Nephrotoxicity Induced by Cancer Chemotherapy With Special Emphasis on Cisplatin Toxicity

F. Ries, MD, and J. Klastersky, MD

INDEX WORDS: Nephrotoxic drugs; chemotherapy; renal failure; cisplatin; methotrexate; mitomycin; semustine; streptozotocin; cancer.

Since the kidney is highly susceptible to toxic injury by a multitude of different drugs, it is not surprising that several antineoplastic agents may exert potent nephrotoxicity. In cancer patients, however, one must always be aware of additive or synergistic effects that may potentiate chemotherapy-induced nephrotoxicity. Cancer patients are frequently treated with nephrotoxic antibiotics (e.g., aminoglycosides or amphotericin B). They may suffer from radiation-induced nephrotoxicity, or present with hypercalcemia, hyperuricemia, lysozymuria, cancer-related microangiopathic hemolysis, or disseminated intravascular coagulopathy. These patients also may present with immune complex-mediated glomerulopathy or paraprotein-related nephropathy, and with amyloidosis as well as minimal-change nephritis. They may have direct infiltration of the kidney by tumor cells as well as an obstructive nephropathy caused by lower urinary tract invasion and compression. Different radiologic investigations with iodine contrast media may be potentially harmful to the kidney; cancer patients frequently suffer from urinary tract infections. It is, therefore, important to take into account every potentially harmful effect when looking for chemotherapy-related nephrotoxicity.

The agents whose potential for nephrotoxicity has been clearly established will be discussed in the following review. These are methotrexate, cisplatin, semustine (methyl-CCNU), streptozotocin, mitomycin, mitomycin C, and azacytidine. Cisplatin nephrotoxicity will be reviewed in greater detail. In addition, the reader is informed that the problem of chemotherapy-related nephrotoxicity has been analyzed in several review articles.1,3

METHOTREXATE

Methotrexate (MTX), an inhibitor of folate synthesis, is one of the earliest and one of the most used agents in cancer chemotherapy. Used for more than 30 years, MTX has shown activity in a great number of tumors, such as leukemia, lymphoma, choriocarcinoma, osteosarcoma, and tumors of the breast, head and neck, and lung.2,3

Since MTX is excreted primarily by the kidney, any changes in renal function will have an effect on MTX plasma levels and MTX clearance, with subsequent exposure of the whole organism to per-
NEPHROTOXICITY OF CYTOSTATICS

Persistently elevated concentrations of the drug. Proliferating or cycling cells, since those of the bone marrow and gastrointestinal tract are most susceptible to the toxic effects of MTX and intoxication with MTX secondary to renal failure, primarily result in marrow hypoplasia and severe mucositis. Apart from causing important systemic toxicity, high plasma concentrations of MTX are also nephrotoxic per se, and renal failure has been implicated in 20% of the deaths associated with high-dose MTX administration.

Several mechanisms may contribute to MTX-related renal failure: precipitation of MTX in renal tubules, direct antimitotic effect on renal tubular cells, and possibly, alteration of change with urinary pH, and the drug was shown accepted. MTX solubility has been shown to be two to ten times more soluble at pH 6.9 than at pH 5.7. Precipitation of the drug may occur in concentrated and acid urine resulting in renal tubular obstruction by an amorphous yellow material; this has been shown at autopsy examinations of MTX-treated patients dying from acute renal failure. The amorphous material was identified as MTX by immunofluorescent techniques. The risk of tubular MTX precipitation can be minimized by hydration as well as alkalinization.

In patients with established nephrotoxicity, leucovorin rescue treatment may counteract the cytotoxic effects of MTX. Leucovorin (tetrahydrofolate), inhibiting MTX activity by competition, is administered in high-dose MTX programs at conventional doses of 15 mg, repeated at regular intervals: since MTX concentrations are sometimes extremely high in MTX-induced renal failure, the doses of leucovorin rescue should be appropriately increased. Lowering of MTX levels by means of peritoneal dialysis, hemodialysis, or hemoperfusion seems to be of marginal value.

