MINIREVIEW
THE NEPHROTOXICITY OF CISPLATIN
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Summary
Cisplatin is a cancer chemotherapeutic agent whose clinical use is complicated by its dose-related kidney toxicity. Since the histopathological profile of cisplatin nephrotoxicity appears similar to that of other heavy metals, it has been commonly presumed that cisplatin nephrotoxicity is related to the platinum moiety. However, the delayed time course and development of cisplatin nephrotoxicity is not characteristic of heavy metal nephropathy. Furthermore, cisplatin nephrotoxicity is stereospecific to the cis and not the trans isomer, indicating that the platinum atom is not the proximate nephrotoxicant. It is likely that a metabolite of cisplatin, possibly an aquated and/or hydroxylated complex, mediates the nephrotoxicity of cisplatin.

Although the cancer chemotherapeutic agent, cisplatin, is effective in the management of a variety of tumors, its clinical use is often complicated by kidney toxicity, ototoxicity (tinnitus, hearing loss), gastrointestinal disturbances (nausea, vomiting), myelosuppression (leukopenia, thrombocytopenia, anemia) and allergic reactions (eczema, dermatitis) (1,2). Of these toxicities, clinical use of cisplatin has been limited by its dose-related renal toxicity, an effect which has been well documented in all species studied to date including mice (3,4), rats (5-9), dogs (4,10,11) and humans (12,13,14). Early clinical trials revealed that the incidence of nephrotoxicity may range from 25-33% and 50-75% following single and multiple course therapy with cisplatin, respectively (2,14). However, the current use of intravenous hydration and/or osmotic diuretics before, during and after cisplatin administration has significantly reduced both the incidence and severity of nephrotoxicity.

Acute tubular necrosis is a prominent feature of cisplatin nephrotoxicity and is clinically manifested by elevations in blood urea nitrogen and serum creatinine, proteinuria and hyperuricemia (2,4). Other clinical indices of renal functional impairment include decreased creatinine clearance (12,13), marked enzynuria, characterized by elevated urinary N-acetyl-β-glucosaminidase, leucine aminopeptidase, alanine aminopeptidase and β-glucuronidase (15-17), and increased urinary excretion of β₂-microglobulin (17). Electrolyte disturbances have also been recently described in treated patients and may be related to impaired renal tubular reabsorption (18-20). Specifically, hypomagnesemia has been observed in 50% of patients receiving cisplatin and may represent a potentially serious toxic side effect associated with inappropriate urinary losses of magnesium (18).

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Light microscopic studies of human kidneys have revealed focal acute tubular necrosis, affecting primarily the distal and collecting tubules, dilatation of convoluted tubules and formation of casts at autopsy (12,13). A marked persistence of renal pathological damage, lasting at least 12 months following cisplatin treatment, has also been reported in patients (13) and suggests that cisplatin exerts continuing damage to the kidneys, causing irreversible injury. In contrast to humans, laboratory animal data indicate that cisplatin nephrotoxicity primarily involves degenerative changes in the proximal tubule (8,21,22). Although the effects of cisplatin on the proximal tubule have been a consistent finding in laboratory animals, there is little agreement regarding the effects of this agent on the distal tubule of rodent kidneys, with some studies reporting either moderate to severe (5,22) or an absence of (7,21,23) damage.

The time course of cisplatin nephropathy in laboratory animals is characterized by early degenerative changes in the proximal tubule and consists of cytoplasmic vacuolization, tubular dilatation, pyknotic nuclei and hydropic degeneration (5,8,21). By 3-5 days following cisplatin treatment in rats, pathologic changes are the most profound and are characterized by widespread tubular necrosis of the corticomedullary region, predominantly in the third segment (S₃) or straight portion of the proximal tubule (pars recta) (5,7,8,21,23). Electron microscopic studies reveal several ultrastructural changes in the pars recta including: profound thinning or focal loss of brush border, cellular swelling, condensation of nuclear chromatin, cytoplasmic vacuolization, rounded mitochondria with swollen cristae, dissociation of mitochondria from basal infoldings, loss of basal infoldings and an increased number and size of pinocytotic vesicles and lysosomal bodies in the apical region bordering the lumen (21-22). Animals surviving cisplatin nephrotoxicity demonstrate renal tubular regeneration as indicated by enlarged nuclei and mitotic figures. However, the presence of necrotic debris in the tubular lumen coupled with persistent tubular damage following a single administration of cisplatin suggests incomplete recovery (21). Chronic treatment with cisplatin may further result in cyst formation (24), interstitial fibrosis and thickening of tubular basement membranes (5), causing irreversible renal damage.

