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REVIEW

Prevention of cisplatin nephrotoxicity: state of the art and recommendations from the European Society of Clinical Pharmacy Special Interest Group on Cancer Care

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Abstract Antineoplastic drugs used in the treatment of cancers present with variable renal tolerance profiles. Among drugs with a potential for renal toxicity, platinum salts, and especially cisplatin is a well-known agent that may induce acute and chronic renal failure. The mechanisms of its renal toxicity and the means of its prevention are presented in this article which represent the Clinical Recommendation from the Special Interest Group on Cancer Care of the European Society of Clinical Pharmacy (ESCP).

Keywords Platinum salts · Cisplatin · Renal toxicity

Introduction

Patients with cancer are at high risk for drug-induced renal effects and overdosage since they often present with pre-existing renal dysfunction from multiple origins, as recently shown in the IRMA study in France [1]. In 2006, the European Society of Clinical Pharmacy (ESCP) Special Interest Group (SIG) on Cancer Care decided to focus on issues related to this topic and the question of the prevention of cisplatin-induced nephrotoxicity has risen as a priority. Together with two nephrology specialists, Professor Gilbert Deray, Head of the Department of Nephrology at Pitié-Salpêtrière Hospital in Paris and Professor Corinne Isnard-Bagnis from the same department, the authors, members of the ESCP SIG Cancer Care Board, reviewed the available literature and established recommendations for cisplatin-induced renal toxicity prevention protocols.

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Background

Nephrotoxicity is an inherent adverse effect of a number of anticancer drugs. Antineoplastic drugs have a narrow therapeutic index and the amount of drug necessary to produce a significant reduction in tumor burden usually produces significant nephrotoxicity. The dosage used in clinical trials often represents the maximum tolerated doses determined during phase I drug evaluation. Greater toxicity is acceptable during curative therapy than during palliative therapy. Cancer patients often exhibit excretory reduced organ function. Modulation of pharmacokinetics and pharmacodynamics of these drugs in cancer patient is therefore necessary in order to improve tolerance. Patients with malignancies are particularly vulnerable to renal abnormalities [1]. Clinical syndromes of renal involvement are diverse and sometimes insidious. Despite the recent physiopathological advances in understanding the mechanism of anticancer drug nephrotoxicity, and especially cisplatin, prevention still relies on drug dosage decrease, specific measures of hydration, and active screening for renal abnormalities as part of the pre-therapeutic usual

biological work up in patients treated with anticancer drugs.

cis-Dichlorodiammine platinum [II] or cisplatin, has emerged as a principal chemotherapeutic agent in the treatment of otherwise resistant solid tumors and is currently among the most widely used agents in the chemotherapy of cancer (SCLC, NSCLC, lymphomas, gastric, oesophagus, pancreas cancers, etc.). The chief limit to its greater efficacy, however, is its nephrotoxicity, which has made it necessary both to lower its dosage and actively hydrate patients to reduce it. These techniques have proved to be only partially successful as acute renal failure occurs even at such low doses and especially after its repeated administration [2, 3]. Use of other means to protect the kidney [4–6] are only partially successful and of uncertain clinical application [7].

Pharmacology

The kidney is the principal excretory organ of cisplatin. In the rat, 50% of injected cisplatin is excreted in the urine 24 h after its administration [8] and most of excreted platinum appears in the urine within the first hour [9]. Platinum is extensively bound to plasma protein. Free cisplatin in the plasma, by virtue of its low molecular weight and uncharged character, is freely filtered at the glomerulus [10]. Rat and human studies suggest that there may be secretion of cisplatin as well [11, 12]. Proximally microinjected radiolabeled cisplatin is almost completely recovered in the urine and is not reabsorbed to any significant degree [13]. Kidney concentration of platinum is several folds above plasma levels and above that in other organs [8]. Almost all of the platinum in the kidney is contained within the cortex and can be found in all subcellular organelles as well as the cytosol [9]. The process by which the kidney accumulates cisplatin is dependent upon normal oxygen utilization [10] and is inhibitable by drugs that compete for the transport of organic bases in a dose dependent manner. Drugs that compete for the organic anion transport system, such as PAH and pyrazinoic acid, do not inhibit uptake. Taken together, these observations suggest that the renal uptake of cisplatin involves some specific interaction of the drug with the kidney, perhaps involving transport or binding to components of the base transport system.

