ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 10, Issue – 6, November – 2025, Page No. : 103 – 112

A Study of Organ-Specific Toxicities of Cisplatin and Underlying Molecular Mechanisms

[1]Sanjeyan N, [1]Kokila K, [1]Gunabalan R, [1]Sasindran D

[1]Department of Pharmacy Practice, JKKMMRF's Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Namakkal District, Tamil Nadu, India.

Corresponding Author: Sanjeyan N**,** Assistant Professor, Department of Pharmacy Practice, JKKMMRF's Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Namakkal District, Tamil Nadu, India.

Citation this Article: Sanjeyan N, Kokila K, Gunabalan R, Sasindran D, "A Study of Organ-Specific Toxicities of Cisplatin and Underlying Molecular Mechanisms", IJMSIR - November – 2025, Vol – 10, Issue - 6, P. No. 103 – 112.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Cisplatin is a platinum-based chemotherapeutic agent extensively used in the treatment of various solid malignancies, including cancers of the testis, ovary, bladder, lung, and head and neck. Despite its remarkable therapeutic efficacy, its clinical application is limited by several dose-dependent toxicities that affect multiple organ systems. Ototoxicity manifests as irreversible sensorineural hearing loss caused by the destruction of cochlear hair cells and the stria vascularis, primarily mediated through reactive oxygen species (ROS) and mitochondrial dysfunction. Nephrotoxicity, one of the most significant adverse effects, is characterized by proximal tubular injury, oxidative stress, and inflammatory processes leading to acute kidney injury. Neurotoxicity typically presents as peripheral neuropathy resulting from damage to the dorsal root ganglia, axonal degeneration, and defective neuronal DNA repair. Reproductive toxicity involves gonadal impairment, reduced fertility, and apoptosis of germ cells, often attributed to oxidative stress and DNA cross-linking. Nausea and vomiting are also frequent and distressing side effects that arise from the stimulation of the chemoreceptor trigger zone and serotonin release from enterochromaffin cells in the gastrointestinal tract. A clear understanding of these mechanisms is essential for developing strategies to mitigate toxicity, improve cisplatin-based therapy, and enhance patient quality of life.

Keywords: Cisplatin, Ototoxicity, Nephrotoxicity, Neurotoxicity, Reproductive Toxicity, Nausea, Vomiting, Oxidative Stress, Chemotherapy Side Effects.

Introduction

Platinum-based compounds represent an important class of chemotherapeutic agents used extensively in both pediatric and adult cancer treatment. Their inclusion in therapeutic regimens has significantly improved long-term survival rates in pediatric oncology patients. The primary platinum-based drugs—cisplatin, carboplatin, and oxaliplatin—act by forming covalent bonds with purine bases in DNA, thereby interfering with DNA replication and transcription.

Cisplatin, first discovered by Rosenberg and colleagues in 1965 during studies on bacterial cell division under electric fields, entered clinical use in the early 1970s. Its cytotoxic activity results from the formation of cisplatin–

DNA adducts, particularly at the N7 position of guanine and adenine bases, leading to apoptosis. Following intravenous administration, approximately 90% of cisplatin binds to plasma proteins. It demonstrates high tissue penetration into organs such as the liver, kidneys, testes, and colon but does not cross the blood–brain barrier effectively.

Therapeutic management for cisplatin-induced ototoxicity remains limited. Sodium thiosulfate has been approved by the U.S. FDA to prevent hearing loss in pediatric patients with localized, non-metastatic solid tumors. Other pharmacologic interventions are still under evaluation.

Approximately 90% of administered cisplatin is eliminated via renal excretion through glomerular filtration and tubular secretion, while about 10% is excreted in bile. Roughly 25% of the total dose is eliminated within 24 hours, but platinum–DNA adducts can persist in tissues for years.

Cisplatin is used to treat various pediatric malignancies, including germ cell tumors, hepatoblastoma, medulloblastoma, neuroblastoma, and refractory lymphomas. The major dose-limiting toxicities of cisplatin are nephrotoxicity, neurotoxicity, and ototoxicity, which often necessitate dose reductions. Carboplatin, a structural analogue of cisplatin, is less reactive and causes fewer side effects due to its lower protein-binding capacity and higher renal clearance.

Ototoxicity

Cisplatin is recognized as one of the most ototoxic chemotherapeutic drugs. The incidence of irreversible, bilateral sensorineural hearing loss among patients ranges from 20% to 75%, while 20%–40% may experience persistent tinnitus. The risk of permanent auditory damage increases substantially with cumulative doses exceeding 600 mg/m². Cisplatin exerts antineoplastic effects through covalent binding to DNA, forming intra- and interstrand cross-links that disrupt replication and transcription and induce apoptosis.

