Cisplatin Nephrotoxicity: A Review

XIN YAO, MD; KESSARIN PANICHPISAL, MD; NEIL KURTZMAN, MD; KENNETH NUGENT, MD

ABSTRACT: *Background:* Cisplatin is a major antineoplastic drug for the treatment of solid tumors, but it has dose-dependent renal toxicity. *Methods:* We reviewed clinical and experimental literature on cisplatin nephrotoxicity to identify new information on the mechanism of injury and potential approaches to prevention and/or treatment. *Results:* Unbound cisplatin is freely filtered at the glomerulus and taken up into renal tubular cells mainly by a transport-mediated process. The drug is at least partially metabolized into toxic species. Cisplatin has multiple intracellular effects, including regulating genes, causing direct cytotoxicity with reactive oxygen species, activating mitogen-activated protein kinases, inducing apoptosis, and stimulating inflammation and fibrogenesis. These events cause tubular damage and tubular dysfunction with sodium, potassium, and magnesium wasting. Most patients have a reversible decrease in glomerular filtration, but some have an irreversible decrease in glomerular filtration. Volume expansion and saline diuresis remain the most effective preventive strategies. *Conclusions:* Understanding the mechanisms of injury has led to multiple approaches to prevention. Furthermore, the experimental approaches in these studies with cisplatin are potentially applicable to other drugs causing renal dysfunction. **KEY INDEXING TERMS:** Cisplatin; Toxicity; Acute renal insufficiency; Apoptosis; Reactive oxygen species. **[Am J Med Sci 2007;334(2):115–124.]**

Cisplatin is a major antineoplastic drug used for the treatment of solid tumors. Its chief dose-limiting side effect is nephrotoxicity; 20% of patients receiving high-dose cisplatin have severe renal dysfunction. Cisplatin-DNA crosslinks cause cytotoxic lesions in tumors and other dividing cells. DNA-damaging agents usually have less toxicity in non-proliferating cells, yet the quiescent proximal tubule cells are selectively damaged by cisplatin. The mechanism for this renal cell injury has been the focus of intense investigation for many years, and recent studies suggest that inflammation, oxidative stress injury, and apoptosis probably explain part of this injury. Understanding the mechanism(s) for this side effect should allow clinicians to prevent and/or treat this problem better and provides a model for investigating drug-induced nephrotoxicity in general.[1–3]

Pathogenesis

Cisplatin Uptake into Renal Cells

Uptake of cisplatin is mainly through the organic transporter pathway. The kidney accumulates cisplatin to a greater degree than other organs and is the major route for its excretion. The cisplatin concentration in proximal tubular epithelial cells is about 5 times the serum concentration.[4] The disproportionate accumulation of cisplatin in kidney tissue contributes to cisplatin-induced nephrotoxicity.[5]

In the rat, cisplatin excretion occurs predominantly by glomerular filtration and to a lesser extent by secretion. There is no evidence of tubular reabsorption. Cisplatin is accumulated by peritubular uptake in both the proximal and distal nephrons.[5,6] The S3 segment of the proximal tubule accumulates the highest concentration of cisplatin, followed by the distal collecting tubule and the S1 segment in the proximal tubule.[6] In addition to a transporter-mediated process, cisplatin enters the cell through passive diffusion.[7] The contribution of active uptake by a transport system and passive diffusion through the cellular membrane may vary at different sites. Transporter mediated uptake is likely the major pathway in renal cells.[6] The organic cation transporter (OCT 2) is the critical transporter for cisplatin uptake in proximal tubules in both animals and humans. Transport mediated by these membrane proteins is polyspecific, electrogenic, voltage-dependent, bi-directional, pH-independent, and Na^+-independent. Three isoforms of OCT have been identified in humans. OCT2 is the main OCT in the kidney, OCT1 is the main isoform of the liver, and OCT3 is widely expressed, especially in the placenta. Cisplatin is not transported through human OCT1, which may help explain its organ-specific toxicity. Carboplatin and oxaliplatin, the less nephrotoxic ana-

From the Department of Internal Medicine, Texas Tech University Health Science Center, Lubbock, Texas.

Submitted October 6, 2006; accepted in revised form January 4, 2007.

Correspondence: Dr. Kenneth Nugent, Department of Internal Medicine, Texas Tech University Health Science Center, 3601 4th Street, Lubbock, TX 79430 (E-mail: Kenneth.Nugent@ttuhsc.edu).

logues of cisplatin, have no interaction with human OCT2.[8] Cimetidine, an organic cation competitor for the transport at human OCT2, reduces cisplatin-induced proximal tubule cell apoptosis.[9] Diabetic animals have reduced gene and protein expression of OCT isotypes and are resistant to cisplatin toxicity.[10] Whether these transporters mediate cisplatin entry into tumor cells is unknown. A recent study demonstrates that a different transporter system, the copper transport protein 1 regulates the uptake of cisplatin in human ovarian cancer cells.[11]

Cisplatin Metabolism

Conversion of cisplatin to nephrotoxic molecules in the proximal tubule cells is required for cell injury.[12] The highest concentration of cisplatin is found in cytosol, mitochondria, nuclei, and microsomes.[4] Cisplatin is conjugated to glutathione and then metabolized through a γ-glutamyl transpeptidase and a cysteine *S*-conjugate β-lyase–dependent pathways to a reactive thiol, a potent nephrotoxin. γ-Glutamyl transpeptidase is located on the cell surface, whereas cysteine-*S*-conjugate β-lyase is an intracellular enzyme. Inhibition of these 2 enzymes has no effect on the uptake of cisplatin into the kidney but reduces nephrotoxicity. Inhibition of γ-glutamyl transpeptidase activity, however, renders cisplatin inactive as an antitumor drug. Whether inhibition of cysteine *S*-conjugate β-lyase affects the antitumor activity of cisplatin is not known.[12,13] The only report of cysteine *S*-conjugate β-lyase activity in tumor cells shows a very low level of activity in some human renal cell carcinomas.[14] Cisplatin can form monohydrated complexes by hydrolytic reactions. The monohydrated complex is more toxic to the renal cells than cisplatin but it is not kidney specific. The normal low intracellular chloride concentrations promote its formation. Using hypertonic saline to reconstitute cisplatin can decrease the amount of monohydrated complex formed. This approach attenuates nephrotoxicity but may also compromise its antitumor activity.[15]

