

# Trends toward amelioration of cisplatin nephrotoxicity

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## Abstract

Cisplatin is an antineoplastic substance extensively administered in chemotherapy of various cancers like ovarian, lung, bladder, breast, head and neck, and testicular malignancies. Conversely, its clinical application was significantly restricted due to unanticipated and very severe nephrotoxicity. Additionally effective cancer chemotherapy with this agent has been further complicated by the lack of information regarding the manner of action and factors responsible for provoking the anticancer activity. Studies regarding the side effects of cisplatin, showed acute and cumulative nephrotoxicity associated with morphological injury, has been detected in both animal and human investigations.

## Introduction

Cisplatin is an antineoplastic substance described in 1965 by Rosenberg et al, who were investigating the impact of electrolysis products from a platinum electrode on growing cells (1-4). Rosenberg et al detected that certain electrolysis results of platinum mesh electrodes were able of preventing cell division in *Escherichia coli* and this produced considerable attention in the probable application of these products in chemotherapy for malignancies. While the documentation of cis-dichlorodiammineplatinum (cisplatin) (Figure 1) as the substance accountable for this activity, considerable interest has been made toward the administration of coordination complexes of platinum, palladium, and other noble metals in the therapy of cancers (2-6).

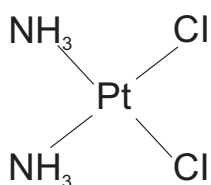
In fact, cisplatin was clinically examined in 1972 by Hill et al, however, despite its suitable antineoplastic activity against lung, bladder, breast, ovarian, head and neck, and also testicular cancers, its clinical administration was promptly restricted according to its unanticipated and sometimes very severe kidney injury (4-8). Acute and cumulative kidney injury accompanying with histological injury has been described in both animal and human investigations. Various hypothesis regarding the pathophysiological mechanisms following this nephrotoxicity have been proposed. While the therapeutic efficiency of cisplatin appears to be related to the administered dose, hence, there

## Core tip

Cisplatin is one of the most potent antineoplastic substance in chemotherapy of various malignancies. Regardless of the high risk for kidney injury, the application of high doses of cisplatin is often desirable due to of the drug's dose-dependent property. The most recent toxicity-modulating modalities to date have been mostly directed against acute cisplatin kidney injury. The renal toxicity is a function of serum peak concentrations, which can be diminished by increasing the hydration, hyperosmolar solutions and appropriate herbal antioxidant.

has been a continuous investigation for pharmacological and biological substances to protect the kidney function and structure, which allow the application of appropriate quantities of this substance to better treatment of malignancies. These modalities consist alteration of administration modes and administration of chemo-protectors (2-7). Furthermore, other platinum analogs with minor nephrotoxicity have been investigated, however these substances have fewer antitumor action than cisplatin or having other inherent toxic effects, which restricting their application (2-7).

It noteworthy that, acceptable cancer chemotherapy with this substance has been further confused by the few information regarding the manner of action and the species accountable for eliciting the anticancer property. Studies sought to



**Figure 1.** Structure of cisplatin.

determine body distribution and renal clearance of cisplatin and also possible bio-transformation of this drug have been hindered by the absence of specific analytical methodologies competent of finding and quantitating cisplatin in complex biological environment (6-9).

The present mini-review comprises a brief discussion of the nature and underlying pathophysiological mechanisms interacting of cisplatin-induced renal damage.

### Materials and Methods

This mini-review article discusses the pathophysiological mechanism responsible for cisplatin nephrotoxicity. For this review, we used a variety of sources by searching through Web of Science, PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was performed using combinations of the following key words and or their equivalents such as cisplatin, nephrotoxicity, herbal drugs, medicinal plants and cancer chemotherapy.

### The pathophysiology of renal morphological injury

Comparable to other kinds of malignancy chemotherapy, the main inconvenience of cisplatin in the therapy of malignancies has been the toxic effects associated with its administration. The side effects of cisplatin is demonstrated in various aspects, the most severe of them consist kidney and gut problems (5-12). Additionally, ophthalmic toxicities (ototoxicities) and allergic reactions to the drug have also been observed (1-4).

Firstly the kidney damage, which happens as tubular injury, was dose limiting. The severity of such nephrotoxicity was enough to preclude the administration of the drug at therapeutic ranges. Nonetheless, various recent investigations established substantial reduction in kidney damage in both animals and human by applying a modality which included sufficient hydration and installation of appropriate diuresis (10-15). Indeed, this modality allowed the continued and expanded application of cisplatin in the therapy of human cancers. Various investigations have stated the administration of appropriate fluid and installation of hydration together with furosemide prior to using of cisplatin (5-13).

Regarding the gastrointestinal problems, presently the primary dose-limiting consideration in the administration of cisplatin is nausea and vomiting. Nausea and vomiting cause substantial patient morbidity. Cisplatin therapy results in oxidant gut damage, which is assumed to be the primary cause of nausea and vomiting (10-18).