The main dose-limiting toxicities of cisplatin include nephrotoxicity, neurotoxicity, and ototoxicity. Although hydration and diuresis help mitigate nephrotoxicity, no approved therapy exists to prevent hearing loss. Ototoxicity draws clinical attention due to its high prevalence and irreversible nature, significantly affecting quality of life. Recent studies have revealed that cisplatin's cytotoxicity results not only from nuclear DNA binding but also from cytoplasmic mechanisms involving the generation of reactive oxygen species (ROS) and nitric oxide (NO), which trigger mitochondrial dysfunction and apoptosis.

Cisplatin binds to nucleophilic sites on purine bases in DNA, forming adducts repaired by the nucleotide excision repair (NER) pathway. The xeroderma pigmentosum proteins XPC and XPA play critical roles in global genome and transcription-coupled NER, respectively. In experimental models, cisplatin exposure leads to nuclear translocation of these proteins in cochlear cells, confirming their involvement in DNA repair.

Structural lesions associated with cisplatin ototoxicity include apoptotic degeneration of outer hair cells in the organ of Corti, demyelination of spiral ganglion neurons, and atrophy of the stria vascularis. Genetic predispositions, such as polymorphisms in detoxification enzyme genes, contribute to interindividual variability in ototoxicity. Cumulative exposure leads to progressive cochlear damage due to oxidative stress overwhelming endogenous antioxidant systems, ultimately activating proinflammatory cytokines and apoptotic signaling pathways.

Nephrotoxicity

Cisplatin-induced nephrotoxicity manifests as a rapid decline in renal function, leading to accumulation of nitrogenous waste products such as urea and creatinine. Acute kidney injury (AKI) is primarily caused by necrosis of tubular epithelial cells, tubular obstruction, and afferent arteriolar vasoconstriction, which decrease the glomerular filtration rate. Despite hydration and diuretic therapy, nephrotoxicity remains a major limitation of cisplatin use.

Cisplatin enters proximal tubular epithelial cells through organic cation transporter 2 (OCT2) and copper transporter 1 (CTR1). Once inside, it triggers oxidative stress, inflammation, and apoptosis. Histone acetylation and deacetylation play key roles in gene regulation during nephrotoxicity. Overexpression of histone deacetylases (HDACs), especially class II, correlates with increased apoptosis, while inhibition of HDACs offers nephroprotection.

Cisplatin causes acute kidney injury in approximately 20–30% of patients. Chronic kidney disease may develop with repeated low-dose regimens due to unresolved tubular injury, vascular rarefaction, and interstitial fibrosis. These chronic effects result in progressive renal dysfunction and kidney atrophy over time.

Neurotoxicity

Neurotoxicity is one of the most significant limitations of cisplatin therapy. Platinum-based chemotherapeutics are essential for treating malignancies such as neuroblastoma and leukemia, but they often lead to peripheral and central nervous system complications. Peripheral neuropathy occurs in nearly 50% of patients, typically presenting as sensory ataxia due to damage to the dorsal root ganglia (DRG). Cognitive dysfunctions, such as memory impairment, may result from hippocampal injury and mitochondrial damage.

Cisplatin-induced apoptosis in neurons involves p53 activation, Bax translocation, cytochrome c release, and caspase-3/9 activation. Elevated reactive oxygen species and calcium dysregulation contribute to neuronal injury. Mitochondrial p53 inhibitors and antioxidants have shown neuroprotective effects in experimental models.

Reproductive Toxicity

Cisplatin therapy is associated with gonadal toxicity, hormonal imbalance, and impaired fertility. Approximately 40% of female patients experience premature ovarian failure. Cisplatin damages ovarian follicles and disrupts the hypothalamic–pituitary–gonadal axis. Male fertility is also affected due to decreased sperm count, motility, and testosterone levels.

Animal studies have shown that mesna co-administration can reduce testicular and ovarian injury. Prolonged exposure leads to reduced mating success and higher fetal loss, indicating cumulative reproductive toxicity.

Nausea And Vomiting

Cisplatin frequently causes chemotherapy-induced nausea and vomiting (CINV), one of the most distressing adverse effects. Acute CINV occurs within 24 hours due to serotonin release from enterochromaffin cells and activation of 5-HT_3 receptors, while delayed CINV (24–120 hours) is mediated by substance P acting on neurokinin-1 (NK1) receptors.

5-HT_3 receptor antagonists such as ondansetron control acute CINV, whereas NK1 antagonists such as aprepitant are effective for delayed CINV. Dopaminergic antagonists like metoclopramide are also used. Herbal extracts and natural compounds (e.g., [6]-gingerol and Bacopa monnieri) have shown potential antiemetic activity comparable to standard drugs.

