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Clinical report

The use of reduced doses of amifostine to ameliorate nephrotoxicity of cisplatin/ifosfamide-based chemotherapy in patients with solid tumors

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This study evaluates the degree of kidney damage during cisplatin/ifosfamide-based combination chemotherapy and its possible prevention by amifostine. Thirty-one patients with solid tumors stratified according to pretreatment were randomized to receive cisplatin/ifosfamide-based chemotherapy with or without amifostine (1000 mg absolute) given as a short infusion prior to cisplatin. Chemotherapy consisted of cisplatin (50 mg/m^2), ifosfamide (4 g/m^2) and either etoposide (500 mg/m^2) (VIP regimen) or paclitaxel (175 mg/m^2) (TIP regimen) repeated at 3 weekly intervals. For all patients the glomerular filtration rate (GFR) measured by creatinine clearance, serum creatinine, electrolytes and differential urinary protein excretion were determined prior to, during and after each treatment cycle. A total of 62 cycles of chemotherapy were evaluable. In the amifostine arm the GFR was almost completely maintained after application of two cycles of chemotherapy (121 to 108 ml/min), whereas in the control group a 30% reduction of the GFR (105 to 80 ml/min) was observed. In both groups marked increases of glomerular and tubular marker profiles peaking at day 3 after chemotherapy were found with a nearly complete reversibility of these changes prior to the next chemotherapy cycle. Patients receiving amifostine had a lower degree of hypomagnesemia, as well as a lower urinary excretion of *N*-acetyl-glucosaminidase and albumin, indicating less tubular damage compared to the control patients. Treatment with 1000 mg amifostine resulted in an almost complete preservation of GFR. This corresponded to a slightly reduced excretion of tubular marker proteins and a lower incidence of hypomagnesemia during chemotherapy in amifostine patients compared to controls. This dose of amifostine may be sufficient for nephroprotection in patients without pre-existing risk factors for renal damage who undergo a restricted number of chemotherapy cycles. [© 2000 Lippincott Williams & Wilkins.]

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Introduction

The anticancer drug cisplatin (*cis*-diamino-dichloroplatinum) is an effective compound in the treatment of a variety of solid tumors. However, its clinical use is associated with potential side effects such as oto-, neuro- and nephrotoxicity.[1] The degree of cisplatin-induced renal dysfunction has been studied in animal models, resembling the findings of acute polyuric renal failure, i.e. polyuria, decreased urinary osmolarity and a decrease in the glomerular filtration rate (GFR).[2–4] To reduce cisplatin nephrotoxicity patients usually receive pre- and posthydration with 2–3 l/m^2 of electrolyte-balanced fluid. Despite these precautions, cisplatin has been found to still cause permanent renal damage.[5]

Amifostine, WR-2721, an organic thiophosphate cytoprotective agent developed in the late 1950s, is a prodrug which is dephosphorylated to its active metabolite, WR-1065, by tissue-bound alkaline phosphatase. WR-1065 acts via different mechanisms including radical scavening, hydrogen donation and, in the case of platinum compounds, prevention or reversal of platinum–DNA adducts. The rationale for the use of amifostine in controlled clinical trials in cancer patients is based on the exclusion of a significant pharmacokinetic interaction between amifostine and cisplatin,[6] the evidence of the reduction of both hematologic and non-hematologic side effects of cisplatin without evidence of tumor protection in a large randomized trial of patients with ovarian cancer,[7] and the identification of cisplatin as a major con-

tributor to the long-term toxicity of chemotherapy.[8] The recommended standard dose of amifostine is 910 mg/m^2. Clinical investigations comparing different doses of amifostine provided evidence that dosages of 740 mg/m^2 produce similar cytoprotection.[9,10] At 740 mg/m^2 or even at lower doses, optimal biologic effects may have already plateaued. Thus, it is unclear whether a reduced dose of amifostine provides a clinically sufficient prevention.[11] On the other hand, the use of amifostine is associated with dose-related side-effects such as hypotension and nausea/vomiting, and the costs of treatment particularly at higher doses are considerable. On this background and on a former randomized trial confirming a complete preservation of the GFR with the use of 910 mg amifostine/m^2 prior to cisplatin-based chemotherapy,[12] we have conducted a second randomized study to evaluate the degree of kidney damage during single-day cisplatin/ifosfamide-based chemotherapy in patients with solid tumors and its possible prevention by using dose-reduced amifostine (1000 mg absolute dose=2 vials) which may cause less toxicity, lower costs and comparable efficacy.