The mechanisms underlying cisplatin nephrotoxicity, and in particular, the profound necrosis of the pars recta, remain unclear. The localization and severity of tubular necrosis following cisplatin treatment may be related to the prolonged retention of platinum in the kidney. Choie and coworkers (5) estimated the kidney t½ of platinum as 50 hours, with specific platinum concentrations (mg Pt/mg protein) highest in kidney nuclei and microsomes. Furthermore, platinum is preferentially concentrated in the renal corticomedullary junction following cisplatin treatment in rats, an effect correlating with the localization of tubular necrosis (5). The mechanisms responsible for the selective accumulation of platinum in corticomedullary tissue are not well identified. However, it is known that the pars recta is a major site of active tubular secretion of organic anions, a process which initially involves active transport from peritubular fluid into proximal tubular cells, resulting in intracellular accumulation of the transported anion. On this basis, it has been suggested that cisplatin (or metabolite) may be transported by a similar mechanism and may account for the selective intracellular accumulation of platinum in the pars recta (21). If cisplatin is handled by the renal organic anion transport system, competitive inhibition for transport sites between cisplatin and a prototype organic anion, such as p-aminohippurate (PAH), would be anticipated. Indeed, cisplatin does inhibit the in vitro transport of PAH in isolated flounder tubules (25) and rat renal cortical slices (9). However, cisplatin also inhibits the in vitro renal cortical transport of an organic cation, tetraethylammonium (TEA) (9). Since PAH and TEA are transported by independent systems, competitive inhibition for both transport carriers by cisplatin is unlikely. Rather, the inhibition of the renal cortical accumulation of PAH by cisplatin is
probably nonspecific and related to impaired renal metabolism associated with its nephrotoxicity rather than competitive inhibition of transport. Peritubular transport of cisplatin (or metabolite) cannot be readily discounted, however, since it has been recently reported that the renal clearance of free platinum exceeds creatinine clearance in treated patients, suggesting tubular secretion of platinum (26). Although these studies suffer from the nonspecific determination of total platinum concentration and may not reflect clearance of intact cisplatin, they do suggest that one or more platinum containing compound(s) is(are) handled by peritubular transport. In addition, it is also conceivable that cisplatin (or metabolite) is transported across the luminal membrane into proximal tubular cells. It is well documented that mannitol diuresis and/or intravenous hydration reduce cisplatin nephrotoxicity by diluting its tubular urinary concentration rather than by altering its half-life, plasma clearance, tissue distribution or total urinary excretion (27-29). Since dilution of tubular urine represents an important factor in the development of cisplatin nephrotoxicity, it seems likely that luminal transport of cisplatin (or metabolite) may be important to its intracellular accumulation and toxicity. Clearly, more direct evidence characterizing the renal handling of cisplatin (or metabolite) and its relationship to its intracellular accumulation and tubular necrosis of the pars recta is needed.

An important aspect of cisplatin nephrotoxicity which has not been adequately researched is the chemical nature of the immediate nephrotoxicant. Because the gross characteristics of cisplatin nephrotoxicity are similar to those of other heavy metals, particularly mercury, it has been presumed that the nephrotoxicity of cisplatin is related to the toxicity of the platinum atom (2,5,30). Characteristics common to both cisplatin and mercuric chloride nephrotoxicity include: (1) acute tubular necrosis affecting primarily the pars recta (5,8,21), (2) increased size and number of renal lysosomes (22), and (3) depletion of protein-bound SH groups (28). However, several lines of evidence suggest that the nephrotoxicity of cisplatin and mercuric chloride are quite distinct:

(1) Time course and development. The earliest detectable changes in the kidney appear several days following cisplatin treatment (7,9). Although glomerular filtration rate is compromised 3, 7, 14 and 22-30 days following a single administration of cisplatin (5 mg/kg) to rats, no differences are observed on days 1 and 2 (7). Similarly, changes in urinary composition and volume are not evident until several days following treatment (7,9). In contrast, alterations in renal function following administration of even a small dose of mercuric chloride are rapidly induced within 24 hours (30). Thus, the delayed appearance of cisplatin nephrotoxicity suggests that its underlying mechanisms probably differ from mercuric chloride and may be related to the time needed for biotransformation. In addition, tubular regeneration is complete 9-14 days following mercuric chloride (32), but not cisplatin (21,33) treatment, further suggesting differences in the time course of kidney damage and repair between these chemicals.

(2) Chelation therapy. Mercuric chloride nephrotoxicity is often reversible following treatment with sulphydryl reacting chelating agents, i.e., cysteamine, penicillamine and N-acetylcysteine. In contrast, cisplatin nephrotoxicity is not reduced by metal chelators (34), suggesting a dissociation between the nephrotoxic actions and molecular reactivity of cisplatin and mercury.