Since, in most cases, patients are not oliguric or anuric in MTX-related renal failure, high fluid intake with alkalinization should always be maintained. Apart from vigorous hydration, alkalinization, and administration of leucovorin during high-dose MTX therapy, care should be taken to avoid the drug in patients who suffer from preliminary renal insufficiency or to postpone its use in patients who are dehydrated; urine acidifying agents and salicylate derivatives should be avoided before and during MTX treatment. Good knowledge and careful application of these efficient measures for prevention of MTX-related nephrotoxicity have been associated with the near disappearance of this potentially harmful complication.

SEMUSTINE (METHYL-CCNU)

Semustine, like the other nitrosourea compounds, is a highly lipid-soluble drug that has some clinical activity in neoplasms of the brain, gastrointestinal tract, as well as malignant melanoma. Nephrotoxicity of this compound had been described in early preclinical toxicity experiments, but evidence for possible nephrotoxicity in humans appeared only much later in 1978 and 1979. Since then, numerous other reports on semustine nephrotoxicity have been published.
The most frequent clinical manifestation is a slowly rising serum creatinine level with progressive irreversible renal failure. Pathologic findings are generally consistent with the presence of small and atrophic kidneys, signs of tubular atrophy, hyaline casts, glomerulosclerosis, and interstitial fibrosis.\textsuperscript{32} 

Semustine nephrotoxicity is cumulative; renal dysfunction has been noted in 26\% of patients who received total cumulative doses in excess of 1,400 mg/m\textsuperscript{2}.\textsuperscript{31} The median cumulative dose at which nephrotoxicity is likely to occur has been estimated to be near 2,000 mg/m\textsuperscript{2}.\textsuperscript{32} It is, thus, not surprising that this problem generally appears only in patients being treated for more than 1 year, which requires a prolonged survival time.

Compared to the other nitrosoureas, it can be noted that semustine nephrotoxicity totally differs from that of streptozotocin, the most nephrotoxic compound of the nitrosourea group. The other nitrosoureas, ie, chlorozotocin, lomustine, and carmustine, seem to be much less nephrotoxic, with only occasional cases reported.

The specific mechanisms of semustine-related nephrotoxicity remain unclear and there are no established recommendations for toxicity protection. Prochlorperazine, a commonly used phenothiazine with antiemetic properties, has been reported in animal studies to reduce the frequency and the severity of semustine-related renal lesions\textsuperscript{33}: the clinical impact of this observation has not yet been established.

**STREPTOZOTOCIN**

Streptozotocin is a nitrosourea that has been used successfully in the treatment of islet cell tumors.\textsuperscript{14-36} Renal toxicity is the major dose-limiting side effect of this drug. Nephrotoxicity seems to be dose-related and, to some extent, cumulative, occurring most frequently at doses in excess of 1.5 g/m\textsuperscript{2}/wk.\textsuperscript{37,38} 

Toxicity generally presents initially as mild proteinuria,\textsuperscript{39} but with continued use, proximal renal tubular damage may develop.\textsuperscript{31} Fanconi syndrome, renal tubular acidosis, hypokalemia, renal glycosuria, hypophosphatemia, and most significantly, life-threatening oliguria and anuria have been reported. Nephrogenic diabetes insipidus seems to be less frequent.\textsuperscript{40,41} 

The best prevention for potentially harmful nephrotoxicity should be afforded by an optimal dosage schedule and frequent examinations for proteinuria.\textsuperscript{37,42} The drug should be discontinued when proteinuria or other signs of renal dysfunction develop; with resolving proteinuria, drug administration might be carefully continued.

**MITHRAMYCIN**

Mithramycin, a naturally occurring cytotoxic antibiotic, has shown some activity against gonadal cancer, as well as glioblastomas\textsuperscript{43-46}; however, its multiple toxic side effects have precluded its widespread use. Apart from causing important hematologic and clotting abnormalities, gastrointestinal, central nervous, and hepatic dysfunction, as well as hypocalcemia, it also induces renal toxicity, manifested by signs of renal failure and proteinuria.