Patients and methods

Patients

Thirty-one patients receiving chemotherapy for different solid tumors were followed for a total of 62 cycles. Patient characteristics are listed in Table 1. Patients had given informed consent prior to the collection of urine and blood samples. The study was approved by the ethical committee of Tübingen University.

Treatment schedules

All patients received either V(etoposide)I(ifosfamide)P(cisplatin) or T(paclitaxel)IP chemotherapy with granulocyte colony stimulating factor (G-CSF) support as outlined in Table 2. Patients had to have solid tumors eligible for treatment with the above described cisplatin/ifosfamide-based regimens. Two cycles of chemotherapy were given at 3 weekly intervals.[13] Criteria for inclusion were required as follows: ECOG performance status of 0 or 1, adequate bone marrow function (WBC count $\geqslant 4000/\mu$l, platelet count $\geqslant 100\,000/\mu$l and granulocyte count $\geqslant 2000/\mu$l), and adequate renal (serum creatinine concentration $\leqslant 1.2$ mg/dl and creatinine clearance $\geqslant 80$ ml/min) and liver function (bilirubin level $\leqslant 2.0$ mg/dl, and AST and ALT $\leqslant 3$ times normal). Parameters for ineligibility included brain metastases, symptoms of ischemic heart disease, and history of congestive heart failure or myocardial infarction within the immediate preceding 6 months and/or clinically significant arrhythmias. Also excluded were pregnant women and patients with a history of prior malignancies other than previously removed basal cell carcinoma of the skin or carcinoma *in situ* of the cervix.

Table 1. Patient characteristics

	Arm	
	Control	Amifostine
N (patients)	15	16
Sex (male/female)[a]	9/6	10/6
Age (years)[a]	37 (24–53)	43 (23–60)
Median body surface area (range) (m^2)	1.85 (1.7–2.0)	1.80 (1.65–2.0)
Type of solid tumor (*N* patients)[a]		
breast cancer	1	3
testicular cancer	4	4
NHL	6	4
ovarian cancer	1	1
Hodgkin	2	2
other	1[b]	2[c]
Previous chemotherapy (*N* patients)[a]		
none	3 (20%)	5 (31%)
cisplatin containing	4 (27%)	3 (19%)
non-cisplatin containing	8 (53%)	8 (50%)
Treatment regimens (*N* patients)[a]		
VIP	10	12
TIP	5	4

[a]Not signifiacant (*t*-test or χ^2-test).
[b]Lung cancer.
[c]Stomach cancer.

Table 2. Chemotherapy schedules

Agents/dose/infusion schedule			
VIP	vepeside (etoposide)	500 mg/m^2	(4 h)[a]
	ifosfamide	4 g/m^2	(18 h)[b]
	cisplatin	50 mg/m^2	(1 h)[b]
TIP	paclitaxel	174 mg/m^2	(3 h)[b]
	ifosfamide	4 g/m^2	(16 h)[b]
	cisplatin	50 mg/m^2	(1 h)[b]
No. of cycles analyzed per patient		2	
Mesna (mercaptoethanesulfonate)[c]		4 g/m^2 (16 respectively 18 h)	
Hydration		2000 ml isotonic NaCl/m^2	
Diuretics		250 ml mannitol (20%)	
Hematopoietic support		G-CSF (5 μg/kg) from day 2 until leukocytes >5000 μl	
Amifostine dose (group A) /infusion time		1000 mg/15 min (prior to cisplatin)	

[a]Solved in 2000 ml NaCl 0.9%.
[b]Solved in 500 ml NaCl 0.9%.
[c]To prevent isofamide-induced hemorrhagic cystitis.

