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REVIEW

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Cisplatin-induced renal toxicity and toxicity-modulating strategies: a review

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Introduction

Cisplatin, or *cis*-diamminedichloroplatinum(II) (CDDP), is an antineoplastic agent developed in 1965 by Rosenberg et al. [70], who were studying the effects of electrolysis products from a platinum electrode on growing cells. Cisplatin was clinically tested in 1972 by Hill et al. [40]. In spite of its good antineoplastic activity against ovarian, lung, bladder, breast, head and neck, and testicular cancer, its clinical use was rapidly limited due to unexpected and very severe renal toxicity. Acute and cumulative renal toxicity associated with histological damage has been shown in both animal and human studies. Several theories concerning the pathophysiological mechanism behind this toxicity have been suggested [13, 59].

Since the therapeutic efficacy of cisplatin seems to be proportional to the delivered dose [80], there has been a continuous search for biological and pharmacological strategies to protect the renal function and thus permit the administration of high quantities of the drug; these strategies include modification of administration modes, development of new galenic forms, and the use of chemoprotectors, among others. Additionally, other platinum analogs with less nephrotoxicity have been studied, but these agents have less antitumor activity than cisplatin or have other inherent toxicities restricting their use [78].

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The present review includes a discussion of different renoprotective strategies that have been developed, which follows a brief description of the nature and underlying mechanism of CDDP nephrotoxicity.

Histological damage and pathophysiology

Histological damage

CDDP nephrotoxicity has been shown to be dose-related in both animals and humans [50, 55]. The principal site of damage is the proximal tubule. In studies on rats, pathological alterations were most prominent 3 days after CDDP injection. A range of morphological changes were present in the distal parts of the proximal tubule, including focal loss of brush border, cellular swelling, condensation of nuclear chromatin, and focal necrosis [25]. After 5 days, the predominant findings were tubular necrosis in the distal parts of the proximal segment, leading to tubular atrophy of cortical nephrons with intratubular debris. Some regeneration of the distal parts was seen after 7 days, characterized by tubules with widely dilated lumina, which were lined by many low-lying epithelial cells. These injury patterns are similar to those reported in experimental models of ischemia-induced acute tubular necrosis.

In humans, renal damage has been observed at cisplatin doses of 50 mg/m^2 given without adequate hydration [38]. The anomalies are mainly situated in the more distal parts of the proximal tubule or in the distal nephron segment, occurring rarely in the glomeruli and the renal mitochondrial and cytosolic organs, and persist for about 1 month after CDDP treatment [33, 52].

Pathophysiology

The mechanism of cisplatin nephrotoxicity is unclear. The vulnerability of the kidney to cisplatin may be related to its role as the primary excretory organ for platinum [45, 72]. In

the glomeruli, cisplatin is filtered by passive diffusion through cell membranes to enter the cell, or it may require a carrier molecule [69]. Until recently, cisplatin-induced renal toxicity was thought be initiated by hemodynamic changes, with tubular impairment occurring later. Recent studies, however, including work by Daugaard et al. [18], have shown that proximal tubular impairment is the primary event and that this tubular impairment secondarily leads to hemodynamic changes, i.e., reductions in the renal plasma flow and glomerular filtration rate, as these were not seen during the first few hours following CDDP administration but 2–3 days later. Moreover, there was a tendency toward increased fluid delivery from the proximal tubule to the thin, descending limb of Henle's loop producing an increased fluid load to the distal nephron segments [20]. Consequently, cisplatin administration caused impairment of proximal tubular resorption, but distal tubular function also seemed to be affected. Fjeldborg et al. [29], who investigated long-term CDDP toxicity, found an equally delayed reduction in the glomerular renal filtration rate that persisted for up to 16–52 months after the treatment. This effect may partially explain the cumulative toxicity of cisplatin observed after subsequent treatments. However, in animal studies, Safirstein et al. [73] have suggested that the renin-angiotensin system does not play a significant role in cisplatin-induced reduction in the glomerular filtration rate.