This renal toxic effect tends to be cumulative and may be irreversible; drug-related deaths due to renal failure have been reported in 6 of 32 patients treated with the drug.\textsuperscript{43} Histopathologic changes consist primarily of renal tubular swelling, degeneration, necrosis, and atrophy with sparing of the glomeruli. Mithramycin still has some applications in refractory cancer-related hypercalcemia, where lower doses are generally effective.\textsuperscript{47,48}

**MITOMYCIN C**

Mitomycin C (MMC) is a naturally occurring alkylating agent, introduced for clinical use as early as 1958. It has been demonstrated to be active against carcinomas of the gastrointestinal tract, breast, prostate, and a few other carcinomas as well.\textsuperscript{49,50}

Activation of mitomycin seems to require in vivo metabolism to form short-lived metabolites that are highly reactive. Its serum half-life varies from nine to 17 minutes, and inactivation of the drug occurs in various organs including the liver and the kidney. Renal excretion of mitomycin is negligible.\textsuperscript{49}

Early reports on animal studies had shown various nephrotoxic effects in dogs, monkeys, and mice.\textsuperscript{51-53} Reports on possible renal toxicity in humans occurred only much later.\textsuperscript{54} These studies generally showed microangiopathic changes in the renal circulation with hemolytic anemia, thrombocytopenia, proteinuria, hematuria, renal failure, systemic hypertension, pulmonary edema, and congestive heart failure. This clinical syndrome has been variously described as microangiopathic
Nephrotoxicity of Cytostatics

Hemolytic anemia, MMC-related hemolytic-uremic syndrome, and MMC nephrotoxicity. Several clinical manifestations show similarities with cancer-related microangiopathy and coagulopathy, and different authors have suggested a possible relation between both problems.

In one large series, 140 of 143 patients treated with mitomycin had renal impairment; among these, 6% died of renal failure. Three patients developed rapidly progressive renal disease with sharp elevations of BUN and creatinine level, hypertension, proteinuria, hematuria, signs of microangiopathic hemolytic anemia, and death from renal failure. Several other patients in that series presented with some degree of red-cell fragmentation, thrombocytopenia, proteinuria, and hypertension, but the clinical course was generally less fulminant and renal failure frequently developed without signs of hemolysis. As in other studies, toxic reactions to mitomycin could be related to repeated doses of 10 to 20 mg/m², with a total dose-range between 40 and 115 mg/m². The time interval between the onset of MMC therapy and renal failure was 4 to 16 months, with an average of 10 to 11 months.

Renal toxicity of MMC is apparently not dose-related and the precise pathogenetic mechanism remains unknown. Renal biopsies and studies of autopsy material have shown microangiopathic lesions with fibrous thrombi in the glomeruli and small arteries, glomerular nuclear degeneration and thickened basement membrane, intimal hyperplasia of arteries, glomerular necrosis, and mesangiopathy.

Immune complexes have been detected in six patients with MMC-associated hemolytic-uremic syndrome; these immune complexes showed high platelet aggregation activity in vitro. The constituent antibody of each complex failed to react with MMC antigen preparations, whereas in vitro reactivity to endodermally derived neoplasms could be detected. These data suggest that MMC might not be the only etiologic factor of this syndrome, but that some tumor-specific relationship might exist as well.

Mitomycin-associated nephrotoxic reactions must be considered refractory to most treatments studied until now. In small studies, steroids, anticoagulants, and platelet inhibitors have been tried unsuccessfully. Plasmapheresis has shown variable resolution of the hematologic manifestations without any effect on progressive renal failure. Combinations of immunosuppressive and antiplatelet drugs, with or without plasmapheresis, has been shown to be only of marginal benefit. Temporary progression of the disease activity has been attributed to blood transfusions, which should, therefore, be administered with caution. Hemodialysis may be necessary for life-threatening renal failure, but it will not effect the underlying disease process.

For patients treated with MMC, renal and hemato logic function should be monitored regularly after initiation of chemotherapy. MMC should be discontinued if early toxic manifestations, especially azotemia or hematuria, are detected. To date, there are no data available to predict individual susceptibility to this complication. Further studies are needed to clarify the causes, prevention, and treatment of the renal complication, and to establish general recommendations for MMC use.