Hydration and application of amifostine

Beginning 12 h before the application of cisplatin, patients received i.v. hydration at a rate of 200 ml/h (see Table 2). Prior to amifostine, patients received 500 ml of normal saline i.v. Amifostine was applied at 1000 mg as a 15 min i.v. infusion completed 15 min before the start of the cisplatin infusion. Blood pressure was monitored every 5 min during the amifostine infusion. Amifostine was interrupted in the case of a >20–50 mmHg decrease in systolic blood pressure depending on the patients baseline blood pressure level. Immediately before and following cisplatin, patients received 125 ml bolus application of mannitol 20%. Intravenous furosemide was applied for significant fluid imbalance or for urine output less than 200 ml/h despite mannitol. The i.v. fluid rate was also adjusted for renal insufficiency. Fluid rate was increased for an increase in serum creatinine concentration and i.v. furosemide was applied to maintain forced diuresis. As emesis prophylaxis 5-HT_3 antagonists and dexamethasone (20 mg i.v.) were administrated 45 min prior to chemotherapy application just before the start of amifostine infusion. Dexamethasone 4 mg was applied 4 and 12 h after chemotherapy. All patients underwent serum creatinine measurement on days 0, 3 and 5, which was repeated weekly with blood count. Creatinine clearance was measured at the beginning and the end of each treatment cycle (day 0, 21 and 42). Antihypertensive medication was not applied within 24 h after amifostine administration.

Urine sample collection

Urine samples were collected during the control phase (day −1). Treatment began the following day (day 0 of the observation period). Further samples were collected on days 3 and 5 after treatment. After collection urine was stored at −20°C. Urine samples were supplemented with 0.01% NaN_3 and adjusted to pH 7.4 with a 1 M phosphate buffer.

Parameters of glomerular and tubular renal function

Serum and urinary creatinine values were measured using a Beckman creatinine analyzer and reagents supplied by the manufacturer (Creatinine analyzer 2 Reagents; Beckman, Munich, Germany). Total protein was determined with the Coomassie brilliant blue binding method.[14] Electrophoretic separation of urinary proteins was performed on sodium dodecyl sulfate (SDS) gradient gels. Gels were stained with Coomassie brilliant blue, scanned on an Epson GT6000 scanner, and the fraction of albumin and the total of low molecular weight (LMW) proteins (<albumin) and high molecular weight (HMW) proteins (>albumin) were determined with Gel-Imagel 1.3 and Gel-Scan XL2.0 software (Pharmacia, Uppsala, Sweden) using bovine albumin as a standard. Following gel filtration on Sephadex G-25M (PD 10 columns; Pharmacia, Uppsala, Sweden) the urinary activity of the enzyme *N*-acetyl-β-D-glucosaminidase (NAG) was determined using β-4-nitrophenyl-2-acetamido-2-deoxy-D-glucoside as substrate.[15] α_1-Microglobulin was quantified with a commercially available immunoassay (Synelisa; Pharmacia & Upjohn, Freiburg, Germany).

Calculations and statistics

Patient characteristics were compared using the χ^2-test or the *t*-test. Ratios for the creatinine clearance ($C_{creatinine}$) were calculated using the general clearance formula for a substance *y*: $clearance_y=([urine]_y/[plasma]_y) \times$ urine volume. Statistical analysis was performed with SPSS 6.0 (SPSS, Chicago, IL). Statistical evaluation of changes in the excretion rate of urinary analytes was performed using the *t*-test. Significance was defined as $p \leq 0.05$. Friedman one-way ANOVA procedures were applied in the follow-up of groups to evaluate whether the variance of the excretion rates of the analytes was influenced by the time point of collection.