Further evidence that links the kidney's vulnerability to its role in cisplatin transport is provided by autoradiographic studies that show greater uptake of radiolabeled cisplatin in the S3 segment of the proximal nephron, also called "proximal straight tubule" [13]. As the S3 segment of the proximal tubule is the principle site of cell toxicity of cisplatin and contains the most platinum, these studies provide further evidence that the particular vulnerability of this cell type depends on its ability to accumulate cisplatin.

Cisplatin is excreted largely unchanged in the urine [10]. Upon entry into the renal cell, however, cisplatin undergoes biotransformation. In addition to binding to cell macromolecules, a large portion (30–50%) of the total cell platinum is in a form whose molecular weight is below 500 Da and whose chromatographic behavior is different from cisplatin. Another characteristic of this platinum metabolite is the loss of its biological activity as a mutagen. Whereas excreted platinum is mutagenic, cell platinum is not [14]. Mutagenic compounds react with or can be converted to compounds that react with DNA to form DNA adducts. The cisplatin DNA adducts cause errors during DNA replication, which lead to mutations, especially G → T transversions [15]. Such mutations may be responsible for second malignancies that arise after cisplatin therapy [16].

Renal toxicity

The clinical use of cisplatin is hampered by nephrotoxicity, expressed by a reduction in glomerular filtration rate in proportion to the repeated cycles of cisplatin chemotherapy. Progressive and partially irreversible declines in glomerular filtration rate and renal blood flow may develop with each successive treatment course [17]. Renal plasma flow, whole kidney glomerular filtration rate, single nephron glomerular filtration rate, and stop-flow pressure are reduced compared to controls [17]. Intratubular hydrostatic pressure is the same as control in euvolemic and volume expanded animals and it is unlikely that intratubular obstruction plays an important role in early cisplatin induced acute renal failure. With the withdrawal of the drug, renal function may recover or remain indefinitely impaired. The cisplatin-induced hypofiltration is usually associated with minimal proteinuria due to tubular injury. Severe salt wasting with orthostatic hypotension has been observed after cisplatin administration in a minority of patient [18].

Polyuria uniformly accompanies cisplatin administration and occurs in two distinct phases. Urine osmolality initially falls over the first 24–48 h after it is given but glomerular filtration rate in this phase is normal. This early polyuria usually ameliorates spontaneously. A second phase of increased volume and reduced osmolality occurs between 72 and 96 h after cisplatin. This later phase is accompanied by reduced glomerular filtration rate and is persistent.

Hypomagnesemia is a particularly common complication of cisplatin administration in humans [19] and persistent excretion of magnesium in the presence of severe hypomagnesemia suggests that the hypomagnesemia is due

to a renal defect in magnesium reabsorption [20]. Some studies in a rat model of this syndrome suggest that abnormal magnesium excretion may be due to a defect in magnesium transport in juxtamedullary nephrons or collecting ducts [21], much like the situation that exists for defective water transport described above. Secondary hypocalcemia and hypokaliemia may accompany this situation. Cisplatin may also induce and incomplete distal tubular acidosis by altering the cellular respiration leading to changes in tubular handling of hydrogen, magnesium, potassium and calcium ions [22].