Regarding, cisplatin renal toxicity, it has been revealed

to be dose-related in both animals and humans. The primary site of injury is the renal proximal tubular cells. In recent experimental investigation, the major modification was most prominently seen in three days after cisplatin administration (15-20). However, other morphological modifications was also found in the distal parts of the proximal tubule, containing focal loss of brush border and flattening of tubular cells, cellular swelling, condensation of nuclear chromatin, focal necrosis and tubular lumen dilatation. After five days of administration, the predominant findings were tubular necrosis in the distal parts of the proximal segment, directing toward tubular atrophy of cortical nephrons with tubular lumen debris. In summary, the causative mechanisms of cisplatin-induced acute renal damage include kidney inflammation, activation of p53 tumor suppressor protein and tubular apoptosis and necrosis (14-20).

This condition presented widely by dilated tubular lumen, which was lined by many low-lying tubular epithelial cells. These damage aspects are resemble to those reported in experimental models of ischemia-induced acute tubular cell necrosis (15-21).

Importantly signs of tubular cell regeneration of the distal parts of proximal tubules can detectable after several days after cisplatin administration, distinguished by mitosis of tubular cells (20-25).

In clinical investigation, renal injury has been detected at cisplatin doses of 50 mg given without suitable hydration. The morphologic changes of injury are mainly located in the more distal parts of the proximal tubular cells or in the distal nephron segments. Morphological alterations occurring rarely in the glomeruli (12-20).

### Tempering of cisplatin nephrotoxicity

In more recent clinical investigations regarding cisplatin-induced renal injury, only plasma levels of creatinine and/or clearance of creatinine or blood urea nitrogen are applied to assess renal function (12-19). However, the sensitivity of these bounds in identifying early damage of kidney function have been broadly evaluated by various experiments. In fact, in patients with muscular atrophy, serum creatinine has been indicated not to be a suitable indicator of renal function. A better correlation was detected between the clearance of [51Cr]-ethylenediaminetetraacetic acid ([51Cr]-EDTA) and inulin and also the variations in glomerular function alongside with drug administration. Few studies have been conducted to assess proximal tubular cell function (10-19).

### Amelioration of cisplatin nephrotoxicity by antioxidants

Oxidative stress is produced by a rise in reactive oxygen species (ROS) and reactive nitrogen species (RNS) and/or reduction in body antioxidants. Indeed it is assumed that as an imbalance among the level of creation and removal of cell oxidants is responsible of cisplatin nephrotoxicity. This disproportion produces a regression in the capability

of organs in detoxification of the reactive intermediate substances or inability to repair which results to tissue damage (2-9).

A large number of natural products, chemical substances and dietary nutrients have been postulated as potential renoprotective substances. In fact, recently various cisplatin protective agents have been suggested in experimental and clinical investigations in an effort to improve cisplatin-induced renal toxicity (1-7).

Dietary supplements, mostly antioxidants, are largely administered not only by the population at large for healthiness promotion but also by persons diagnosed with cancer (2-9). Antioxidants are able to detoxifying free radicals or inactivating the free radicals' intermediates produced by anti-neoplastic agents. Furthermore, preclinical studies have detected that various antioxidant substances, like flavonoids, are capable to augment the cytotoxic action of the chemotherapeutic substances without injuring normal cells (20-28). The flavonoids that frequently found in fruits and vegetables has been detected to induce cell death in human head and neck squamous cell carcinoma cells in vitro and synergistically augments the anti-proliferative property of cisplatin in these cells (25-30). Significantly, the synergistic efficacies induced by flavonoids appeared due to the potentiation of cisplatin-induced apoptosis in malignant cells (20-29).

Medicinal plants which have a lot of phytochemicals with antioxidant efficacies have been currently in the focus of studies for therapy or prevention of numerous oxidative stress-related complications (20-28). These herbal drugs have antioxidant properties due to phytochemicals consisting phenolic and carotenoid compounds and can diminish the risk of acute or chronic renal disease (19-29). Medicinal plants antioxidants are sources of endogenous antioxidants capacity to keep kidney injury by decrease of lipid peroxidation (LPO). Thus, they are hopeful treatments for diminution of cisplatin renal toxicity (25-31).

## Conclusion

Cisplatin is one of the most potent antineoplastic substance in chemotherapy of various malignancies. Regardless of the high risk for kidney injury, the application of high doses of cisplatin is often desirable due to of the drug's dose-dependent property. The most recent toxicity-modulating modalities to date have been mostly directed against acute cisplatin kidney toxicity. The renal toxicity is a function of serum peak concentrations, which can be diminished by increasing the hydration, hyperosmolar solutions and appropriate herbal antioxidant (26-31).

## Author's contribution

HN was the single author of the paper.

## Conflicts of interest

The author declared no competing interests.

## Ethical considerations

Ethical issues (including plagiarism, data fabrication, double

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