Biochemical Changes in the Renal Cell

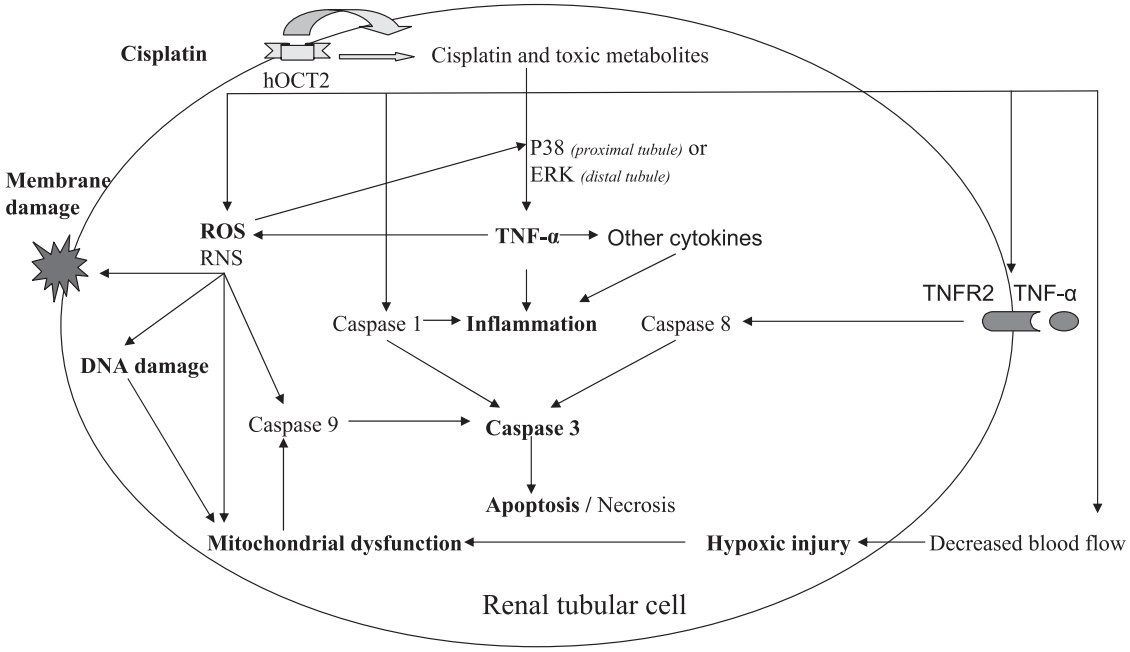
Cisplatin induces specific gene changes. Genes involved in drug resistance (MDR1, P-gp), in cytoskeleton structure and function (*Vim, Tubb5, Tmsb10, Tmsb4x, Anxa2*), in cell adhesion (*Spp1, Col1a1, Clu, Lgals3*), in apoptosis (cytochrome c oxidase subunit I, BAR, heat-shock protein 70-like protein, Bax), in tissue remodeling (clusterin, IGFBP-1, TIMP-1), and in detoxification (*Gstm2, Gstp2*) are upregulated after cisplatin-induced injury. Genes downregulated by cisplatin include those that localize to the proximal tubules (*Odc1, Oat, G6pc, Kap*), those that control intracellular calcium homeostasis (SMP-30), and those that encode growth factors or their binding proteins (*Egf, Ngfg, Igfbp3, Ghr*). These gene changes are associated with cisplatin damage to proximal tubules, tissue remodeling, and regeneration.[16–18]

Cisplatin-induced nephrotoxicity is mediated by mitogen-activated protein kinase (MAPK) intracellular signaling pathways. The MAPK pathways are a series of parallel cascades of serine/threonine kinases that are activated by diverse extracellular physical and chemical stresses. They regulate cell proliferation, differentiation, and survival. The 3 major MAPK pathways terminate in the extracellular regulated kinase (ERK), p38, and Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) enzymes. The ERK pathway is typically activated by extracellular growth factors and has been linked to both cell survival and cell death. The p38 and JNK/SAPK pathways are activated by a variety of stresses, for example, oxidants, UV irradiation, hyperosmolality, and inflammatory cytokines; they have been linked to cell death. Cisplatin was recently shown to activate all three MAPKs in the kidney, both *in vitro* and *in vivo*.[19] ERK and p38 function as an upstream signal stimulating tumor necrosis factor-α (TNF-α) production. ERK also activates caspase 3, which controls apoptosis in renal tubular cells. Phosphorylated-ERK is exclusively localized in the distal nephron; therefore ERK1/2 activation may mediate distal nephron injury. Whether the ERK pathway contributes to proximal tubule injury is not clear, but certain responses in the distal nephron could induce adjacent proximal tubule injury through autocrine and paracrine processes.[20] P38 activation mediates proximal tubule cells injury. Stimulation of p38 is mediated by hydroxyl radicals, which are induced by cisplatin.[21] The JNK/SAPK pathway in the cisplatin-induced nephrotoxicity has not been well studied.

Intracellular Events that Damage Renal Cells

The *in vivo* mechanisms of cisplatin nephrotoxicity are complex and involve oxidative stress, apoptosis, inflammation, and fibrogenesis. High concentrations of cisplatin induce necrosis in proximal tubule cells, whereas lower concentrations induce apoptosis through a caspase-9–dependent pathway.[22] The major pathways in cisplatin-induced acute tubular cell injury are shown in Figure 1 and summarized in Table 1.

Oxidative stress injury is actively involved in the pathogenesis of cisplatin-induced acute kidney injury. Reactive oxygen species (ROS) directly act on cell components, including lipids, proteins, and DNA, and destroy their structure. ROS are produced via the xanthine-xanthine oxidase system, mitochondria, and NADPH oxidase in cells. In the presence of cisplatin, ROS are produced through all these pathways and are implicated in the pathogenesis of acute cisplatin-induced renal injury.[23] Cisplatin induces glucose-6-phosphate dehydrogenase and hexokinase activity, which increase free radical production and decrease antioxidant production.[24] It increases intracellular calcium level which activates



Abbreviations: ERK- extracellular regulated kinase; hOCT2- human organic cation transporter 2; RNS- reactive nitrogen species; ROS- reactive oxygen species; TNF-α- tumor necrosis factor-α; TNFR2- tumor necrosis factor receptor 2.

Figure 1. Major pathways in cisplatin-induced acute tubular cell injury.

NADPH oxidase and to stimulates ROS production by damaged mitochondria.[23] Superoxide anion ($O_2^{\bullet}$),[25] hydrogen peroxide (H_2O_2),[26] and hydroxyl radical ($^{\bullet}OH$)[27] are increased in cisplatin-treated kidneys. These free radicals damage the lipid components of the cell membrane by peroxidation and denature proteins, which lead to enzymatic inactivation. Free radicals can also cause mitochondrial dysfunction.[24] Antioxidant enzymes are inhibited by cisplatin, and renal activities of superoxide dismutase, glutathione peroxidase, and catalase are significantly decreased.[28,29] Antioxidants melatonin,[30] vitamin C[26], and vitamin E[31] have been shown to prevent cisplatin-induced acute nephrotoxicity. The role of oxidant-antioxidant systems in chronic nephrotoxicity is uncertain.