AZACYTIDINE

5-Azacytidine, a pyrimidine analogue, is a useful agent in acute nonlymphocytic leukemia. This drug was shown to be associated with azotemia and renal tubular dysfunction. Abnormalities of proximal and distal tubules, as well as of the collecting ducts, have been described. Polyuria, salt wasting, defective reabsorption of phosphate, aminoaciduria, and renal glycosuria have also been documented.

CISPLATIN

In 1969, platinum compounds were reported by Rosenberg et al to exert potent antitumor activity in mice; cis-diamminedichloroplatinum II (cisp latin) was the most active drug among these compounds. Cisplatin, therefore, entered toxicologic evaluation in animals before introduction into phase I clinical trials. Since then, cisplatin has been studied in numerous phase II/III trials (alone or with other agents), and it has proven to be one of the most potent chemotherapeutic agents, being active in cancer of the ovary, testis, bladder, head and neck, lung, uterine cervix, and many others. Several excellent reviews deal with problems such as mechanism of action, activity on diverse tumors, as well as toxicity of cisplatin.

Since 1971, animal studies have shown a major
cisplatin-induced nephrotoxicity\textsuperscript{75} that proved to be dose related.\textsuperscript{76} These and other reports with studies performed on various animal models showed a strong relationship between the administered dose and uremia, as well as dose-related structural alterations detected on microscopic kidney examination. These alterations consisted predominantly in tubular necrosis. As could be expected from animal studies, early clinical reports showed similar toxicity in humans.\textsuperscript{77-80,92,93} In patients with normal kidney function, rising BUN levels were noted during the second week after a bolus cisplatin administration in excess of 50 mg/m\textsuperscript{2} of body surface area (BSA); reversible nephrotoxicity was generally noted between 50 and 75 mg/m\textsuperscript{2}/d, while doses $\geq$ 100 mg/m\textsuperscript{2}/d were frequently followed by acute renal failure with pronounced tubular cell necrosis. Renal failure progressing from reversible to irreversible stages was described with repeated treatment courses. These early studies were performed without particular hydration or drug-induced diuresis programs. Several authors have reviewed the problem of cisplatin-related nephrotoxicity\textsuperscript{101-103}; the conclusions of their articles, as well as more recent information, will be analyzed in the following discussion. In fact, cisplatin nephrotoxicity remains of particular interest since renal damage is one of its most critical side effects and frequently constitutes a dose-limiting factor.

**Mechanism of Action and Implications for Renal Toxicity**

Several studies suggest that cisplatin exerts its activity in a manner similar to alkylating agents by drug interaction with the nucleophilic sites of pyrimidines in DNA.\textsuperscript{97,98,106} These intrastrand DNA cross-links will occur after physiologic activation of the drug, which will take place in a low chloride concentration environment: cisplatin passage from a chloride-rich plasmatic milieu (103 mEq/L) to a low-chloride intracytoplasmic milieu (4 mEq/L) constitutes a passage from electrical neutrality (with a stable bis-chloro molecule [II]) to aqueous activation (II, III, V), chloride ligands in the cis position being replaced by water molecules (Fig 1). These aquated forms are highly reactive with nucleophiles and can loose hydrogen ions to form cytotoxic hydroxyl radicals (IV, V); these latter compounds can also form cytotoxic oxygen-bridged dimers and trimers. At equilibrium, the proportion between these diversely cytotoxic complexes depends on chloride concentration and, to a lesser extent, on pH and total platinum concentration.\textsuperscript{107,108}

Since platinum tissue concentrations are particularly high in the kidneys after drug administration in dogs and humans,\textsuperscript{93-109} and data suggesting an active tubular secretion of cisplatin or metabolites,\textsuperscript{110-112} it can be hypothesized that renal toxicity might be similar to its general cytotoxic effects. This implies that intratubular reduction of cisplatin concentration by abundant hydration, as well as activation of tubular chloride reuptake by forced chloresis, might favorably influence the equilibrium between stable nontoxic cisplatin (I) and aquated forms (II, III, V), as well as cytotoxic hydroxyl species (IV, VI), thereby reducing renal tubular damage without affecting general cytotoxicity.