Results

Patient characteristics

The groups studied were comparable in terms of age, sex distribution and degree of pretreatment (Table 1). Out of 15 patients randomized to amifostine pretreatment (group 1), three (20%) had received no chemotherapy prior to the cycles examined here, four patients (27%) had received previous cisplatin-based chemotherapy and eight patients (53%) chemotherapy not containing cisplatin. Three patients (19%) randomized to the control group without amifostine (group 2) had received cisplatin-based chemotherapy prior to the VIP/TIP regimen [(other chemotherapy regimen *n*=8 (50%); no pretreatment *n*=5 (31%)]. The median body surface area in the amifostine arm was 1.85 m^2 (range 1.7–2.0 m^2). Thus 1000 mg amifostine resulted in a median dose of 540 mg/m^2 (range 500–588 mg/m^2).

Effects on kidney function

All 31 patients were evaluable for the analysis of creatinine clearance and magnesium values, and 30 patients for urinary marker studies. Both groups had a comparable volume load of either saline or saline plus glucose solution, as well as a comparable use of diuretics. For parameters examined at baseline on day −1 no differences existed between both groups ($p > 0.05$). Following two cycles of treatment the median GFR values were significantly reduced in control group patients with a decrease from 105 (range 62–182) to 80 (range 49–157) ml/min (p=0.003; Table 3). In contrast, in the amifostine group the GFR was nearly preserved at 121 (range 65–159) prior to and 108 (range 80–179) ml/min after chemotherapy (p=0.2).

Determination of urinary markers revealed significant effects in both treatment groups (Table 4). Protein excretion for all fractions was increased about 3- to 5-fold by days 3 and 5 in both groups. There were no signs of any pre- or post-renal causes for these changes, e.g. hemorrhagic cystitis. The changes observed in the urinary marker profile found after the first cycle of chemotherapy were nearly completely reversible within 3 weeks. Cumulative effects resulting in more pronounced changes in the subsequent cycle could not be observed (data not shown). The excretion of NAG and albumin at days 3 and 5 as an indicator of tubular damage was significantly lower in the amifostine group compared to control patients (Table 4). In addition, the incidence of hypomagnesemia during treatment was 6% in amifostine-pretreated patients versus 69% in control patients. Nadirs of magnesium serum concentrations were 1.51 (with amifostine) versus 1.33 mmol/l in control patients (p=0.01). Magnesium levels almost completely recovered in both groups at the end of cycles.

Side effects observed during or shortly after the application of amifostine were rather mild: rash (10/30 cycles=33%), nausea/vomiting (13%), sneezing (7%) and hypotension (blood pressure decrease $\geqslant$20 mmHg) (3%). All side effects were completely reversible within hours after application.

Discussion

Hyperhydration and forced diuresis have dramatically reduced the incidence of renal complications following cisplatin-based chemotherapy.[16] However, a persistent 20–30% reduction in GFR was demonstrated in long-

Table 3. Parameters of renal toxicity following two cycles of cisplatin/ifosfamide-based combination chemotherapy ± amifostine (1000 mg)

	Amifostine group [median (range)]	Control group [median (range)]	p value[a]
Serum creatinine (mg/dl)			
baseline	0.8 (0.7–1.3)	0.8 (0.6–1.3)	0.4
end of cycle 2	0.8 (0.6–1.3)	0.9 (0.6–1.3)	0.8
p value	0.4	0.3	
GFR (ml/min[b]			
baseline	121 (59–168)	105 (62–182)	0.8
end of cycle 2	108 (41–149)	80 (49–157)	0.1
relative reduction (%)	11	30	
p value	0.2	0.003	
Serum magneisum (mmol/l)			
baseline	1.55 (1.38–1.78)	1.59 (1.47–1.89)	0.2
nadir	1.51 (1.17–2.06)	1.33 (0.55–1.75)	0.01
p value	0.8	0.008	
patients with sub-normal levels (%)	6	69	

[a] t-test.
[b] Creatinine clearance. Cisplatin was applied at 50 mg/m^2 as a 1 h infusion at day 1.