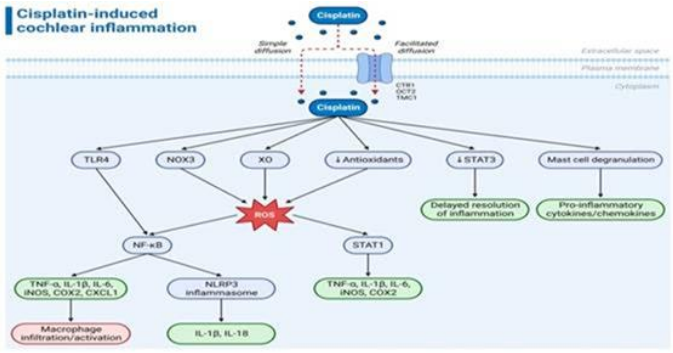

Figure 1: proposed mechanism of cisplatin-induced cochlear inflammation

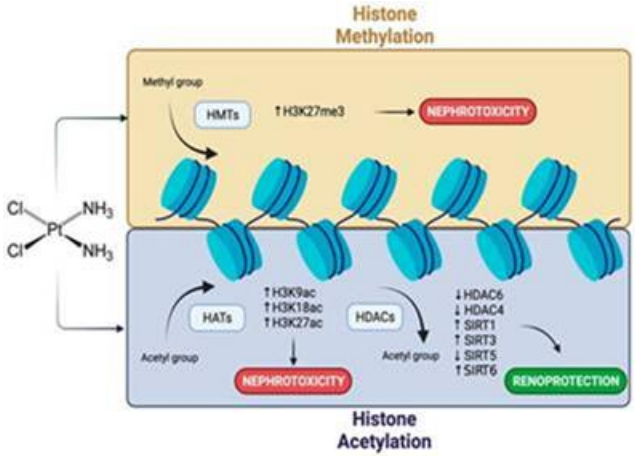

Figure 2: Proposed role of histone modifications in cisplatin-induced nephrotoxicity.

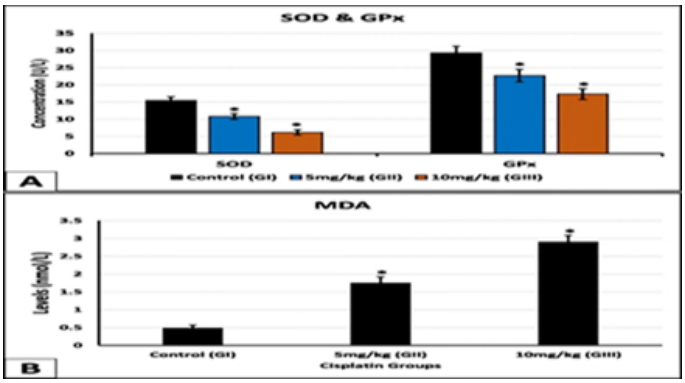

Figure 3: (a) Activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx). (b) Levels of lipid peroxidation and MDA in serum of mice intraperitoneallyinjected with 5 and 10 mg/kg bwcisplatin twice/week for 4 weeks. Data are expressed as mean ± SD. N = 10 mice. *Significant differences at values of $P \leq 0.05$.

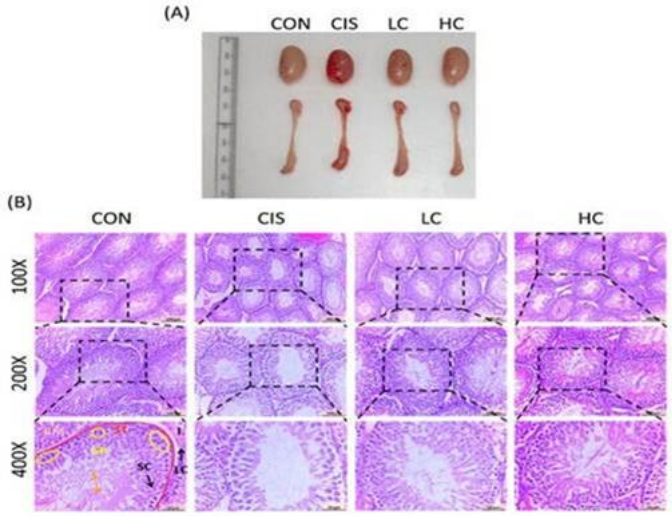

Figure 4: Testicular Histopathology in Cisplatin-Induced Male Rats

Conclusion

Cisplatin remains a cornerstone in cancer chemotherapy but is associated with multiple organ toxicities that limit its use. Understanding the molecular mechanisms underlying ototoxicity, nephrotoxicity, neurotoxicity, reproductive toxicity, and gastrointestinal effects is essential for developing preventive strategies and protective agents. Optimizing therapeutic protocols and identifying biomarkers of toxicity will help improve patient outcomes and quality of life.

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