Taking into account the load dependency of sodium reabsorption in the loop of Henle, an increased fluid load usually produces an increased reabsorption rate in distal nephron segments and, thus, the reabsorption of sodium, potassium, magnesium, and calcium [19, 27]. Hypomagnesemia and hypocalcemia are in fact considered to be among the earliest signs of CDDP toxicity [77]. In some cases, severe hyponatremia and hypokalemia may occur. Magnesium deficiency and metabolic alkalosis associated with CDDP-induced vomiting may contribute to the hypokalemia [77]. The degree of urinary excretion of proteins and enzymes may indicate the degree of renal damage and, especially, of proximal tubular dysfunction. Daugaard [16] and Jones et al. [46] have studied the excessive excretion of proteins, beta-2-microglobulin, amino acids, and enzymes such as *N*-acetyl-beta-D-glucosamidase, alanine peptidase, or leucine aminopeptidase in the urine. Daugaard [16] suggested the existence of an early proteinuria (increased beta-2-microglobulin excretion) of tubular origin and a delayed proteinuria (increased immunoglobulin G excretion) of glomerular origin.

Another theory is that cisplatin interferes with the mechanisms that control cellular homeostasis. Sobrego et al. [80] have suggested that the active transport mechanism may become saturated, leading to an overconcentration of CDDP in tubular cells and, thus, to cellular necrosis. Magnesium and calcium are involved in the active CDDP-transport system, and decreases in their concentration may contribute to CDDP accumulation in renal cells.

A more recent theory is based on the findings of intracellular molecular abnormalities during acute renal failure. The primary biochemical effect of cisplatin in cancer cells is inhibition of DNA synthesis, and there may be a relationship between this effect and the renal-cell injury. Cisplatin interacts with adenine triphosphate and may thereby impair the activity of sodium-potassium/adenine triphosphatase, leading to a rapid decline of intracellular potassium [34]. Levi et al. [52] have investigated the effect of cisplatin on renal sulfhydryl groups, considering this toxicity as a heavy-metal toxicity. Sulfhydryl groups play an important role in maintaining the integrity of membrane structures and participate in a variety of active transport processes, and heavy metals such as mercury are thought to be nephrotoxic by reacting with such groups on vital proteins. The findings of Levi et al. [52] show that a depletion of protein-bound sulfhydryl groups does indeed take place, but certain conclusions concerning a cause-and-effect relationship could not be drawn.

Strategies for the modulation of cisplatin-induced renotoxicity

The different strategies are summarized in Table 1. In most of the clinical studies concerning cisplatin-induced nephrotoxicity, only plasma levels of creatinine and/or clearance of creatinine or blood urea nitrogen are used to evaluate the

Table 1 Strategies for the prevention of cisplatin-induced nephrotoxicity

Strategies	Putative mechanisms
Fractional doses, slow infusions	Dilution of CDDP in the tubule
Local infusions, preparations for organ-specific drug release	Decreasing systemic peak concentrations
Saline hydration protocols	Dilution of CDDP in the tubule, inhibition of the formation of toxic aquated metabolites
Mannitol, furosemide, acetazolamide	Decreasing drug-contact time renal tubule
Renin angiotensin blockers and calcium blockers	Increasing the renal blood flow, opposition to the vasoconstrictive action of angiotensin
Probenecid	Inhibition of active CDDP secretion
Thiosulfate, WR-2721, mesna, selenium compounds	Affinity of sulfur-containing ligands for platinum(II) complexes, chelating properties
Diethyldithiocarbamate	Removal of platinum from monoguanine adducts
Glutathione	Increasing the intracellular cysteine level, chelating properties
Bismuth compound	Induction of metallothionein synthesis, chelating properties
Steroids	Membrane stabilization
Urinastatin	Membrane stabilization, improving the renal blood flow

glomerular filtration rate. However, the sensitivity of these parameters in detecting early impairment of renal function have been broadly critiqued by Daugaard et al. [19]. Indeed, in patients with muscular atrophy, serum creatinine has been shown not to be a good indicator of the glomerular filtration rate. A better correlation was found between the clearance of [^{51}Cr]-ethylenediaminetetraacetic acid ([^{51}Cr]-EDTA) and inulin and the variation in glomerular function. Few studies have been performed to evaluate proximal tubular function.

Decreasing the systemic concentration of CDDP

Attempts to reduce cisplatin-induced toxicity have been centered on decreasing the exposure of the kidney to active cisplatin. The first methods used to reduce renal toxicity involved administration of the scheduled dose in multiple daily fractions and prolongation of the infusion time in attempts to lower cisplatin peak concentrations and, thus, slow the rate of delivery of drug to the kidney.