The mediators of the fall in glomerular filtration rate and renal blood flow have not been determined although extensively studied, but calcium channel blockers [23] and angiotensin converting enzyme inhibitors [24] have been unable to demonstrate a reversal in cisplatin-induced acute renal failure. Several suspected targets of pathogenetic importance in cisplatin nephrotoxicity have been studied extensively, including renal tubule energy production and DNA synthesis. Mitochondrial dysfunction is involved in the pathogenesis of cisplatin-induced renal failure [25, 26]. In vitro incubation of normal tubules with cisplatin inhibits basal and stimulated rates of oxygen consumption but at very high concentrations (10^{-3}M) only. Transplatin, which is neither antineoplastic nor nephrotoxic, but also binds to DNA and protein, decreases respiration at lower concentrations (10^{-4}M) and is even a more potent inhibitor of respiration than cisplatin [13]. But in tubules isolated from rats given a nephrotoxic dose of cisplatin, basal and stimulated rates of respiration are entirely normal up to 48 h after cisplatin administration [13]. In these studies the concentration of platinum in proximal tubules were several hundred fold less than that of tubules exposed to cisplatin in vitro at a dose that inhibited respiration [13]. The results of these studies would seem to indicate that neither the renal cell mitochondria nor the membrane associated Na–K ATPase are important early pathogenetic targets of cisplatin.

There is convincing evidence that the primary biochemical lesion induced by cisplatin in cancer cells is inhibition of DNA synthesis [27, 28]. The inhibition of DNA synthesis is persistent and occurs at much lower doses than that necessary to inhibit RNA and protein synthesis [29]. Cisplatin binds to two sites in DNA [30] inducing DNA inter- and intra-strand as well as DNA–protein cross-links [30, 31]. What relationship such cisplatin DNA-binding has to renal cytotoxicity is unknown. How such a decline in DNA synthesis throughout the kidney would explain cell-specific necrosis is problematic but at least two explanations might account for such specificity. First, other cells of the kidney repair their DNA lesions while those of the pars recta cannot. Studies in cells whose repair processes are deficient show that cisplatin is especially toxic in them [32] making such a possibility likely. Second, it may be that the levels of the DNA adducts formed in the pars recta cells are lethal while lower levels in other nephron segments are not. Further studies will be necessary to determine the importance of the reduction in DNA synthesis in renal cytotoxicity.

Among the recent works in this field, those of Oishi and colleagues are of a particular interest since their findings suggest that cisplatin may additionally directly induce necrosis and apoptosis of renal tubular cells. The toxic mechanisms have been suggested to imply the p53-mediated activations of caspases-2, -8 and -3 in cisplatin-induced renal cell apoptosis, while oxidative stress-induced TNF-alpha synthesis via p38 MAPK phosphorylation may be the cornerstone for renal tubular cells necrosis [33, 34].

Recovery from nephrotoxic acute renal failure requires replacement of damaged tubule cells with new ones that are actively dividing. Recovery from cisplatin induced acute renal failure is accompanied by increased mitosis in renal epithelial cells, which is preceded by increases in nucleic acid synthesis [35].

Prevention of cisplatin-induced nephrotoxicity

Early in the development of cisplatin, more than 70% of patients developed acute renal failure that appeared to be cisplatin dose-related [36, 37]. Despite aggressive hydration, especially with normal saline solutions, which are routinely applied in the clinical setting to prevent nephrotoxicity [38], renal failure still occurs [39–41]. Therefore several attempts have been made to reduce nephrotoxicity by either coadministration of other compounds, alternate method of administration, or by developing analogues with an improved therapeutic index.

As mannitol and furosemide reduce the concentration of platinum in the urine, it has been suggested that these agents may attenuate cisplatin nephrotoxicity [42, 43]. However, neither platinum content in the plasma or the kidney, nor the degree of cellular necrosis it produces is positively influenced by these diuretics [43]. Platinum is not reabsorbed to an important degree after its intra tubular microinjection and, therefore, platinum content in the cell should not be dependent on its luminal concentration [13].

