

## Cisplatin-induced renal toxicity: A short review

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**Abstract:** Cisplatin is an antineoplastic agent widely used in chemotherapy of ovarian, lung, bladder, breast, head and neck, and testicular cancers. However, its clinical use was rapidly limited due to unexpected and very severe renal toxicity and effective cancer chemotherapy with this agent has been further complicated by the lack of information concerning the mode of action and the species responsible for eliciting the anticancer activity. In this regard, acute and cumulative renal toxicity associated with histological damage has been shown in both animal and human studies. The present review includes a brief discussion of the nature and underlying mechanism of cisplatin-induced nephrotoxicity.

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### 1. Introduction

Cisplatin is an antineoplastic agent developed in 1965 by Rosenberg et al. who were studying the effects of electrolysis products from a platinum electrode on growing cells(1-10). Rosenberg et al. observed that certain electrolysis products of platinum mesh electrodes were capable of inhibiting cell division in *Escherichia coli* and this created much interest in the possible use of these products in cancer chemotherapy. Since the identification of cis-dichlorodiammineplatinum (cisplatin) as the agent responsible for this activity, much interest has been generated in the use of coordination complexes of platinum, palladium, and other noble metals in the treatment of cancer(1, 11-22).

Cisplatin was clinically tested in 1972 by Hill et al. In spite of its good antineoplastic activity against ovarian, lung, bladder, breast, head and neck, and testicular cancer, its clinical use was rapidly limited due to unexpected and very severe renal toxicity (23-35). Acute and cumulative renal toxicity associated with histological damage has been shown in both animal and human studies. Several theories concerning the pathophysiological mechanism behind this toxicity have been suggested. Since the therapeutic efficacy of cisplatin seems to be proportional to the delivered dose, there has been a continuous search for biological and pharmacological strategies to protect the renal function and thus permit the administration of high quantities of the drug; these strategies include modification of administration modes, development of new galenic forms, and the use of chemoprotectors, among others

(36-50) Additionally, other platinum analogs with less nephrotoxicity have been studied, but these agents have less antitumor activity than cisplatin or have other inherent toxicities restricting their use(51-62).

It should be noted that, effective cancer chemotherapy with this agent has been further complicated by the lack of information concerning the mode of action and the species responsible for eliciting the anticancer activity. Studies aimed at determining the distribution and clearance of cisplatin as well as possible biotransformations of this agent have been hampered by the lack of specific analytical methodologies capable of detecting and quantitating cisplatin in complex biological media (60-69).

The present review includes a brief discussion of the nature and underlying mechanism of cisplatin-induced nephrotoxicity.

### 1.2. Histological damage and pathophysiology

Similar to other types of cancer chemotherapy, the primary disadvantage of cisplatin in the treatment of cancer has been the toxic reactions associated with its use. The toxicity of cisplatin is manifested in various forms, the most severe of which include renal and gastrointestinal problems (1, 30-68). Ophthalmic toxicities (Ototoxicities) and allergic reactions have also been noted(1-6).

Initially the renal toxicity, which appears as tubular necrosis, was dose limiting. The severity of such renal toxicity was sufficient to preclude the use of the drug at therapeutic levels. However, some studies demonstrated substantial reduction in renal

toxicity in both animals and men by utilizing protocol which included prehydration and mannitol-induced diuresis (70-79). It was the development of this dosage regimen that allowed the continued and expanded use of cisplatin in the treatment of human cancers. Other studies have reported the use of prehydration together with furosemide prior to administration of cisplatin but the results obtained were not as satisfactory as those obtained with mannitol. Presently the primary dose-limiting consideration in the use of cisplatin is nausea and vomiting (1,50-87).

Cisplatin induced nephrotoxicity has been shown to be dose-related in both animals and humans. The principal site of damage is the proximal tubule. In studies on rats, pathological alterations were most prominent 3 days after cisplatin injection(88-106). A range of morphological changes were present in the distal parts of the proximal tubule, including focal loss of brush border, cellular swelling, condensation of nuclear chromatin, and focal necrosis. After 5 days, the predominant findings were tubular necrosis in the distal parts of the proximal segment, leading to tubular atrophy of cortical nephrons with intratubular debris. Some regeneration of the distal parts was seen after 7 days, characterized by tubules with widely dilated lumina, which were lined by many low-lying epithelial cells. These injury patterns are similar to those reported in experimental models of ischemia-induced acute tubular necrosis(107-124).

In humans, renal damage has been observed at cisplatin doses of 50 mg given without adequate hydration. The anomalies are mainly situated in the more distal parts of the proximal tubule or in the distal nephron segment, occurring rarely in the glomeruli and the renal mitochondrial and cytosolic organs, and persist for about 1 month after cisplatin treatment(125-142).

### 1.2. Modulation of cisplatin-induced renotoxicity

In most of the clinical studies concerning cisplatin-induced nephrotoxicity, only plasma levels of creatinine and/or clearance of creatinine or blood urea nitrogen are used to evaluate the glomerular filtration rate(143-150). However, the sensitivity of these parameters in detecting early impairment of renal function have been broadly critiqued by recent experiments. Indeed, in patients with muscular atrophy, serum creatinine has been shown not to be a good indicator of the glomerular filtration rate. A better correlation was found between the clearance of [<sup>51</sup>Cr]-ethylenediaminetetraacetic acid ([<sup>51</sup>Cr]-EDTA) and inulin and the variation in glomerular function. Few studies have been performed to evaluate proximal tubular function (151-167).

## 2. Conclusions

Cisplatin is one of the most potent antineoplastic agents in chemotherapy of various cancers use. Despite the high risk for renal toxicity, the administration of high doses is often desirable because of the drug's dose-dependent activity. The most current toxicity-modulating strategies to date have been most effective against acute cisplatin renal-induced toxicity. This toxicity is a function of serum peak concentrations, which can be reduced by increasing the excretion of hydration, hyperosmolar solutions or by limiting its systemic absorption.

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