In initial clinical trials of CDDP given as an i.v. bolus, a dose of 50 mg/m^2 was associated with renal failure in 100% of the cases [38]. Splitting up the dose into five daily i.v. administrations reduced the incidence of renal failure to 30% [35]. Administration by slow 6- to 8-h infusion reduced it to 21% [57], and treatment by 24-h infusion lowered it to 5% [43, 74]. However, these findings must be interpreted with caution, since CDDP doses, hydration, and diuretic regimens varied significantly between the different clinical trials. In addition, the results of more recent studies are not consistent with these findings. Gandara et al. [30] found no difference in nephrotoxicity between rapid 2- to 3-h infusion and slow 24-h infusion; moreover, slow infusion appeared to have less antitumor efficacy. Therefore, the current tendency is to go back to administration by rapid 2- to 3-h infusion in some centers and treatment protocols.

In 1982, Levi et al. [51] presented a theory concerning circadian variations in CDDP toxicity. This theory was based on the observation that the toxicity was lower in animals that received the drug near the circadian maximum of urinary volume. The authors found a positive correlation between urinary beta-*N*-acetylglucosamidase activity and the extent of cisplatin nephrotoxicity. In a clinical study based on a small number of patients, no statistical difference in nephrotoxicity, computed pharmacokinetic parameters, or electrolyte concentrations was found between drug administration at 6 a.m. and treatment at 6 p.m. [23]. Other clinical studies must be performed to ascertain the importance of timing as a method of preventing cisplatin toxicity.

Another way of decreasing the systemic CDDP peak concentration is to give CDDP by local infusion or in formulations permitting organ-specific drug exposure. Local infusion of cisplatin is in widespread use. An example is i.p. infusion in the treatment of ovarian tumors, which provides elevated drug concentrations in the affected organs [63]. As the percentage of systemic drug availability is not negligible, the problem of CDDP nephrotoxicity is not overcome by this mode of administration. Moreover, various local side effects (chemical peritonitis, poor local diffusion) occur [56]. Recent research has led to the development of new formulations enclosed in microspheres, liposomes, and microcapsules for intravascular administration. These new products are targeted against hepatic tumors, and preliminary results issuing from preclinical studies indicate that systemic exposure and, thus, renal damage are indeed diminished [66]. The earliest formulations used a water-in-oil emulsion technique [89], but these preparations demonstrated a rapid release of CDDP during the first few minutes after infusion and therefore presented a risk of high systemic exposure. A new generation of encapsulation formulations using polylactide-co-glycolide microspheres, tried out in animals, is more feasible, as there is no rapid CDDP release and no local hepatic side effect [89]. However, this has to be confirmed in clinical trials. The latter approach is very promising but will unfortunately be possible only in a limited number of tumor types.

Modulating CDDP elimination

Hydration and administration of diuretics are the most commonly used methods to prevent cisplatin-induced nephrotoxicity. The exact mechanism for the renoprotective effect is not clear, but a dilution of cisplatin in the tubule and a decrease in its transit time as well as the prevention of a fall in the glomerular filtration rate are thought to be implicated [17, 21]. However, animal studies shown that a high urine flow does not reduce cisplatin nephrotoxicity [2].

Simple conventional hydration regimens provide adequate protection against nephrotoxicity at CDDP doses of up to 100 mg/m^2. The incidence of nephrotoxicity may decrease from 40% to 5% [1]. The hydration may be done before, during, and at up to 24 h following CDDP administration [14]. In normal hydration protocols, a saline isotonic 24-h infusion of 1–4 l ensures a high intra- and extracellular fluid volume and prevents a diminution of the glomerular filtration rate [35]. The 24-h urinary volume should be kept at 3 l as a minimum. This reduces the duration of contact between the drug and the renal tubule and also lowers the peak drug concentration [16].