**Cisplatin Tissue Distribution, Pharmacokinetics, and Renal Handling**

After IV administration, cisplatin undergoes rapid distribution to nearly all organs. Tissue platinum concentration studies at various points after cisplatin administration in dogs show a very rapid accumulation of the metal in the kidney (three to four times the plasma concentration ten minutes after administration) with persistently elevated values for more than 1 week.\textsuperscript{109} A very high postmortem renal concentration of platinum has also been reported in humans two days after administration of a single dose of 2 mg/kg of cisplatin.\textsuperscript{95} Platinum concentrates in various other tissues (gonadal tissue, lung, liver, fat)\textsuperscript{106}; studies in humans have shown that 90% of the drug is protein-bound in plasma and that 27% to 45% of the drug is excreted in the urine within five days of administration.\textsuperscript{113} Data on free platinum renal clearance in humans indicate that platinum clear-
Nephrotoxicity of Cytostatics

Excessive age-associated cisplatin-induced nephrotoxicity generally results in a lower 24-hour creatinine clearance, but as has been shown in a recent clinical study, they are not associated with greater renal toxicity if standard hydration is performed and if cisplatin dosage does not exceed 60 mg/m²/d. This study even suggests a protective mechanism in patients with unique kidneys (14 of 43 patients studied) compared with those with two normally functioning kidneys. In fact, the reduced number of nephrons will produce a higher flow of ultrafiltrate per tubule with lower tubular cisplatin concentration and probably less tubular "contact" between the toxin and tubular epithelium. This is illustrated by a higher than normal 24-hour diuresis, with lower cisplatin urinary concentrations for an identical cisplatin dose and hydration program in these patients, compared with those with two normally functioning kidneys. A similar mechanism is thought to contribute to the relative lack of excessive age-associated cisplatin-induced nephrotoxicity.

Other studies (in animals and humans), based on rhythmic changes in kidney function, according to circadian rhythms, have shown that optimal renal tolerance of cisplatin occurs very near to the time of day associated with the normal circadian maximum in urinary volume. This beneficial effect is potentiated by concurrent hydration and is correlated by lower urinary cisplatin concentrations. These studies, along with those on hydration and forced diuresis suggest the primordial role of reducing cisplatin urinary concentrations by high urinary output; in fact, direct tubular exposure for a few hours to a concentration of 200 µg/mL of cisplatin seems to be necessary for tubular damage to occur.

Pathologic Kidney Changes

As documented by animal and human studies, cisplatin induces several microscopic kidney changes that are dose-related and, to a lesser degree, cumulative. These changes include epithelial cell degeneration, proximal tubular necrosis, dilatation and necrosis of distal tubules, interstitial edema, and lymphocytic infiltration. Glomerular changes are generally not observed and most alterations are considered to be nonspecific. Tubular damage is also suggested by sensitive assays for tubular enzymes, thought to be liberated by renal injury: alanine-aminopeptidase, N-acetyl-β-glucosaminidase (NAG), and α-glucosidase. These studies support the concept that all areas of the tubule may be injured to some extent.

Studies on urinary activity of NAG, a lysosomal enzyme released into the urine from the brush border of proximal tubular cells, have shown a positive correlation between cisplatin nephrotoxicity and NAG urinary activity. Potentiation of cisplatin tissue uptake by NAG tissue activity has been reported, as well as a circadian rhythm of urinary NAG activity, suggesting that rhythmic changes in NAG activity may cause variations in cisplatin nephrotoxicity along with circadian rhythms. β2-microglobulin, possibly another mediator of tubular injury, was shown to be significantly elevated in the urine 12 hours after treatment with cisplatin: since no patient in that report developed laboratory evidence of renal toxicity, this increased β2-microglobulinuria has been interpreted as reflecting subclinical renal damage.

