations against drug resistance

Nanoparticles that carry cisplatin alone can only improve the tumor-specific accumulation of the drug. However, it is difficult to address the multiple and interconnected resistance mechanisms related to cisplatin in tumors simultaneously [4]. Tumor resistance is not driven by a single mechanism; drug detoxification processes, DNA damage repair mechanisms, and immunosuppressive environments can all contribute to helping tumors evade the effects of platinum-based drugs. Simply increasing the local concentration of cisplatin without addressing these protective mechanisms still fails to completely decrease the survival number of resistant tumors. In light of this reality, researchers have developed co-delivery systems in which cisplatin is combined with another functional payload within the same carrier [4].



(a) Immune checkpoint inhibitors inhibit T cell activation (b) Immune checkpoint inhibitors permit T cell activation

Figure 3. The diagram of cisplatin modulating immune checkpoint signaling to regulate T-cell anti-tumor immunity [6]

The active components in these co-delivered systems can be chosen based on the specific points of resistance: they may include inhibitors that block DNA damage repair, molecules that counteract the detoxification process by consuming intracellular glutathione, substances that induce iron death, or immunomodulators that help restore an immunosuppressive environment. This allows for the

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simultaneous disruption of tumor resistance mechanisms from various angles [3, 4]. The regulatory process of cisplatin combined with immune checkpoint inhibitors for T-cell anti-tumor immunity is illustrated in Figure 3.

6. Research limitations and bottlenecks for commercial drug development

6.1. Challenges for large-scale production and formulation stability

Many laboratory-scale nanocarriers encounter numerous difficulties during large-scale production processes. Minor changes in temperature, mixingg rate, or the quality of raw materials can lead to variations in particle size, drug loading, and surface properties [4]. For example, some certain nanofluids may accumulate or leak their pharmaceutical component during storage, resulting in a significant decrease in efficacy. However, when freeze-drying technology can improve stability in some extent, but it can also increases production costs accordingly [4].

6.2. Limitations of targeted therapy and complexity of drug-resistance mechanisms

Even after being modified with ligands, the nanoparticles still accumulate in large amounts in the liver and spleen, rather than in the tumor sites . The heterogeneity within tumors leads to differences in receptor expression and the microenvironment, which prevents the nanoparticles from targeting all malignant subclones. This method would reduce the accuracy of drug delivery and may even harm other normal organs. Resistance to cisplatin involves multiple factors, such as cellular, matrix, and the immune microenvironments; those factors may provide opportunities for tumor cells to evade the treatment. However, most current nanotechnological approaches only interfere with one or two resistance pathways, also leaving room for tumor cells to escape [4].

7. Conclusion

Nanoparticles containing only cisplatin can only improve the accumulation of the drug in tumor tissues; they are unable to overcome the multiple resistance pathways that are intertwined within the tumor cells. Tumors develop resistance through various mechanisms, such as drug detoxification, DNA repair, and an immunosuppressive microenvironment. Simply increasing the local concentration of platinum-based drugs is not sufficient to eliminate resistant tumor cells.

To address this challenge, researchers have already developed co-delivery nanocarriers that can encapsulate cisplatin along with other functional components. There are many types of functional components that can combine, such as DNA repair inhibitors, glutathione depleters, iron death inducers, and immunomodulators. These substances can balance the elimination of tumor resistance through multiple pathways.

Although cellular and animal experiments have demonstrated promising synergistic therapeutic effects, this technology still faces practical challenges. For the desired combined therapeutic effect to be achieved, both active substances need to reach the tumor site simultaneously and be released there. Therefore, it is necessary to carefully regulate the ratio of these two substances in the carrier and coordinate their pharmacokinetic properties. If the carrier design is not correct, the drugs may leak out prematurely or not release in a proper way inside the cell, finally reducing the synergistic anti-tumor effect.