The choice of vehicle in cisplatin-infusion preparations is important. Heidemann et al. [36] concluded that water, isotonic saline solution, or glucose 5% solution had no protective effect against renal toxicity when used as a vehicle in cisplatin infusions. On the other hand, a protective effect has been demonstrated for preparations based on hypertonic saline solution (4.5% sodium chloride solution). This was first described in Litterst's studies on rats [54], where the products also provided a better diffusion of CDDP into tissues. Ozols et al. [63] were the first investigators to perform clinical investigations, and they stated that when 3% saline solution is used as a vehicle and vigorous parenteral isotonic saline hydration is performed,

high doses of CDDP (200 mg/m^2) can be given safely. Dumas et al. [26] compared CDDP administration in two groups of patients receiving 100 mg/m^2 CDDP in either isotonic (group 1) or hypertonic saline 3% (group 2), the hydration consisting of 5% glucose in group 1 and isotonic saline in group 2. Salt loading was shown to reduce the maximal plasma concentration, protein-binding capacity, and cumulative urinary excretion of cisplatin. The literature on this topic, however, is conflicting; in a study performed by Daugaard et al. [19], a reduction in the glomerular filtration rate was seen despite the use of hypertonic saline. The mechanism for a possible renoprotective effect of hypertonic saline is unknown. It is thought that the high chloride concentration may decrease the concentration of active cisplatin or its metabolites at the level of the renal tubule [27]. It seems that high concentrations of chloride ion in the infusion preparation prevent the formation of toxic aquated CDDP metabolites prior to CDDP administration [15]. The importance of CDDP metabolites was assessed by Daley-Yates and McBrien [15]; the authors compared the use of hydrolyzed species of CDDP with CDDP given alone and concluded that the aquated species of cisplatin were more nephrotoxic and less active against tumors than was cisplatin alone.

Diuretics and hyperosmolar mannitol solutions have been widely used [32, 35, 62, 65]. The exact mechanism by which mannitol-induced diuresis reduces CDDP toxicity is unknown, but it has been suggested that mannitol protects the kidney by preventing immediate platinum binding onto renal tubular proteins rather than by augmenting diuresis [4, 8]. Al Sarraf et al. [1] have observed a protective effect only during the first treatment cycle, not during subsequent cycles. However, Belt et al. [4] reported that mannitol decreased the urinary recovery of platinum and increased plasma drug concentrations. Acetazolamide has also been evaluated, and a renoprotective effect has been demonstrated [36]. In the case of furosemide, there are conflicting reports. No study has convincingly shown any advantage for the use of this diuretic. The observation that mannitol and other diuretics actually lower the chloride concentration in the tubule cast doubt on the hypothesis that urinary chloride concentration plays an important role in CDDP-induced nephrotoxicity. Nevertheless, diuretics are useful in patients with cardiac, hepatic, or renal disturbances.

It is possible that the renin-angiotensin system is involved in the initially occurring decrease in renal plasma flow after cisplatin infusion [60], and the use of renin-angiotensin-system inhibitors to increase CDDP elimination by increasing the renal plasma flow has recently been investigated. Captopril, an angiotensin-converting enzyme inhibitor, and verapamil, a calcium-entry blocker, are capable of opposing a local vasoconstrictive action of angiotensin-II on the glomerular microcirculation, thus bringing about vasodilatation [11, 24, 72, 79]. Although these agents thus limit the early decrease in the renal plasma flow, they do *not* prevent the delayed decrease in the glomerular filtration rate [72]. In addition, their use will be limited by their antihypertensive effect, which may aggravate CDDP toxicity as demonstrated in the study of Uozumi et al. [88] on rats, where verapamil enhanced CDDP toxicity when given at doses exceeding 5 mg/kg.

Inhibition of the CDDP active transport system in the tubuli, which are presumed sites for renal damage, is another possibility. Some inhibitors of organic anion transport, such as probenecid, or cation transport, such as quinine, cyanine, penicillamine, and cimetidine, have been tried out on animals [6, 7, 37, 79]. These drugs prevent the access of nephrotoxic cisplatin metabolites to the sites of renal damage and increase the passive diffusion of CDDP at glomeruli to provide protection against both lethal and nephrotoxic effects of cisplatin. In a clinical study, Jacobs et al. [44] used probenecid at a dose of 4 g/day, given 1 day before and 1 day after the cisplatin infusion. No patient developed nephrotoxicity (defined by an increase in serum creatinine concentration and/or a decrease in creatinine clearance); ototoxicity was a dose-limiting factor. However, because of its unique site of action, this agent does not offer protection against other cisplatin toxicities. Probenecid has not interfered with the antitumor activity of CDDP in preclinical studies [71]; however, a phase II trial needs to be performed to verify that this drug does not interfere with antitumor activity.