Hypomagnesemia and renal magnesium wasting are the most prominent electrolytic disorders secondary to cisplatin administration. Hypomagnesemia developed in 52% of 44 patients in a series with a treatment schedule of 70 mg/m² cisplatin (on day 1), repeated every 21 days. Among patients with hypomagnesemia, the nadir Mg concentration (median) was 0.92 mEq/L, usually occurring more than 2 weeks after drug administration and generally after one or two courses of cisplatin had been given. Similar hypomagnesemia was also observed in other studies and is frequently complicated by hypocalcemia that is probably secondary to diminished PTH release and/or end-organ resistance to parathyroid hormone induced by hypomagnesemia. Clinical manifestations of hypomagnesemia, including abnormalities in neuromuscular, central nervous system, and cardiac function that may appear for serum levels of less than 1 mEq/L, should be treated by parenteral replacement of magnesium sulfate. Associated hypocalcemia is responsive to magnesium repletion and is unresponsive to calcium replacement alone. The more
rarely seen hypokalemia should be treated by replacement of both potassium and magnesium.

Prevention of Cisplatin-Induced Nephrotoxicity

Preexistent renal insufficiency should always be excluded before starting cisplatin therapy; dehydration, arterial hypertension and hyperuricemia should be corrected; concomitant administration of nephrotoxic drugs, especially aminoglycoside antibiotics, should be avoided.128

Numerous clinical trials proposing various hydration programs have been described.55.86.119 All of these schedules are valuable, provided that hydration status is closely monitored. Most hydration programs are performed with normal saline solution or glucose 5% in saline and are given for various durations, before, during, and after cisplatin administration. Hydration alone can be considered sufficiently effective if cisplatin is administered as 20 mg/m²/d by one- to two-hour infusion for five consecutive days.

Forced-diuresis programs, combining hydration with furosemide or mannitol administration, have proved clinically beneficial in numerous studies.54.130-132 and superiority of hydration-diuretic programs compared to hydration alone has been suggested.133 Most of the more recent programs permit administration of cisplatin at doses of 100 to 120 mg/m² as short daily infusions or administration of 20 to 40 mg/m²/d for five consecutive days. Intensive parenteral hydration with mannitol-induced diuresis even permits prevention of dose-limiting nephrotoxicity. In these patients, myelotoxicity might become a major problem;34 combined with cisplatin administration in hypertonic saline, doses as high as 200 mg/m² have been administered, with thrombocytopenia being the most prominent toxic effect.133 In a recent study, three "high-dose" regimens, with doses between 180 and 220 mg/m²/d, were compared: cisplatin was dissolved in 5% saline and was administered along with a well-defined prehydration-mannitol-induced diuresis and posthydration program. In that study it was concluded that cisplatin, given at a dose of 200 mg/m² in five daily fractions, combined with an appropriate hydration and diuresis program, was devoid of significant nephrotoxicity and was probably much less ototoxic than single-bolus high-dose administration.136 High chloride diuresis may improve the therapeutic index of cisplatin by reduced nephrotoxicity without loss of antitumor activity. Animal studies have shown increased nephrotoxicity in chloride-deprived rats and significantly reduced renal damage with pharmacologically induced chloruresis; this favorable effect could be explained by the reduction of highly toxic aqueous-cisplatin complexes in chloride-rich urine.108

Continuous infusion of cisplatin results in reduced gastrointestinal and renal toxicity129.137-140 when compared with earlier studies with equal daily doses. Continuous infusion should, however, always be associated with adequate hydration programs, the influence on renal toxicity of vigorous urinary output being more important than the duration of infusion.