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References

[1] Li, G., Che, X., Wang, S., Liu, D., Xie, D., Jiang, B., Zheng, X., & Wu, G. (2025). The role of cisplatin in modulating the tumor microenvironment and its combination therapy strategies: A new approach to enhance anti-tumor efficacy. *Annals of Medicine, 57*(1), 2447403. https://doi.org/10.1080/07853890.2024.2447403

[2] Dasari, S., & Tchounwou, P. B. (2014). Cisplatin in cancer therapy: Molecular mechanisms of action. *European Journal of Pharmacology, 740*, 364–378. https://doi.org/10.1016/j.ejphar.2014.07.025

[3] Cecati, M., Pozzi, V., Pompei, V., Schiavoni, V., Fumarola, S., Romagnoli, A., Tossetta, G., Montana, A., Polizzi, A., Sartini, D., & Campagna, R. (2026). Cisplatin as a xenobiotic agent: Molecular mechanisms of actions and clinical applications in oncology. *Journal of Xenobiotics, 8*(16), 1-9. https://doi.org/10.3390/jox16010009

[4] Gao, J., Navai, N., Alhalabi, O., et al. (2020). Neoadjuvant PD-L1 plus CTLA-4 blockade in patients with cisplatin-ineligible operable high-risk urothelial carcinoma. *Nature Medicine, 26*(12), 1845–1851. https://doi.org/10.1038/s41591-020-1086-y

[5] Wang, T., Wu, C., Hu, Y., & Zhang, Y. (2023). Stimuli-responsive nanocarrier delivery systems for Pt-based antitumor complexes: A review. *RSC Advances, 13*(24), 16488-16511. https://doi.org/10.1039/d3ra00846e

[6] Lei, S.-Y., Qin, H., Liu, S., & Sheng, J. (2025). Key nano-strategies for cisplatin resistance in advancing anti-cancer therapy. *International Journal of Nanomedicine, 20*, 13255-13292. https://doi.org/10.2147/IJN.S551752

[7] Rajkumar, P., Mathew, B. S., Das, S., Isaiah, R., John, S., Prabha, R., & Fleming, D. H. (2016). Cisplatin concentrations in long and short duration infusion: Implications for the optimal time of radiation delivery. *Journal of Clinical and Diagnostic Research, 10*, XC01–XC04. https://doi.org/10.7860/JCDR/2016/19177.8238

[8] Liston, D. R., & Davis, M. (2017). Clinically relevant concentrations of anticancer drugs: A guide for nonclinical studies. *Clinical Cancer Research, 23*(14), 3489–3498. https://doi.org/10.1158/1078-0432.CCR-16-3083

[9] Ibrahim, M. E., Chang, C., Hu, Y., Hogan, S. L., Mercke, N., Gomez, M., O'Bryant, C. L., Bowles, D. W., George, B., Wen, X., et al. (2019). Pharmacokinetic determinants of cisplatin-induced subclinical kidney injury in oncology patients. *European Journal of Clinical Pharmacology, 75*(1), 51–57. https://doi.org/10.1007/s00228-018-2576-2

[10] Food and Drug Administration. (1978). Cisplatin for injection, for intravenous use. Food and Drug Administration.

[11] Gold, J. M., & Raja, A. (2023). Cisplatin. *StatPearls*, StatPearls Publishing.

[12] Urien, S., & Lokiec, F. (2004). Population pharmacokinetics of total and unbound plasma cisplatin in adult patients. *British Journal of Clinical Pharmacology, 57*(6), 756–763. https://doi.org/10.1111/j.1365-2125.2004.02082.x

[13] Hollis, L. S., Amundsen, A. R., & Stern, E. W. (1989). Chemical and biological properties of a new series of cis-diammineplatinum(II) antitumor agents containing three nitrogen donors: cis-[Pt(NH3)2(N-donor)Cl]$^{+}$. *Journal of Medicinal Chemistry, 32*(1), 128–136. https://doi.org/10.1021/jm00121a020

[14] Wilson, J. J., & Lippard, S. J. (2012). In vitro anticancer activity of cis-diammineplatinum(II) complexes with beta-diketonate leaving group ligands. *Journal of Medicinal Chemistry, 55*(11), 5326–5336. https://doi.org/10.1021/jm300404x

[15] Crom, W. R., Glynn-Barnhart, A. M., Rodman, J. H., Teresi, M. E., Kavanagh, R. E., Christensen, M. L., Relling, M. V., & Evans, W. E. (1987). Pharmacokinetics of anticancer drugs in children. *Clinical Pharmacokinetics, 12*(3), 168–213. https://doi.org/10.2165/00003088-198712030-00002

[16] Murry, D. J. (1997). Comparative clinical pharmacology of cisplatin and carboplatin. *Pharmacotherapy, 17*(5P2), 140S–145S. https://doi.org/10.1002/j.1875-9114.1997.tb03816.x

[17] O'Dwyer, P. J., Stevenson, J. P., & Johnson, S. W. (2000). Clinical pharmacokinetics and administration of established platinum drugs. *Drugs, 59*(Suppl 4), 19–27. https://doi.org/10.2165/00003495-200059004-00003

[18] Chabner, B. A., & Longo, D. L. (2001). *Cancer chemotherapy and biotherapy*. Lippincott Williams & Wilkins.