In conclusion, strategies modulating the elimination of CDDP are simple and useful methods in the prevention of acute renal toxicity. Saline hydration and diuretics are in widespread use. Modification of the renin-angiotensin system remains under evaluation and will be limited by the risk of provoking hypotension and, thus, a reduction in renal flow in treated patients. Because of the ease of administration and lack of toxicity of probenecid, it may be used in combination with other protectors in future trials.

The use of antidotes

An antidote is a substance that can antagonize the activity of a drug. The most important clinical studies on antidotes against cisplatin-induced toxicity are presented in Table 2.

Nucleophilic thiol reagents have a potential for reacting with and inactivating toxic cisplatin metabolites, their action being based upon the affinity of sulfur-containing ligands for platinum(II) complexes. Sodium thiosulfate (STS) was the first clinically studied agent that should be capable of preventing the adverse renal effects of CDDP. The mechanism of thiosulfate protection is not yet fully understood, but STS may inhibit the cellular uptake of platinum [87]. However, this hypothesis could not be confirmed by Uozumi and Litterst [87]. The mechanism of STS protection is also based upon its intracellular reaction with cytotoxic CDDP metabolites rather than with cisplatin itself [10, 22]. In addition, STS may exert significant antitumor activity when given simultaneously with CDDP, according to the results of studies on animals [28]. In humans, STS was first proposed for use in "two-route chemotherapy" regimens (i.p. cisplatin and i.v. STS), since preclinical data suggested that simultaneous administration of cisplatin and thiosulfate by the same route might decrease the activity of the cytotoxic drug [42]. However,

Table 2 Clinical trials with antidotes (*M.A.* Median age, *STS* sodium thiosulfate, *DDTC* diethyldithiocarbamate, *WR-2721* *S*-2-[3-aminopropylamino]ethyl phosphorothioic acid, *GSH* glutathione, *PKS* pharmacokinetics, *CR* complete response, *PR* partial response, *ECOG* Eastern Cooperative Oncology Group)