While several experimental reports have suggested that diuretics (mannitol and furosemide) decrease cisplatin nephrotoxicity [38, 43] others have shown that they may aggravate it [44]. Further, in humans, there is no convincing evidence that diuretics may attenuate cisplatin nephrotoxicity as shown in a randomized study by Al-Sarraf et al. [45] where hydration + cisplatin was compared to hydration + mannitol + cisplatin. Protection of kidney function by mannitol was observed after the first cycle, but

no convincing effect was observed during the subsequent cycles. Furthermore, in the study by Santoso et al., the authors concluded that Hydration with saline or saline + furosemide was associated with less cisplatin nephrotoxicity than saline + mannitol [46]. So far there is thus no reason to advocate for the use of diuretics in prevention of cisplatin induced nephrotoxicity. Hydration well in advance [at least 12 h] of cisplatin administration will induce a diuresis of at least 100 ml/h and will not make compensation of electrolytes losses mandatory, as it is the case with diuretics.

The use of hypertonic saline was first introduced in the clinic by Schilsky et al. [19] who concluded that when 3% saline was used as a vehicle for cisplatin, no renal toxicity was observed as measured by serum creatinine and creatinine clearance in patients treated with a high dose of cisplatin. However, when ^{51}Cr-EDTA was used as a measure of the actual glomerular filtration rate, a significant decrease in the latter was observed despite the use of 3% saline [12, 13]. Thus the interest of hypertonic saline in the prevention of high dose cisplatin nephrotoxicity will have to be further delineated in randomized studies.

As compared to bolus dose, fractionation or continuous infusion of the total dose of cisplatin over 3–5 days is equally effective from the therapeutic standpoint but probably spares renal function [47]. Indeed, for a given total amount of cisplatin, the fall in glomerular filtration rate is dependent on the amount given as single dose.

Infections are a frequent cause of morbidity in the immunocompromised cancer patients and often necessitate antibiotic therapy. The use of certain broad-spectrum antibiotics, which are potentially nephrotoxic by themselves, may add to the renal toxicity of the anticancer agents. Clinically, the incidence of nephrotoxicity has been recognized to be greater in patients receiving cisplatin in combination with aminoglycosides than in patients receiving cisplatin alone [48]. The degree of renal impairment has usually been mild and not clinically significant [46]. However, acute renal insufficiency has been reported following the combined use of cisplatin with gentamicin-cephalotin [49]. Further, it has been shown in rats that even a non-nephrotoxic dose of aminoglycosides immediately following a single dose of cisplatin causes a marked potentiation of the impairment to renal function caused by cisplatin alone [50, 51]. The administration of nephrotoxic drugs such as aminoglycosides, non-steroidal antiinflammatory drugs or iodinated contrast media simultaneously with cisplatin should therefore be avoided.

An impressive list of compounds has been used to decrease cisplatin nephrotoxicity (ANF, glycine, diethyldithiocarbamate, calcium channel blockers, cimetidine, sodium thiosulphate, glutathione, other sulfidryl compounds, etc.). Among them only sodium thiosulphate has received a significant clinical application and has been reported to reduce the renal toxicity of cisplatin administered locally by either the intra-arterial, intra-peritoneal or intra-thoracic routes [52, 53]. However, controversies still exist as to the effect of sodium thiosulphate on cisplatin antitumor activity. Thus sodium thiosulphate may be most useful in combination with intraperitoneal cisplatin where it confers renal protection without altering local effects of cisplatin [51].

ESCP SIG Cancer Care recommendation for the prevention of cisplatin nephrotoxicity in adults

We suggest not to administer platinum compounds to patients before objective evidence of euvolemia is present.

Assessment of the patient's renal function should be routinely performed before each administration. Such an evaluation should not rely only on a serum creatinine. It must consist of an estimation of glomerular filtration rate or creatinine clearance with the use of the aMDRD [54] formula or the Cockcroft–Gault [55] formula, respectively, as stated in the international guidelines and recommendations from the K/DOQI [56] and the KDIGO [57].