[19] Repchinsky, C. (Ed.). (2004). *Compendium of pharmaceuticals and specialites*. Canadian Pharmacists Association.

[20] Zhang, Y., Wang, H., Guo, H., Gou, X., Hao, X., Li, J., Deng, H., & Zhang, W. (2026). Transforming cisplatin into targeted photothermal chemotherapeutics through the platinum-phosphate coordination within a hyaluronan nanogel. *Science Advances, 12*(20), eadz7615. https://doi.org/10.1126/sciadv.adz7615

[21] Stinson, J., Chan, K., Lee, J., Chow, R., Cheon, P., Giotis, A., Pasetka, M., Wan, B. A., Chow, E., & DeAngelis, C. (2017). Managing chemotherapy-induced nausea and vomiting in head and neck cancer patients receiving cisplatin chemotherapy with concurrent radiation. *Annals of Palliative Medicine, 6*(Suppl 1), S13–S20. https://doi.org/10.21037/apm.2017.08.05

[22] Aleksunes, L. M., Goedken, M. J., Rockwell, C. E., Thomale, J., Manautou, J. E., & Klaassen, C. D. (2010). Transcriptional regulation of renal cytoprotective genes by Nrf2 and its potential use as a therapeutic target to mitigate cisplatin-induced nephrotoxicity. *The Journal of Pharmacology and Experimental Therapeutics, 335*(1), 2–12. https://doi.org/10.1124/jpet.110.169588

DOI: 10.54254/2753-8818/2027.MB39130

[23] Kamel, K. M., Abd El-Raouf, O. M., Metwally, S. A., Abd El-Latif, H. A., & El-Sayed, M. E. (2014). Hesperidin and rutin, antioxidant citrus flavonoids, attenuate cisplatin-induced nephrotoxicity in rats. *Journal of Biochemical and Molecular Toxicology, 28*(7), 312–319. https://doi.org/10.1002/jbt.21567

[24] Ozkok, A., & Edelstein, C. L. (2014). Pathophysiology of cisplatin-induced acute kidney injury. *BioMed Research International, 2014*, 967826. https://doi.org/10.1155/2014/967826

[25] Seretny, M., Currie, G. L., Sena, E. S., Ramnarine, S., Grant, R., MacLeod, M. R., Colvin, L. A., & Fallon, M. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain, 155*(12), 2461–2470. https://doi.org/10.1016/j.pain.2014.09.020

[26] Aldossary, S. A. (2019). Review on pharmacology of cisplatin: Clinical use, toxicity and mechanism of resistance of cisplatin. *Biomedical and Pharmacology Journal, 12*(1), 7-15. https://doi.org/10.13005/bpj/1608

[27] Chattaraj, A., Syed, M. P., Low, C. A., & Owonikoko, T. K. (2023). Cisplatin-induced ototoxicity: A concise review of the burden, prevention, and interception strategies. *JCO Oncology Practice, 19*(5), 278–283. https://doi.org/10.1200/OP.22.00472

[28] Raja, W., Mir, M. H., Dar, I., Banday, M. A., & Ahmad, I. (2013). Cisplatin induced paroxysmal supraventricular tachycardia. *Indian Journal of Medical and Paediatric Oncology, 34*(4), 330–332. https://doi.org/10.4103/0971-5851.125262

[29] Oun, R., & Rowan, E. G. (2017). Cisplatin induced arrhythmia; electrolyte imbalance or disturbance of the SA node? *European Journal of Pharmacology, 811*, 125–128. https://doi.org/10.1016/j.ejphar.2017.08.020

[30] National Institute of Diabetes and Digestive and Kidney Diseases. (2012). *LiverTox: Clinical and research information on drug-induced liver injury*. https://livertox.nih.gov/