Reference	Trial; patients (*n*); median age (years); [pathology (*n*)][a]	Antidote (doses)	Protocol	Degree of nephrotoxicity[b]	Interaction with CDDP PKS and antitumor effect	Adverse effect of the antidote
Howell et al. [42]	Phase I; 7; M.A. 51; [ovarian (4) melanoma (1), mesothelioma (1), carcinoid (1)]	STS (6–29.5 g/m^2)	STS i.v.: 0.8–4 g/l at start of CDDP, then 0.43–2.13 g/l over 12 h; CDDP i.p.: 90 mg/m^2 over 10 min in 2 l warm 0.9% saline solution; 0.9% saline hydration, mannitol 42.5 g, furosemide 20 mg	15% (serum creatinine >40%)	No change in clearance of CDDP	Not available
Pfeifle et al. [67]	Phase I; 26; M.A. 56; [lung (5), sarcoma (4), mesothelioma (3), others (14)]	STS (9.9 g/m^2)	STS i.v. over 3 h after CDDP infusion; CDDP: 135–225 mg/m^2 over 2 h; 2 l hydration, furosemide 20 mg	19.2%	No interaction as estimated by the AUC, elimination half-life, and volume of distribution of CDDP	Not available
Paredes et al. [64]	Phase III; Group A: 31; M.A. 57; [head and neck]	DDTC Day 1 (600 mg/m^2), days 8, 15 (200 mg/m^2)	Group A: CDDP: 120 mg/m^2; 5-fluorouracil: 5 g over 5 days, 3 l hydration (5% dextrose, 0.45% normal saline), mannitol 37.5 g	Group A: 19%	Group A: 41% CR+PR	Burning sensation
	Group B: 29; M.A. 62; [head and neck]		Group B: DDTC over 30 min, 30 min after CDDP 600 mg/m^2 on day 1, 200 mg on days 8, 15; CDDP: 120 mg/m^2; 5-fluorouracil: 5 g over 5 days; 3 l hydration (5% dextrose, 0.45% normal saline), mannitol 37.5 g	Group B: 14%	Group B: 29% CR+PR; no interaction with CDDP pharmacokinetic parameters	
Berry et al. [5]	Phase I; 19; M.A. 52; [non-small-cell lung (11), melanoma (3), others (5)]	DDTC (4 g/m^2)	DDTC: 45 min after CDDP over 1 h; CDDP: 120–160 mg/m^2, 3 l hydration (5% dextrose, 0.45% normal saline), furosemide 40 mg	Day 8: 14% Day 15: 5%	No interaction; 1PR (lung cancer) 1PR (melanoma)	Flush, burning sensation, hypertension, diaphoresis, agitation
Glover et al. [31]	Phase I; Trial 2: 80, M.A. 53	WR-2721 (740–910 mg/m^2)	Trial 2: WR-2721: 740 mg/m^2 over 15 min prior to CDDP; CDDP: 120–150 mg/m^2, hydration 200 ml/h, mannitol diuresis	Trial 2: 15% at CDDP 120 mg/m^2, 3% at 135 mg/m^2, 35% at 150 mg/m^2	No interaction Trials 2–4: 47% PR+CR (melanoma), 55% PR+CR (head and neck)	
	Trial 3: 22; M.A. 54		Trial 3: WR-2721: 740–1300 mg/m^2 over 15 min prior to CDDP, CDDP: 120 mg/m^2; hydration 200 ml/h, mannitol diuresis	Trial 3: 21%	54% PR+CR (breast)	Trial 3: Hypotension, nausea, vomiting, flush
	Trial 4: 13; M.A. 54		Trial 4: WR-2721: 740–910 mg/m^2, CDDP: 150 mg/m^2, hydration 200 ml/h, mannitol diuresis	Trial 4: 0 at WR-2721 740 mg/m^2, 23% at 910 mg/m^2		
	Trials 2–4: [breast (12), head and neck (11), melanoma (50), esophagus (11), others (9)]					
Oriana et al. [61]	Phase III; Group 1: 9; M.A. 51	GSH (1.5 g/m^2)	Group 1: CDDP: 90 mg/m^2 over 30 min; cyclophosphamide: 600 mg/m^2; 2 l hydration (normal saline)	Group 1: 22% (grade 2 ECOG toxicity criteria)	Group 1: 22% CR, 33% PR	Not available
	Group 2: 7; M.A. 51; [ovarian (6), unknown (1)]		Group 2: GSH: i.v. 15 min before CDDP over 15 min; CDDP: 90 mg/m^2 over 30 min; cyclophosphamide:	Group 2: 0	Group 2: 85% CR, 14% PR	

[a] Numbers given in parentheses represent the numbers of cases reported
[b] Measured by serum creatinine level (>2 mg/m^2)

more recent pharmacokinetic data indicate that this is not a serious problem [41, 49]. A phase I study has been conducted in which the two substances were given by i.v. infusion into opposite arms [67]. STS was infused over 3 h at a total dose of 10 g/m^2 starting at 1 h prior to the CDDP infusion, whereas CDDP was given as a 2-h infusion, with the dose being escalated to 225 mg/m^2. In patients receiving 200 mg/m^2, the area under the curve generated for cisplatin (with thiosulfate) was twice that achieved in patients receiving 100 mg/m^2, suggesting that the STS did *not*

inactivate cisplatin in plasma to a significant extent. These studies suggest that STS might provide protection against cisplatin-induced nephrotoxicity; however, serum creatinine and blood urea nitrogen were the only variables used for determination of nephrotoxicity. The rate of the cisplatin-thiosulfate reaction is very slow, which presumably explains why thiosulfate does not alter plasma cisplatin pharmacokinetics or activity [10]. With regard to side effects, STS has a long period of experience against cyanide toxicity and is known to be well tolerated. It has no effect on other adverse reactions to cisplatin such as myelosuppression, ototoxicity, or neurotoxicity [42, 67].