Reactive nitrogen species have also been studied in cisplatin-induced nephrotoxicity. The renal content of peroxynitrite and nitric oxide is increased in cisplatin-treated rats.[32,33] Peroxynitrite causes changes in protein structure and function, lipid peroxidation, chemical cleavage of DNA, and reduction in cellular defenses by oxidation of thiol pools. Cisplatin-induced nitrosative stress and nephrotoxicity are attenuated by FeTPPS-treatment, a soluble complex which metabolizes peroxynitrite. These data suggest that peroxynitrite is involved, to some degree, in cisplatin-induced nephrotoxicity and protein nitration.[32] However, it is still

Table 1. Selected Summary of Drug Metabolism and Toxic Processes

	Process	Relevance
Pharmacokinetics and excretion	Renal excretion	Drug concentration in tubules
Cellular uptake and metabolism	Transporter mediated	Inhibition-reduced uptake
	Intracellular hydration	Increased toxicity
Genomic effects	Gene upregulation	Caspase 3→ apoptosis
	Gene downregulation	Superoxide dismutase→ ↑ROS
Direct toxic effects	ROS	Lipid peroxidation
	Mitochondrial injury	↑ROS, ↓ATP production
Indirect toxic effects	MAPK pathways	↑TNF-α production activate apoptosis
Organ effects: histology	Tubular injury	Apoptosis, necrosis
Organ effects: function	↓Tubular function	Na, K, Mg wasting
Therapy	Limit toxicity, if prevention fails, see Table 2	Not available yet, possible approach-stop apoptosis

ATP, Adenosine triphosphate; MAPK, mitogen-activated protein kinase; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α.

controversial whether nitric oxide plays a toxic role in kidney injury.[24,32,33]

Hypoxia and mitochondrial injury are involved in cisplatin nephrotoxicity. Pathological changes in cisplatin-induced nephrotoxicity occur mainly in the S3 segment of the proximal tubule in the outer stripe of the outer medulla. This zone of the kidney is more susceptible to ischemic insult, and injury to this segment occurs in other toxic acute renal failure models.[34] Hypoxic tubules in the outer medulla have been identified by pimonidazole staining in cisplatin nephrotoxicity. Analyses using serial sections indicate that a significant portion of hypoxic cells are proximal tubular cells.[35] Therefore, hypoxia may have an important role in cisplatin-induced nephrotoxicity, and this probably develops during the decreased renal blood observed during the initial phase of cisplatin nephrotoxicity. However, hypoxia-inducible factor 1(HIF-1) is activated in the S3 segment of proximal tubules in cisplatin injury *in vivo*. HIF-1 is a transcription factor that mediates cellular responses to hypoxia, including angiogenesis, erythropoiesis, and glycolytic adaptation. Dominant negative HIF-1 α-subunit animals have increased susceptibility to cisplatin injury mediated by apoptosis which was associated with the increased release of cytochrome *c*, loss of mitochondrial membrane potential, and increased caspase 9 activity.[35] Therefore, the net effect of hypoxia in cisplatin-induced renal injury is uncertain.

Apoptosis is now recognized as an important mode of cell death in normal and pathologic states. Caspase 1, 8, and 9 are initiator caspases that activate caspase 3, which is the principal executioner caspase in renal tubules apoptosis. This process may proceed through either activation of an extracellular surface receptor pathway or an intracellular mitochondrial pathway. DNA fragments and oxidative stressors initiate the mitochondrial pathway that results in caspase 9 activation.[36] Engagement of a cell surface receptor with extracellular tumor necrosis factor-α (TNF-α) activates caspase 8.[37] Both pathways may be involved in cisplatin-injured kidney. In addition, cisplatin can induce a very rapid Fas clustering into the membrane lipid rafts and elicit apoptosis cascade in the absence of Fas ligand. This pathway has been implicated in its cytotoxicity of cancer cells. Whether it is involved in nephrotoxicity is unknown.[38] Caspase 1 directly activates caspase 3 in cisplatin-induced renal injury model. Caspase 1 also increases interleukin 1β (IL-1β) levels and contributes to the inflammation in the cisplatin-treated kidney. Cisplatin-induced apoptosis and ATN are reduced in caspase1-deficient mice.[39] DNA fragmentation associated with cisplatin-induced nephrotoxicity depends on deoxyribonuclease I, a highly active endonuclease I, which represents approximately 80% of the total endonuclease activity in the kidney. Primary renal tubular epithelial cells isolated from deoxyribonuclease I knockout animals are resistant to cisplatin injury *in vitro*.[40]

Cisplatin induces a series of inflammatory changes that mediate renal injury. Recent evidence indicates that inflammation has an important role in the pathogenesis of cisplatin-induced renal injury. Cisplatin increases degradation of IκB in a time-dependent manner and increases nuclear factor-κB (NF-κB) binding activity. These events lead to the enhanced renal expression of TNF-α. Other cytokines, such as transcribing growth factor-β (TGF-β), monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule (ICAM), hemeoxygenace-1, TNF receptor 1 (TNFR1), and TNF receptor 2 (TNFR2), are also increased in kidneys by cisplatin.[41] TNF-α has a central role in mediating the renal injury. It induces apoptosis, produces reactive oxygen species, and coordinates the activation of a large network of chemokines and cytokines in the kidney. Inhibitors of TNF-α production (GM6001 and pentoxifylline) and TNF-α neutralizing antibody reduce serum and kidney TNF-α protein levels from 30% to nearly 100%. They blunt the cisplatin-induced increases in TGF-β, RANTES, MIP-2, and MCP-1 mRNA.[42] In addition, the TNF-α inhibitors ameliorate cisplatin-induced renal dysfunction by 50% and reduce cisplatin-induced structural damage.[42] TNF-α-deficient mice are markedly protected against cisplatin nephrotoxicity.[43]

Cisplatin can also induce fibrosis around the affected tubules, accompanied by infiltration of macrophages and lymphocytes. In a rat model that received 2 mg/kg body weight cisplatin injections once weekly for 7 weeks, fibrotic lesions progressively developed in the corticomedullary junction as early as week 1 and reached a maximum at week 5.[44] All renal damages were repaired during a 19-week observation period after cessation of cisplatin treatment by a reduction in fibrotic tissues and by replacement with regenerated renal tubules. The healing was accompanied by decreases in BUN and creatinine concentrations.[44] Extensive renal tubulointerstitial fibrosis has been shown in a patient[45] and in other large animals[46] treated with multiple courses of cisplatin chemotherapy. Macrophages play an important role in renal interstitial fibrosis via production of TGF-β1 and TNF-α; these fibrogenic factors mediate induction of myofibroblastic cells capable of producing extracellular matrices.[47]

In summary, cisplatin causes direct tubular injury through multiple mechanisms. Significant interactions among these various pathways may occur during this injury. For example, TNF-α induces apoptosis, produces ROS, and coordinates the activity of a network of cytokines that all contribute to cellular injury. However, it also triggers the expression of inducible nitric oxide synthase, increases the production of nitric oxide, and enhances HIF-1 activity in normoxic renal tubule cells, events that could limit injury.[48] How much each pathway and the interactions among these pathways contribute to

the cisplatin nephrotoxicity has not been determined (Figure 1).