Pharmacologic Interaction With Cisplatin Nephrotoxicity

Unlike mannitol and furosemide, which exert their activity by inducing a potent diuresis, various other compounds have been proposed on the basis of a potential for detoxification. Among these, probenecid has been studied in animals (F344 rat model) and was shown to decrease the peak values of BUN and creatinine if administered one hour prior to cisplatin; this protection has been ascribed to probenecid inhibition of active secretion of cisplatin by the p-aminohippurate system.141

WR-2721[S-2-(3-aminopropylamino)-ethylphosphorothioic acid], a radioprotective agent, has been shown to exert protective activity on renal function in the same F344 rat model.142

Diethylthiocarbamate (DDTC), a potent SH-group chelator administered to F344 rats after a known nephrotoxic dose of cisplatin, may prevent renal pathologic as well as functional changes.143 This protective activity is ascribed to competition with cisplatin for protein-bound sulfhydryl groups within proximal tubular cells. Protein binding of cisplatin in tubular cells, with resultant inhibition of transport enzymes, is one postulated mechanism of cisplatin nephrotoxicity in rats and, perhaps, in humans. The closely related disulfiram (Antabuse: Ayerst Laboratories, New York), being metabolized to diethylthiocarbamate, might exert a similar protective effect.

Sodium thiosulfate has also been studied for its nephrotoxicity preventive effects.144 This sulfur-containing compound is thought to react covalently with cisplatin, resulting in complexes that are neither toxic nor tumoricidal.144 Apart from markedly reducing general cisplatin toxicity by its systemic activity, sodium thiosulfate might exert
NEPHROTOXICITY OF CYTOSTATICS

further reduction in nephrotoxicity through particularly high intratubular thiosulfate to cisplatin concentration ratios. Intravenous sodium thiosulfate seems to be a most interesting agent when administered in combination with intraperitoneal cisplatin, eg, for ovarian cancer. In this indication, parenteral thiosulfate administration allowed escalation of intraperitoneal cisplatin up to a dose of 270 mg/m² without significant nephrotoxicity, thus permitting an increased therapeutic as well as toxic concentration ratios. Intravenous sodium thiosulfate, however, the presence of two sulfur atoms in this molecule could also act by competition with cisplatin for tubular reabsorption, thus promoting cisplatin excretion: however, the presence of two sulfur atoms in this molecule could also permit chemical interaction and detoxification. In an animal study (male F344 rat model), pretreatment with acetazolamide decreased cisplatin nephrotoxicity and diminished renal platinum content, as well as urinary platinum excretion. Comparison of acetazolamide and mannitol in the same animal model (performed by the same authors) shows acetazolamide to be more effective than mannitol in preventing cisplatin-induced nephrotoxicity in male F344 rats. The enzyme copper-zinc superoxide dismutase (organ) has also been associated with reduction of nephrotoxicity in rats, thus suggesting that superoxide radicals may participate in the nephrotoxic effects of cisplatin.

Selenium, known for its ability to combine to metals such as cadmium and mercury, as well as for its resemblance to sulfur by its chemical properties, shows theoretical promise as a cisplatin-precipitating agent. As shown in studies on mice, selenium is able to decrease cisplatin nephrotoxicity without influencing in vivo and in vitro tumor growth. This could suggest either detoxification by ligation to sites not involved in cisplatin antitumor activity or, perhaps, prevention of tubular reabsorption of the molecular complex.

PERSPECTIVES AND CONCLUSIONS

A better knowledge of various factors contributing to cisplatin nephrotoxicity, as well as optimal administration programs with hydration and drug-induced diuresis, have considerably changed the spectrum of cisplatin’s potential for renal toxicity. Introduction of some of the new detoxification agents will probably prove useful as well. Dosing plasma cisplatin levels at various times after drug infusion could be helpful to predict nephrotoxicity early in the course of cisplatin infusion. Finally, several second-generation platinum complexes are being evaluated in preclinical and clinical studies for toxicity and antitumor activity. Among these, iroplatinum (CHIP) and carboplatinum (CBDCA) show little or no nephrotoxicity. These and other platinum compounds are possibly candidates as future alternatives to cisplatin in several conditions. Until then, however, cisplatin remains one of the most potent antineoplastic agents ever developed. Further work should be performed to reduce its potential for renal toxicity.

REFERENCES


NEPHROTOXICITY OF CYTOSTATICS


NEPHROTOXICITY OF CYTOSTATICS


143. Borch RF, Pleasants ME: Inhibition of cis-platinum nephrotoxicity by diethylthiocarbamate rescue in a rat model. Proc Natl Acad Sci 76:6611-6614, 1979