S-2-(3-aminopropylamino)ethyl phosphorothioic acid (amifostine, WR-2721), the phosphate thioester of the diaminothiol WR-1065, provides a selective protection of normal tissue against both radiotherapy damage and alkylating-agent injury. This selectivity is based upon greater accumulation of the diaminothiol metabolite in normal as compared with tumor cells [12, 90]. WR-2721 is hydrolyzed in vivo into the active, free, chelating metabolite WR-1065. The greatest efficacy has been shown to occur when WR-2721 is given 5–30 min prior to cisplatin infusion [84]. During a phase I trial, patients received escalating doses of WR-2721 (from 450 to 1300 mg/m^2) 15 min before cisplatin infusion (50–150 mg/m^2) with mannitol diuresis and were followed for adverse effects, including flushing, sneezing, somnolence, nausea, vomiting, and hypotension. For high doses exceeding 910 mg/m^2 WR-2721, a risk for hypotension and creatinine elevation appears. The results of this study are reported in Table 2. WR-2721 seems to be moderately effective against nephrotoxicity, but it may also offer protection against peripheral neuropathy-induced by CDDP [10]. Moreover, Glover et al. [31] suggested a direct therapeutic effect against metastatic melanoma. WR-2721 must be used with caution because of its inhibitory effect on γ-glutamylcysteine synthetase and, thereby, the risk of causing a reduction in hepatic glutathione levels, leading to increased toxicity of a variety of free-radical agents that may be responsible for membrane damage [83].

Mesna (sodium 2-mercaptoethane sulfonate) is another anion-containing thiol currently used to counteract cyclophosphamide bladder toxicity [39]. Mesna has been shown to be effective in the prevention of cisplatin-induced nephrotoxicity in animals [47]. It has also been tried out in humans, being given 2 h before or 2 h after cisplatin administration [39], but its toxicity-reducing potential and the risk of its interference with cisplatin activity have not been completely elucidated [10].

Diethyldithiocarbamate (DDTC) is a metabolite of disulfiram that has previously been used as a chelating agent in the treatment of metal poisoning. DDTC is unique among the cisplatin chemoprotectors in that it is effective when given *after* the antitumor agent. In studies on rats, Bodenner et al. [9] have shown that DDTC reacts with and removes platinum from all of its binding sites except for those with two guanine residues. Preclinical studies have demonstrated that DDTC given after cisplatin inhibits nephrotoxicity, bone marrow toxicity, and the emetic response without interfering with the antitumor activity of CDDP. In the first clinical study on DDTC used against CDDP-induced toxicity, Paredes et al. [64] found no difference in the incidence of renal dysfunction when DDTC was given with cisplatin at a dose of 120 mg/m^2 (Table 2). However, the DDTC doses may have been too low (600 mg/m^2). Qazi et al. [68] reported no nephrotoxicity in patients treated at CDDP doses of 50–120 mg/m^2 along with DDTC at about 2.5–5 g/m^2. More recent data obtained with higher doses (4 g/m^2) indicate a positive effect [5] (Table 2). In this study, DDTC did not interfere with cisplatin pharmacokinetics or antitumor activity but was associated with several adverse effects (diaphoresis, chest discomfort, flushing, hypertension, and anxiety) that may limit its clinical use. Further investigations are necessary to determine the benefit-risk ratio. Morever, there is some evidence suggesting that DDTC might be effective against cisplatin-induced myelosuppression and gut toxicity [9].

Selenium compounds are interesting chemoprotectors, but the clinical use of inorganic selenium compounds is limited by their potential toxicity [3]. Ebselen is a relatively nontoxic organic selenium compound that is converted into selenol intermediates in thiol-rich tissues, such as the kidneys, through a chemical reaction with glutathione and other thiols. Nucleophilic selenols are in turn capable of reacting with platinum compounds, resulting in a detoxification of cisplatin. In the first assays performed on mice, a dose-dependent renoprotective activity of ebselen was demonstrated [3]. Ebselen (10 mg/kg) was given 1 h before or 1 h after cisplatin infusion. Ebselen did not affect the CDDP antitumor effect and had low toxicity; nevertheless, the well-known risk of hepatic and renal toxicity associated with other selenium compounds should be kept in mind. Clinical studies are required to confirm these observations in humans and to define optimal dose regimens.

The use of antidotes against cisplatin-induced renal toxicity represents a highly interesting concept. Directly inhibiting the platinum uptake into tubular cells this manner could contribute to a limitation of the cumulative toxicity, which remains a significant problem. However, there is a need for clinical trials to determine and compare the benefit-risk ratios of the different agents. Furthermore, consensus protocols concerning standard regimens including hydration therapy need to be elaborated.