Pathophysiological Effects of Cisplatin Injury

Unbound cisplatin is filtered at the glomerulus (80% of a dose is excreted in 24 hours). Renal blood flow can decrease within 3 hours after cisplatin infusion, and glomerular filtration rate (GFR) falls after the decrease in renal blood flow.[49] The mediators responsible for the fall in renal blood flow and GFR have not been determined, and neither calcium channel blockers nor angiotensin converting enzyme inhibitors reverse cisplatin-induced ARF.[50] The changes in GFR and renal blood flow probably reflect increased renal vascular resistance secondary to tubular-glomerular feedback from increased sodium chloride delivery to the macula densa.[49] Intratubular obstruction does not play a primary role in cisplatin-induced nephrotoxicity.[50] Most patients receiving cisplatin treatment have stable renal function. Twenty-five percent of patients have reversible azotemia for 1 to 2 weeks after treatment.[51] However, a significant minority of patients have a progressive decline in renal function. Irreversible renal failure can occur with large doses and with multiple courses.[51,52] Increased age, renal radiation, and alcohol ingestion increase toxicity.[53]

The proximal tubular dysfunction observed in cisplatin nephrotoxicity precedes alterations in renal hemodynamics. Forty-eight to 72 hours after cisplatin administration, there is impaired proximal and distal tubular reabsorption and increased vascular resistance.[51] Acute toxicity causes decreased mitochondrial function, decreased ATPase activity, altered cell cation content, and altered solute transport.[49,51] The expression patterns of outer medullary water channels aquaphorin 1 and 2, of sodium transporters, including the Na,K-ATPase (a-subunit) and the Na,K,2Cl-cotransporter, and of the type III Na,H-exchanger, are decreased in a cisplatin-treated rat model. Hence, cisplatin treatment results in impaired tubular reabsorption and decreased urinary concentration.[51,54] The effect on sodium and water transport represents an early change in cisplatin toxicity since the inhibition of the transporters occurs in rats without elevation of BUN and creatinine.[51,55] There is decreased sodium reabsorption in the proximal tubule and decreased sodium and water reabsorption in distal tubule. This causes increased excretion of sodium and water.[5,55] Polyuria uniformly accompanies cisplatin administration and occurs in 2 distinct phases. The first phase occurs within the first 24 to 48 hours after administration. It is characterized by decreased urine osmolality but stable GFR. It is probably prostaglandin mediated and can be prevented by vasopressin and aspirin. This early phase polyuria usually resolves spontaneously. The second phase starts between 72 and 96 hours after cisplatin administration and is characterized by a decreased GFR. It is associated with medullary urea cycling defect which results in decreased medullary tonicity and impaired NaCl transport in the proximal tubule and thick ascending limb of the loop of Henle. This phase does not respond to either drug.[50,56] Most patients waste sodium, potassium, magnesium, and calcium in their urine and some have orthostatic hypotension.[50,51,57,58]

Pathological Changes in the Kidney

Cisplatin nephrotoxicity primarily causes tubulointerstitial lesions. In animal models cisplatin damages the proximal tubules, specifically the S3 segment of the outer medullary stripe. Mitochondrial swelling and nuclear pallor occur in the distal nephron. The glomerulus has no obvious morphologic changes.[49,56,59] Only a few studies have described the pathological results associated with cisplatin-induced nephrotoxicity in humans.[49,56,59,60] The site of injury involves either the distal tubule and collecting ducts or the proximal and distal tubules.[49,56] The sites affected probably depend on differences in dose and timing of biopsy specimens. Biopsies obtained 3 to 60 days after dosing reveal segmental degeneration, necrosis, and desquamation of the epithelial cells in the pars convoluta and pars recta of the proximal tubules and the distal tubules.[60] In patients with acute renal failure, the predominant lesion is acute necrosis and is located mostly in the proximal convoluted tubules. The severity of necrosis is dose-, concentration-, and time-dependent. There is no interstitial nephritis.[56,59] Patients with chronic nephrotoxicity have focal acute tubular necrosis characterized by cystic dilated tubules lined by a flattened epithelium showing atypical nuclei and atypical mitotic figures with hyaline casts.[49] Long-term cisplatin treatment and injury may cause cyst formation and interstitial fibrosis.[49]

Diagnostic Criteria for Cisplatin Injury

Cisplatin-induced renal injury probably does not have unique diagnostic features. Many patients have changes in glomerular filtration which could be identified by more sensitive tests such as inulin clearance before there are changes in serum creatinine and glomerular filtration measured by creatinine collection. Urinary excretion of a proximal tubular injury markers, such as β-2 microglobulin, *N*-acetyl-β-D-glucosaminidase, and α_1-acid glycoprotein, increase after cisplatin treatment.[53] There is little change in urine protein excretion. Urinalysis typically shows leukocytes, renal tubular epithelial cells, and granular casts.[56] A recent animal study demonstrated the presence of glucose, amino acids, and tricarboxylic acid cycle metabolites in the urine 2 days after cisplatin exposure. If this altered metabolic profile can be demonstrated in human stud-

Table 2. Potential Approaches to Prevention of Cisplatin-Induced Nephrotoxicity

Pathogenesis	Prevention Agent	Mechanism of Prevention	Reference
Uptake by renal cell	Glycation	Decreases human OCT expression	10, 68
	Cimetidine	Competes for the transport at human OCT2	8, 9
	Carboplatin, Oxaliplatin	Decreased interaction with human OCT2	8, 9, 50, 55, 66, 67
	Sulfa-containing amino acid	Blocks cisplatin transportation	6
Conversion to toxic compounds	Normal saline	Increases excretion, reduces formation of toxic agents and induces osmotic stress response	49, 62, 63, 64,
	Procainamide	Coordinates with cisplatin to form a less toxic complex	70, 71
Cisplatin induced signal transduction	Serum thymic factor	Ameliorates sustained ERK activation	79
	U0126	Decreases TNF-α generation and caspase 3 activity	20
Oxidative stress injury	Amifostine	Binds free radicals and reduces platinum-DNA adduct formation	76, 77, 78
	Melatonin, vitamins C and E	Decreases oxidative stress injury	26, 30, 31
	Allopurinol	Inhibits xanthine oxidase to reduce ROS generation	72
	Ebselen	Scavenges peroxynitrite to prevent lipid peroxidation	72
	Erdosteine	Maintains intracellular redox state to suppress oxidant stress	24
	Edaravone and *N*-acetylcysteine	Repletes intracellular stores of glutathione	73
Inflammation	Pentoxifylline, α-MSH, IL-10,	Inhibits production of TNF-α	82
	Salicylates	Inhibit cyclooxygenase activity and prostaglandin synthesis, high doses attenuate TNF-α production	41, 81
	Fibrates	Inhibit free fatty acid accumulation and suppress apoptosis	83

ERK, Extracellular regulated kinase; IL-10, interleukin 10; MAPK, mitogen-activated protein kinase; α-MSH, α-melanocyte stimulating hormone; OCT, organic cation transporter; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α.

ies, it might be used to identify early cisplatin-induced nephrotoxicity.[61]

Approaches to Prevention

These various approaches are summarized in Table 2.