Furthermore, several lines of evidence suggest that cisplatin nephrotoxicity may not be solely attributable to the platinum atom:

(1) Sterospecificity of cisplatin. Although administration of cis-dichlorodiammineplatinum and trans-dichlorodiammineplatinum result in similar renal concentrations of platinum (35), the trans isomer does not produce renal
toxicity (3,36), indicating that the geometry of these complexes, rather than the presence of the platinum atom, plays a crucial role in the development of cisplatin nephrotoxicity.

(2) Structure-activity relationships. Modification of the ligands of the dichlorodiammineplatinum complex significantly alters the incidence and severity of nephrotoxicity. The following chemical properties appear to be related to nephrotoxicity: (a) presence of N-H in coordinating amines, (b) absence of bulky alkyl substituents in coordinating amine, (c) chelate ring size, with the smaller ring associated with enhanced nephrotoxicity and (d) chemistry of the non-amine ligand, with increasing nephrotoxicity observed with: \( \text{thiols} < \text{SO}_3^- < \text{NO}_2^- < \text{citrate} < \text{dicarboxylates} < \text{amino acids} < \text{halide} < \text{SO}_4^- < \text{NO}_3^- - \text{H}_2\text{O} \) (37). In this manner, modulation of cisplatin nephrotoxicity by substitution of its ligands suggests that kidney toxicity is not solely related to the platinum atom.

These studies therefore point to the likelihood that a metabolite of the cisplatin complex, rather than the platinum atom, mediates the nephrotoxicity of this drug. Indeed, biotransformation of cisplatin has been suggested by the in vitro lability of the chloride ligands of the complex in aqueous media (38). Extrapolating these in vitro data to the in vivo disposition of cisplatin has led to the hypothesis that (1) cisplatin exists as a neutral complex in extracellular fluid (ECF) since the chloride concentration of ECF (\( \sim 112 \text{ mM} \)) is sufficiently high to stabilize the complex and prevent hydrolysis and (2) the markedly lower intracellular concentration of chloride (\( \sim 4 \text{ mM} \)) facilitates the displacement of chloride by water molecules, yielding a positively charged aquated and/or hydroxylated complex (39). The former postulate has been recently challenged; that is, cisplatin may be metabolized in ECF, as indicated by the in vitro disappearance of the parent drug and the concomitant appearance of other platinum containing compounds in plasma and plasma ultrafiltrates (40). Although there is a paucity of data comparing the metabolism of cisplatin in extracellular and intracellular compartments, it seems certain that cisplatin is metabolized in vivo, possibly to a form which is nephrotoxic.

It has become increasingly evident that chemically induced cytotoxicity may be related to the generation of reactive metabolites which bind covalently to tissue macromolecules such as protein, lipids or nucleic acids. A similar mechanism may mediate the nephrotoxicity of cisplatin. The reactivity of cisplatin in its aquated/hydroxylated form with nuclear DNA has been well documented and may mediate the inhibition of DNA synthesis in tumor tissue. On this basis it seems reasonable to speculate that such an electrophilic complex may bind to essential macromolecules of the kidney, resulting in nephrotoxicity. This hypothesis would be consistent with the reported increase in cisplatin nephrotoxicity and binding to renal tissue when the drug is prepared in a water vehicle, a manipulation which is known to facilitate formation of an aquated/hydroxylated platinum complex (41). Furthermore, macromolecular binding of a reactive metabolite of cisplatin may account for the persistent and prolonged retention of platinum in kidney tissue following cisplatin treatment. Whether this platinum complex binds to renal DNA or to other essential macromolecules as a primary mechanism of nephrotoxicity has not been studied as of yet and merits further investigation.

In summary, it appears that cisplatin nephrotoxicity is not related to the toxicity of platinum per se as has been commonly presumed. Rather, it seems likely that a metabolite of cisplatin, possibly an electrophile such as the aquated and/or hydroxylated form of cisplatin, mediates its nephrotoxicity. If the mechanisms underlying cisplatin nephrotoxicity are to be better understood, areas of future research should include: (1) characterization of the renal metabolism of cisplatin, (2) delineation of the renal transport of cisplatin and its metabolites and (3) correlation of covalent binding of cisplatin (or metabo-
lute) to renal macromolecules with severity of nephrotoxicity. Once documented, these data should provide the information needed in identifying not only the mechanisms of cisplatin nephrotoxicity but more feasible routes of preventing its development.

REFERENCES