Cellular resistance mechanisms

Glutathione (GSH) is the predominant physiological nonprotein thiol present intracellularly, with a broad range of biological functions, including detoxification of xenobiotics and scavenging of free radicals. Exogenous GSH has been proposed for use against CDDP-induced toxicity [53, 82]. The antitumor efficacy of cisplatin does not seem to be impaired, since GSH is taken up only in tissues with substantial expression of the enzyme γ-glutamyl-transpeptidase on the cell-membrane surface, mainly the kidney. The most common tumor histologies express a relatively

low level of this enzyme. In addition, as GSH is rapidly removed from the blood, a GSH-induced inactivation of CDDP in plasma is unlikely. GSH has been tried out both in animals and in humans [61, 91]. In a preliminary clinical evaluation, GSH was given i.v. (2.5 g/day) 15 min before each cisplatin infusion (90 mg/m^2) [61]. Even though hydration was only moderate, the nephrotoxicity was minimal and GSH was well tolerated.

Metallothionein is a low-molecular-weight endogenous protein that provides protection against heavy-metal toxicity by binding metal atoms [75]. Renal protective effects have been demonstrated for bismuth compounds, which have been shown to be capable of inducing the biosynthesis of this protein in the kidneys [81]. In a study performed by Sommer et al. [81], bismuth was given orally as bismuth subsalicylate at a dose of 1.5 g at 30 h before the onset of cisplatin chemotherapy, albeit to only a small number of patients. Different time schedules and doses may be employed to optimize the effect [81], but an unlimited increase in bismuth doses is not possible because of its severe obstipative effect. Other metal ions, such as zinc given as zinc sulfate, have also been shown to induce metallothionein synthesis, but such findings have thus far been obtained only in studies in vitro. Several authors have reported that elevation of the metallothionein level in tumors leads to resistance against CDDP (data from mice) [58, 76], and if this is the case, the use of these agents will be considerably limited.

The concept of membrane stabilization has recently been introduced. The first agents studied in this connection were the steroids [85]. These agents increase the stability of the lysosomal membrane of proximal tubular cells, important sites for cisplatin nephrotoxicity, thus decreasing the capacity of lysosomes to release hydrolytic enzymes. ORG-2766 is a peptide analog of α-MSH$_{4-10}$ with no pigmentary activity that is devoid of the hormonal effect of adrenocorticotropic hormone (ACTH). This drug is a neurotrophic peptide that has been shown to protect against CDDP nephrotoxicity in animals [83]. The preliminary clinical results are encouraging. Methylprednisolone has been extensively studied in rats by Koikawa et al. [48], and renoprotective effects were demonstrated.

Urinastatin is a Kunitz-type proteinase inhibitor that may depress the release of lysosomal enzymes in the proximal tubular cells of the kidneys in the same way as do the steroids. In addition, urinastatin seems to improve the renal blood flow. In a study performed by Umeki et al. [86], urinastatin was given at a dose of 150,000 units twice a day during the first 3 days of each treatment cycle. Other extensive clinical studies are now being conducted. These most recent developments in the field of chemoprotection, brought about by a better understanding of the mechanism of cellular damage, are very interesting and should be further investigated.

Conclusions

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

However, cumulative toxicity after subsequent treatment cycles remains a major problem. Different antidotes (STS, DDTC, WR-2721, or GSH) have been shown to be efficacious against long-term toxicity when given in combination with hydration and diuretics. These drugs exert their protective activity by preventing the exposure of normal tissues, especially the kidney, to active platinum. Comparative clinical studies should be performed to define optimal treatment regimens. Substances that enhance cellular resistance may also have potential against cumulative toxicity and should be further investigated.

However, the most promising approach is presently the administration of new formulations (i.e., enclosed in microspheres, liposomes, microcapsules) permitting the local release of cisplatin and, thus, decreasing its systemic passage. This could find an application in the treatment of certain primitive and metastatic tumors but not in the treatment of disseminated tumors.

The exact cellular mechanism behind cisplatin-induced nephrotoxicity is insufficiently known and should be further investigated, as this may permit the introduction of new concepts in the modulation of renal toxicity. With the development of successful approaches for reducing CDDP's renal toxicity and the subsequent administration of increased doses of cisplatin, new dose-limiting toxicities have emerged at higher drug doses, namely, neurotoxicity and myelosuppression. For this reason, the need remains for new chemoprotectors.

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