Excretion and Metabolism

Vigorous hydration with saline and simultaneous administration of mannitol before, during, and after cisplatin administration significantly reduce cisplatin-induced nephrotoxicity. This strategy has been accepted as the standard of care.[49] Recently, a randomized trial demonstrated that saline alone or with furosemide provides better renal protection than saline plus mannitol.[62] The mechanism for salt protection is uncertain. Volume expansion with saline or hypertonic saline may increase the rate of cisplatin excretion.[63] Salt also provides a high concentration of chloride ions that prevent the dissociation of the chloride ions from the platinum molecule, thereby reducing the formation of the reactive, aquated species of cisplatin.[64] Alternatively, sodium ions may provide renal protection. A recent study demonstrated that saline does not alter the cellular accumulation of cisplatin but instead triggers a stress response within the cell that modifies sensitivity to cisplatin. The osmotic stress response decreases the accessibility of cisplatin to DNA, induces proximal tubule cell resistance to apoptosis, and changes the metabolic activation of nephrotoxins. However, this approach may interfere with the antineoplastic activity of cisplatin by blocking tumoricidal effects.[65]

Cellular Uptake

Carboplatin and oxiplatin are second- and third-generation platinum drugs that have been introduced into clinical use because of their reduced nephrotoxicity. They have no interaction with human OTC2, and this reduces their entry into renal tubular cells.[8,9] The *in vitro* antitumor activity of carboplatin is quantitatively similar to cisplatin; clinical trials have demonstrated that carboplatin has comparable efficacy in treating ovarian cancer.[50] It can be used in patients who can not take cisplatin either due to existing renal dysfunction or coadministration of other nephrotoxic drugs. Although less severe than with cisplatin, dose-dependent nephrotoxicity has been observed. With carboplatin dosage at 400 mg/m^2, only subclinical tubular damage occurs. Overt nephrotoxicity develops when the dosage reaches 800 mg/m^2. Without hydration, patients have a 36 to 61% reduction in creatinine clearance.[49]

Vigorous saline based hydration with diuretics is utilized with high dose carboplatin to reduce the risk of renal dysfunction.[55] No detrimental effect of oxaliplatin on renal function has been reported, even in patients with renal insufficiency or in patients receiving repeated doses. Oxaliplatin has been approved to treat advanced colorectal cancer. Whether it can replace cisplatin or carboplatin in treating other tumors is being evaluated.[66] Other new platinum complexes, such as nedaplatin, satraplatin, BBR3464, and ZD0473, have encouraging *in vitro* activity but are still under investigation.[67]

Kidneys in diabetic animal models sustain less cisplatin-induced toxicity. There is no difference in cisplatin pharmacokinetics in diabetic rats, but the organic cation transport system is functionally impaired in kidneys of streptozotocin-diabetic rats.[68] Therefore, kidneys of diabetic rats accumulate less cisplatin, and this is associated with decreased renal toxicity. Insulin treatment may reverse protection against cisplatin toxicity either by increasing susceptibility to cisplatin toxicity or by modulating organic cation transport function. Clinical studies are needed to determine whether or not manipulation of serum glucose levels alters cisplatin nephrotoxicity in humans.[69] *In vitro* studies have shown that cimetidine competes with cisplatin for hOCT2; this effect should decrease the uptake of cisplatin by the proximal tubules and attenuate its nephrotoxicity.[8] Cysteine, methionine, *N*-acetylcysteine, and DL-homocysteine inhibit cisplatin uptake in cultured S1, S3 segment proximal tubule cells, and distal collecting tubule cells. The structural element R-CH(NH2)-[CH2]1 2-S-R, which is common to all 4 molecules, may play a crucial role in blocking the transport of cisplatin and could have future clinical applications.[6]

Intracellular Distribution

Procainamide protects against the nephrotoxicity of cisplatin without altering its antitumor activity.[70] Procainamide, after accumulation in the kidney, may coordinate with cisplatin to form a less toxic complex that renders rats less susceptible to cisplatin-induced toxicity.[71]

Antioxidant Drugs

The combination of allopurinol and ebselen reduces cisplatin-induced nephrotoxicity and ototoxicity in a rat model.[72] Allopurinol is a xanthine oxidase inhibitor with the potential to reduce ROS generation. Ebselen, a glutathione peroxidase mimic, is an excellent scavenger of peroxynitrite and can protect against lipid peroxidation in the presence of glutathione or other thiols. Ebselen has excellent oral availability and has been evaluated in human clinical testing for the treatment of acute ischemic stroke. In these studies, no adverse events were observed.[72] Some other agents with potent free radical scavenging activity have been studied extensively to prevent cisplatin-induced renal toxicity. Erdosteine increases glucose-6-phosphate dehydrogenase activity, which helps maintain the proper intracellular redox state and protects against oxidant stress.[24] Edaravone and *N*-acetylcysteine can replete intracellular stores of reduced glutathione.[73] Other compounds with antioxidant property such as silymarin, naringernin, vitamin C, and vitamin E have also been found to have renoprotective function in animal studies.[28,29,74]

A large number of sulfur-containing compounds have been shown to reduce the nephrotoxicity of cisplatin without inhibiting its antitumor effect in patients with ovarian cancer, non–small-cell lung cancer, metastatic breast cancer, and metastatic colon cancer.[55,75] Amifostine, an organic thiophosphate, may diminish cisplatin-induced toxicity by donating a protective thiol group, an effect that is highly selective for normal but not malignant tissue. Amifostine is the only FDA-approved agent for the reduction of cumulative renal toxicity in advanced ovarian and non–small-cell lung cancer patients receiving cisplatin.[76] This drug limits toxicity by binding free radicals.[77] It may also bind and detoxify platinum agents by reduction of platinum-DNA adduct formation.[78] However, use of this drug is limited by side effects and cost. In addition, concerns about possible interference with the antitumor activity of cisplatin should limit its use to clinical trials in tumors other than those listed above.