Cockcroft–Gault formula:

$$\mathrm{CrCl(mL/min)} = k \times [(140 - \mathrm{age}) \times \mathrm{weight\,(kg)}]/\mathrm{SCR\ (\mu mol/L)}$$

k	1.23 (male) or 1.04 (female)
CrCl	creatinine clearance
SCR	serum creatinine.

aMDRD formula:

$$\mathrm{GFR[mL/(min\ 1.73\,m^2)]} = k \times 186 \times (\mathrm{SCR})^{-1.154} \times (\mathrm{age})^{-0.203}$$

k	1 (male) or 0.742 (female)
GFR	glomerular filtration rate
SCR	serum creatinine (mg/dL).

The platinum should be administered slowly in conjunction with a saline solution infusion that produces a brisk diuresis. Urine flow should be maintained at 3–4 l/24 h for the next 2–3 days. We suggest a regimen consisting of prehydration using 100 ml/h of normal saline solution for the 12 h prior to the administration of the compound and continuous infusion of saline during and at least 1 day after cisplatin treatment. Even though several days are required for the changes in renal function to fully develop, some critical events seem to occur immediately after cisplatin administration. Protective measure should therefore be

Table 1 ESCP SIG Cancer Care recommendations on the prevention of cisplatin nephrotoxicity

Before administration
(1) Estimate GFR or CrCl using aMDRD or Cockcroft–Gault formula, respectively
(2) Ensure euvolemia is present
Dosage
Adjust cisplatin dosage according to the patient's renal function
Administration
Administer the platinum slowly
Hydration
(1) Use a saline solution infusion that produces a brisk diuresis.
(2) Urine flow should be maintained at 3–4 l/24 h the preceding day and for the next 2–3 days.
(3) Do not use diuretics, neither mannitol nor furosemide.
(4) There are no data for patients who already are on diuretics, for another concomitant disease such as hypertension.
After administration
(1) When feasible, determine serum creatinine 3–5 days after completion of the course.
(2) Monitor magnesium levels routinely and supplement when necessary.
(3) Avoid co-administration of nephrotoxic drugs (aminoglycosides, non-steroidal antiinflammatory drugs, iodinated contrast media, zoledronate, etc.).
(4) Re-evaluate renal function before the next course.

applied before, during and immediately after cisplatin infusion. We suggest that hydration should be maintained at least for 3 days after the course, by IV or oral route, when feasible. Till now, there are no specific recommendations, or data allowing to make any, on the administration of cisplatin under fractionated doses. In theory, the problematic of hydration remains the same as for "traditional" administration.

There are insufficient data to recommend a serum creatinine determination in the early days, after the course has been completed. However, clinical experience suggests that a serum creatinine determination between day 3 and day 5 may help diagnose acute and transitory serum creatinine increases. Those episodes of acute renal failure have been suggested to be responsible for cumulative renal damage that may in turn result in progressive impairment of renal function. Furthermore, it is recommended that magnesium levels should be measured routinely in all patients receiving cisplatin and that all cisplatin-based chemotherapy regimens should be supplemented routinely with sufficient doses of magnesium (40–80 mmol magnesium per cycle depending on the regimen) [58].

Efficacious antiemetic drugs should be given concomitantly to avoid dehydration. With the introduction of 5-HT3 receptor antagonists, it is now the usual clinical practice to stop intravenous hydration very quickly after cisplatin perfusion to shorten the duration of hospitalization. It should be remembered that these agents are ineffective in avoiding delayed emesis in more than 5% of patients submitted to high emetic risk chemotherapy [59].

Those recommendations are summarized in Table 1.

Conclusion

The high incidence of nephrotoxicity of the currently used inorganic platinum compounds stresses the importance of undertaking research to identify platinum complexes that would feature antitumor properties with less nephrotoxicity. Until this goal is achieved, it seems advisable to attempt to explore further the possibility of utilizing platinum in combination with chemotherapy at doses that are not associated with significant nephrotoxicity and to avoid other concomitant nephrotoxic insults, especially volume depletion. In the meantime, appropriate methods for prevention of cisplatin-induced renal toxicity should be used.

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