Signal Transduction

Serum thymic factor is a nonapeptide thymic hormone isolated from the thymus and is involved in functional activation and differentiation of T cells. Serum thymic factor significantly ameliorates sustained ERK activation and induces the increased level of heat shock protein 70, which prevents cisplatin-induced renal damage in the rat model.[79] Other selective MAPK/ERK inhibitors have also been shown to attenuate cisplatin-induced renal injury by decreasing inflammation and apoptosis.[20] However, because cisplatin-induced apoptosis in human tumor cells is mediated by MAPK/ERK activation, inhibition of this pathway may disturb the anti-tumor activity of cisplatin.[80]

Anti-inflammatory Drugs

Salicylates are used to treat a broad range of inflammatory disorders. The anti-inflammatory action is attributed to their inhibition of cyclooxygenase activity and prostaglandin synthesis. However, high doses of salicylates can stabilize IκB and reduce NF-κB transcription activity, and these effects attenuate TNF-α production and reduce renal inflammation in cisplatin toxicity models.[41] Salicylates do not disturb the anti-neoplastic activity of cisplatin. No reduction in tumor killing is found

when cisplatin is given in conjunction with sodium salicylate.[41,81] This may be explained by the observation that cisplatin nephrotoxicity is mediated via TNFR2, whereas the anti-tumor effect of TNF-α is mediated by TNFR1. Moreover, inhibition of NF-κB, a cell survival factor, by salicylate might increase the effectiveness of chemotherapy.[41] α-Melanocyte stimulating hormone (α-MSH) and IL-10, which suppress the production of TNF-α, ameliorate cisplatin-induced renal injury in animal models.[82] *In in vitro* models, fibrates inhibit free fatty acid accumulation and suppresses apoptosis by preventing the release of cytochrome c from mitochondria and by inhibiting the transfer of Bax proteins from the cytoplasm to mitochondria. Fibrates have been shown to prevent cisplatin-induced nephrotoxicity in an animal study.[83] Human studies are needed to determine if these agents can prevent cisplatin nephrotoxicity.

Treatment of Cisplatin Nephrotoxicity

There is no specific treatment for cisplatin-induced renal dysfunction or injury. These patients need careful attention to hydration and electrolyte treatment. They frequently need magnesium and potassium replacement. Cisplatin and magnesium affect the same sodium and water channels in the outer medulla. Cisplatin induces magnesium depletion, and magnesium deficiency itself may enhance cisplatin nephrotoxicity. Cisplatin treatment often produces extensive gastrointestinal side effects, which might lead to more magnesium depletion through anorexia and diarrhea. Eventually, patients with such side effects might be rendered more susceptible to the nephrotoxicity of cisplatin. Therefore, magnesium repletion may attenuate cisplatin-induced nephrotoxicity. In a small study, 17 patients with germ cell tumor who were receiving cisplatin in a dosage of 20 mg/m^2 per day for 5 days in four series were randomly assigned into a group receiving continuous Mg supplementation and a group receiving supplementation only at serum levels below 0.45 mmol/L. Although there were no differences in serum creatinine or creatinine clearance, there was significantly less tubular damage measured by urine *N*-acetyl-B-D-glucosaminidase excretion in the patients receiving continuous supplementation. There was 2.4-fold higher concentration of urine *N*-acetyl-B-D-glucosaminidase in the nonsupplemented group compared with that in the Mg-supplemented group.[84] In addition, these patients should avoid, to the extent possible, other nephrotoxic agents, including intravenous radiographic contrast and nephrotoxic antibiotics. Ongoing research may identify prophylactic agents with the potential to limit toxicity. However, these studies need careful attention to the possibility of changing antineoplastic effects.

Summary

In this review, we focus on the pathophysiology of toxic renal injury caused by an important chemotherapeutic agent. Critical issues include drug uptake by target cells, drug metabolism within target cells, changes in gene expression, and activation of injury pathways, including oxidative stress, inflammation, and programmed cell death. Since toxins that cause tubular injury share many pathophysiological features with ischemic damage, cisplatin potentially provides an excellent model not only for studying toxic nephrotoxicity but also ischemic nephrotoxicity. Investigation of each step offers the possibility of identifying preventive treatment.

References

1. **Thadhani R, Pascual M, Bonventre JV.** Acute renal failure. N Engl J Med 1996;334:1448–60.
2. **Schrier RW, Wang W, Poole B, et al.** Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. J Clin Invest 2004;114:5–14.
3. **Merouani A, Shpall EJ, Jones RB, et al.** Renal function in high dose chemotherapy and autologous hematopoietic cell support treatment for breast cancer. Kidney Int 1996;50: 1026–31.
4. **Kuhlmann MK, Burkhardt G, Kohler H.** Insights into potential cellular mechanisms of cisplatin nephrotoxicity and their clinical application. Nephrol Dial Transplant 1997;12: 2478–80.
5. **Arany I, Safirstein RL.** Cisplatin nephrotoxicity. Semin Nephrol 2003;23:460–4.
6. **Kroning R, Lichtenstein AK, Nagami GT.** Sulfur-containing amino acids decrease cisplatin cytotoxicity and uptake in renal tubule epithelial cell lines. Cancer Chemother Pharmacol 2000;45:43–9.
7. **Gately DP, Howell SB.** Cellular accumulation of the anticancer agent cisplatin: a review. Br J Cancer 1993;67:1171–6.
8. **Ciarimboli G, Ludwig T, Lang D, et al.** Cisplatin nephrotoxicity is critically mediated via the human organic cation transporter 2. Am J Pathol 2005;167:1477–84.
9. **Ludwig T, Riethmuller C, Gekle M, et al.** Nephrotoxicity of platinum complexes is related to basolateral organic cation transport. Kidney Int 2004;66:196–202.
10. **Thomas MC, Tikellis C, Kantharidis P, et al.** The role of advanced glycation in reduced organic cation transport associated with experimental diabetes. J Pharmacol Exp Ther 2004;311:456–66.
11. **Holzer AK, Samimi G, Katano K, et al.** The copper influx transporter human copper transport protein 1 regulates the uptake of cisplatin in human ovarian carcinoma cells. Mol Pharmacol 2004;66:817–23.
12. **Townsend DM, Deng M, Zhang L, et al.** Metabolism of Cisplatin to a nephrotoxin in proximal tubule cells. J Am Soc Nephrol 2003;14:1–10.
13. **Townsend DM, Hanigan MH.** Inhibition of gamma-glutamyl transpeptidase or cysteine S-conjugate beta-lyase activity blocks the nephrotoxicity of cisplatin in mice. J Pharmacol Exp Ther 2002;300:142–8.
14. **Nelson JA, Pan BF, Swanson DA, et al.** Cysteine conjugate beta-lyase activity in human renal carcinomas. Cancer Biochem Biophys 1995;14:257–63.
15. **Ekborn A, Lindberg A, Laurell G, et al.** Ototoxicity, nephrotoxicity and pharmacokinetics of cisplatin and its monohy-

drated complex in the guinea pig. Cancer Chemother Pharmacol 2003;51:36–42.
16. **Huang Q, Dunn II, RT Jayadev S, et al.** Assessment of cisplatin-induced nephrotoxicity by microarray technology. Toxicol Sci 2001;63:196–207.
17. **Leussink BT, Baelde HJ, Broekhuizen-van den Berg TM, et al.** Renal epithelial gene expression profile and bismuth-induced resistance against cisplatin nephrotoxicity. Hum Exp Toxicol 2003;22:535–40.
18. **Thompson KL, Afshari CA, Amin RP, et al.** Identification of platform-independent gene expression markers of cisplatin nephrotoxicity. Environ Health Perspect 2004;112:488–94.
19. **Arany I, Megyesi JK, Kaneto H, et al.** Cisplatin-induced cell death is EGFR/src/ERK signaling dependent in mouse proximal tubule cells. Am J Physiol Renal Physiol 2004;287: F543–9.
20. **Jo SK, Cho WY, Sung SA, et al.** MEK inhibitor, U0126, attenuates cisplatin-induced renal injury by decreasing inflammation and apoptosis. Kidney Int 2005;67:458–66.
21. **Ramesh G, Reeves WB.** p38 MAP kinase inhibition ameliorates cisplatin nephrotoxicity in mice. Am J Physiol Renal Physiol 2005;289:F166–74.
22. **Lieberthal W, Triaca V, Levine J.** Mechanisms of death induced by cisplatin in proximal tubular epithelial cells: apoptosis vs. necrosis. Am J Physiol 1996;270:F700–8.
23. **Kawai Y, Nakao T, Kunimura N, et al.** Relationship of intracellular calcium and oxygen radicals to Cisplatin-related renal cell injury. J Pharmacol Sci 2006;100:65–72.
24. **Yilmaz HR, Iraz M, Sogut S, et al.** The effects of erdosteine on the activities of some metabolic enzymes during cisplatin-induced nephrotoxicity in rats. Pharmacol Res 2004;50:287–90.
25. **Davis CA, Nick HS, Agarwal A.** Manganese superoxide dismutase attenuates Cisplatin-induced renal injury: importance of superoxide. J Am Soc Nephrol 2001;12:2683–90.
26. **Kadikoylu G, Bolaman Z, Demir S, et al.** The effects of desferrioxamine on cisplatin-induced lipid peroxidation and the activities of antioxidant enzymes in rat kidneys. Hum Exp Toxicol 2004;23:29–34.
27. **Shino Y, Itoh Y, Kubota T, et al.** Role of poly(ADP-ribose-)polymerase in cisplatin-induced injury in LLC-PK1 cells. Free Radic Biol Med 2003;35:966–77.
28. **Badary OA, Abdel-Maksoud S, Ahmed WA, et al.** Naringenin attenuates cisplatin nephrotoxicity in rats. Life Sci 2005;76:2125–35.
29. **Durak I, Ozbek H, Karaayvaz M, et al.** Cisplatin induces acute renal failure by impairing antioxidant system in guinea pigs: effects of antioxidant supplementation on the cisplatin nephrotoxicity. Drug Chem Toxicol 2002;25:1–8.
30. **Sener G, Satiroglu H, Kabasakal L, et al.** The protective effect of melatonin on cisplatin nephrotoxicity. Fundam Clin Pharmacol 2000;14:553–60.
31. **Weijl NI, Elsendoorn TJ, Lentjes EG, et al.** Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study. Eur J Cancer 2004;40:1713–23.
32. **Chirino YI, Hernandez-Pando R, Pedraza-Chaverri J.** Peroxynitrite decomposition catalyst ameliorates renal damage and protein nitration in cisplatin-induced nephrotoxicity in rats. BMC Pharmacol 2004;4:20.
33. **Yildirim Z, Sogut S, Odaci E, et al.** Oral erdosteine administration attenuates cisplatin-induced renal tubular damage in rats. Pharmacol Res 2003;47:149–56.
34. **Winston JA, Safirstein R.** Reduced renal blood flow in early cisplatin-induced acute renal failure in the rat. Am J Physiol 1985;249:F490–6.
35. **Tanaka T, Kojima I, Ohse T, et al.** Hypoxia-inducible factor modulates tubular cell survival in cisplatin nephrotoxicity. Am J Physiol Renal Physiol 2005;289:F1123–33.
36. **Kaushal GP, Kaushal V, Hong X, et al.** Role and regulation of activation of caspases in cisplatin-induced injury to renal tubular epithelial cells. Kidney Int 2001;60:1726–36.
37. **Tsuruya K, Ninomiya T, Tokumoto M, et al.** Direct involvement of the receptor-mediated apoptotic pathways in cisplatin-induced renal tubular cell death. Kidney Int 2003; 63:72–82.
38. **Dimanche-Boitrel MT, Meurette O, Rebillard A, et al.** Role of early plasma membrane events in chemotherapy-induced cell death. Drug Resist Updat 2005;8:5–14.
39. **Faubel S, Ljubanovic D, Reznikov L, et al.** Caspase-1-deficient mice are protected against cisplatin-induced apoptosis and acute tubular necrosis. Kidney Int 2004;66:2202–13.
40. **Basnakian AG, Apostolov EO, Yin X, et al.** Cisplatin nephrotoxicity is mediated by deoxyribonuclease I. J Am Soc Nephrol 2005;16:697–702.
41. **Ramesh G, Reeves WB.** Salicylate reduces cisplatin nephrotoxicity by inhibition of tumor necrosis factor-alpha. Kidney Int 2004;65:490–9.
42. **Ramesh G, Reeves WB.** TNF-alpha mediates chemokine and cytokine expression and renal injury in cisplatin nephrotoxicity. J Clin Invest 2002;110:835–42.
43. **Ramesh G, Reeves WB.** TNFR2-mediated apoptosis and necrosis in cisplatin-induced acute renal failure. Am J Physiol Renal Physiol 2003;285:F610–8.
44. **Yamate J, Sato K, Ide M, et al.** Participation of different macrophage populations and myofibroblastic cells in chronically developed renal interstitial fibrosis after cisplatin-induced renal injury in rats. Vet Pathol 2002;39:322–33.
45. **Guinee DG Jr, van Zee B, Houghton DC.** Clinically silent progressive renal tubulointerstitial disease during cisplatin chemotherapy. Cancer 1993;71:4050–4.
46. **Robbins ME, Bywaters TB, Jaenke RS, et al.** Long-term studies of cisplatin-induced reductions in porcine renal functional reserve. Cancer Chemother Pharmacol 1992;29:309–15.
47. **Yamate J, Machida Y, Ide M, et al.** Effects of lipopolysaccharide on the appearance of macrophage populations and fibrogenesis in cisplatin-induced rat renal injury. Exp Toxicol Pathol 2004;56:13–24.
48. **Hellwig-Burgel T, Stiehl DP, Wagner AE, et al.** Review: hypoxia-inducible factor-1 (HIF-1): a novel transcription factor in immune reactions. J Interferon Cytokine Res 2005;25: 297–310.
49. **Cornelison TL, Reed E.** Nephrotoxicity and hydration management for cisplatin, carboplatin, and ormaplatin. Gynecol Oncol 1993;50:147–58.
50. **Isnard-Bagnis CDG.** Anticancer drugs. In: De Broe M.E PGA, Bennett W.M, Verpooten G.A, ed. Clinical Nephrotoxins (ed 2nd): Kluwer Academic; 2003:353–72.
51. **Daugaard G, Abildgaard U.** Cisplatin nephrotoxicity: a review. Cancer Chemother Pharmacol 1989;25:1–9.
52. **Kollmannsberger C, Kuzcyk M, Mayer F, et al.** Late toxicity following curative treatment of testicular cancer. Semin Surg Oncol 1999;17:275–81.
53. **Anand AJ, Bashey B.** Newer insights into cisplatin nephrotoxicity. Ann Pharmacother 1993;27:1519–25.
54. **Lajer H, Kristensen M, Hansen HH, et al.** Magnesium depletion enhances cisplatin-induced nephrotoxicity. Cancer Chemother Pharmacol 2005;56:535–42.
55. **Kintzel PE.** Anticancer drug-induced kidney disorders. Drug Saf 2001;24:19–38.
56. **Meyer KB, Madias NE.** Cisplatin nephrotoxicity. Miner Electrolyte Metab 1994;20:201–13.

57. **Goren MP.** Cisplatin nephrotoxicity affects magnesium and calcium metabolism. Med Pediatr Oncol 2003;41:186–9.
58. **Lajer H, Daugaard G.** Cisplatin and hypomagnesemia. Cancer Treat Rev 1999;25:47–58.
59. **Vickers AE, Rose K, Fisher R, et al.** Kidney slices of human and rat to characterize cisplatin-induced injury on cellular pathways and morphology. Toxicol Pathol 2004;32: 577–90.
60. **Tanaka H, Ishikawa E, Teshima S, et al.** Histopathological study of human cisplatin nephropathy. Toxicol Pathol 1986;14:247–57.
61. **Portilla D, Li S, Nagothu KK, et al.** Metabolomic study of cisplatin-induced nephrotoxicity. Kidney Int 2006;69:2194–204.
62. **Santoso JT, Lucci JA III, Coleman RL, et al.** Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. Cancer Chemother Pharmacol 2003;52:13–8.
63. **Dumas M, de Gislain C, d'Athis P, et al.** Influence of hydration on ultrafilterable platinum kinetics and kidney function in patients treated with cis-diamminedichloroplatinum(II). Cancer Chemother Pharmacol. 1990;26:278–82.
64. **Daley-Yates PT, McBrien DC.** A study of the protective effect of chloride salts on cisplatin nephrotoxicity. Biochem Pharmacol 1985;34:2363–9.
65. **Hanigan MH, Deng M, Zhang L, et al.** Stress response inhibits the nephrotoxicity of cisplatin. Am J Physiol Renal Physiol 2005;288:F125–32.
66. **Fu S, Kavanagh JJ, Hu W, et al.** Clinical application of oxaliplatin in epithelial ovarian cancer. Int J Gynecol Cancer 2006;16:1717–32.
67. **Piccart MJ, Lamb H, Vermorken JB.** Current and future potential roles of the platinum drugs in the treatment of ovarian cancer. Ann Oncol 2001;12:1195–203.
68. **Grover B, Auberger C, Sarangarajan R, et al.** Functional impairment of renal organic cation transport in experimental diabetes. Pharmacol Toxicol 2002;90:181–6.
69. **Sarangarajan R, Cacini W.** Early onset of cisplatin-induced nephrotoxicity in streptozotocin-diabetic rats treated with insulin. Basic Clin Pharmacol Toxicol 2004;95:66–71.
70. **Esposito M, Viale M, Vannozzi MO, et al.** Effect of the antiarrhythmic drug procainamide on the toxicity and antitumor activity of cis-diamminedichloroplatinum(II). Toxicol Appl Pharmacol 1996;140:370–7.
71. **Viale M, Vannozzi MO, Pastrone I, et al.** Reduction of cisplatin nephrotoxicity by procainamide: does the formation of a cisplatin-procainamide complex play a role? J Pharmacol Exp Ther 2000;293:829–36.
72. **Lynch ED, Gu R, Pierce C, et al.** Reduction of acute cisplatin ototoxicity and nephrotoxicity in rats by oral administration of allopurinol and ebselen. Hear Res 2005;201:81–9.
73. **Nisar S, Feinfeld DA.** N-acetylcysteine as salvage therapy in cisplatin nephrotoxicity. Ren Fail 2002;24:529–33.
74. **Karimi G, Ramezani M, Tahoonian Z.** Cisplatin nephrotoxicity and protection by milk thistle extract in rats. Evid Based Complement Alternat Med 2005;2:383–6.
75. **Jones MM, Basinger MA, Holscher MA.** Control of the nephrotoxicity of cisplatin by clinically used sulfur-containing compounds. Fundam Appl Toxicol 1992;18:181–8.
76. **Capizzi RL.** Amifostine reduces the incidence of cumulative nephrotoxicity from cisplatin: laboratory and clinical aspects. Semin Oncol 1999;26:72–81.
77. **Myers CE, McGuire WP, Liss RH, et al.** Adriamycin: the role of lipid peroxidation in cardiac toxicity and tumor response. Science 1977;197:165–7.
78. **Treskes M, van der Vijgh WJ.** WR2721 as a modulator of cisplatin- and carboplatin-induced side effects in comparison with other chemoprotective agents: a molecular approach. Cancer Chemother Pharmacol 1993;33:93–106.
79. **Kohda Y, Kawai Y, Iwamoto N, et al.** Serum thymic factor, FTS, attenuates cisplatin nephrotoxicity by suppressing cisplatin-induced ERK activation. Biochem Pharmacol 2005;70: 1408–16.
80. **Schweyer S, Soruri A, Meschter O, et al.** Cisplatin-induced apoptosis in human malignant testicular germ cell lines depends on MEK/ERK activation. Br J Cancer 2004;91: 589–98.
81. **Li G, Sha SH, Zotova E, et al.** Salicylate protects hearing and kidney function from cisplatin toxicity without compromising its oncolytic action. Lab Invest 2002;82:585–96.
82. **Deng J, Kohda Y, Chiao H, et al.** Interleukin-10 inhibits ischemic and cisplatin-induced acute renal injury. Kidney Int 2001;60:2118–28.
83. **Nagothu KK, Bhatt R, Kaushal GP, et al.** Fibrate prevents cisplatin-induced proximal tubule cell death. Kidney Int 2005;68:2680–93.
84. **Willox JC, McAllister EJ, Sangster G, et al.** Effects of magnesium supplementation in testicular cancer patients receiving cis-platin: a randomised trial. Br J Cancer 1986;54: 19–23.