Table 4. Excretion of urinary markers for renal toxicity following one cycle of cisplatin/ifosfamide-based combination chemotherapy ± amifostine (1000 mg)

Marker and day	Amifostine (n=15) [median (range)]	Control (n=15) [median (range)]	p value[a]
α_1-Microglobulin (mg/g creatinine)			
−1	12 (3–85)	23 (1–45)	NS
3	57 (34–206)	124 (26–345)	NS
5	60 (5–179)	80 (29–335)	NS
NAG (U/g creatinine)			
−1	3 (1–56)	3 (1–16)	NS
3	5 (1–68)	16 (0–60)	0.09
5	8 (1–58)	14 (8–50)	0.05[c]
Total protein (mg/g creatinine)			
−1	76 (16–2513)	108 (34–575)	NS
3	141 (72–3109)	399 (85–838)	NS
5	236 (44–876)	275 (132–949)	NS
LMW (mg/g creatinine)			
−1	48 (7–371)	48 (2–132)	NS
3	91 (52–1619)	243 (48–541)	NS
5	81 (23–296)	130 (64–569)	NS
HMW (mg/g creatinine)			
−1	20 (10–690)	16 (5–281)	NS
3	24 (10–446)	57 (13–123)	NS
5	45 (5–236)	61 (16–112)	NS
Albumine (mg/g creatinine)			
−1	13 (5–400)	11 (3–73)	NS
3	16 (10–636)	50 (13–87)	0.01[a]
5	20 (8–271)	48 (12–286)	NS[b]

[a] t-test.
[b] p=0.03 in the second cycle.
[c] p=0.04 in the second cycle.
[d] p=0.03 in the second cycle.

term follow up studies suggesting that some of the changes induced by cisplatin are irreversible.[5,17–23] Most investigators have reported that the acute decrease in GFR does not further detoriate during the months to years after therapy, while tubular function seems to slightly improve.[19] In some studies the severity of persistent renal impairment has correlated to the dose of cisplatin applied.[18,24] Persistent changes in renal tubular function had been mostly identified by magnesium wasting. Although cisplatin is responsible for most of the nephrotoxicity observed during the treatment of testicular cancer, other nephrotoxic agents such as ifosfamide or aminoglycoside antibiotics may contribute to this problem.[25–27]

In a former investigation we have compared the nephrotoxicity of different cisplatin-based chemotherapy schedules in terms of changes in GFR, serum magnesium levels and urinary marker excretion. The repeated application of cisplatin at doses of 50 mg/m^2, given on a single day (day_{1+22}), has led to significant decreases in GFR and magnesium levels. The effect on GFR was less pronounced in patients receiving cisplatin fractionated at daily doses of 20 mg/m^2 over five consecutive days. However, both investigated groups showed significant increases in urinary levels of low molecular weight proteins, NAG and α_1-microglobulin, demonstrating that conventional approaches can reduce but not completely prevent nephrotoxicity (in preparation).[28]

Despite established prevention methods such as hyperhydration and forced diuresis, the GFR was clearly affected in patients receiving VIP/TIP chemotherapy without prior application of amifostine. Patients in the control group had a 30% loss of GFR after two cycles of cisplatin/ifosfamide-based chemotherapy. The reduction of GFR observed in control patients may result in clinically evident long-term effects, particularly when additional therapy in the case of relapse is necessary or when other nephrotoxic agents such as aminoglycoside antibiotics are used. Among patients receiving amifostine prior to chemotherapy the GFR remained almost preserved after two cycles of treatment.

Considerable tubular and glomerular changes are also detectable following cisplatin/ifosfamide-based chemotherapy. Two cycles of treatment lead to signifcant glomerular and tubular toxicity with evidence of enzymuria, tubular proteinuria and hypermagnesuria. These nephrotoxic effects were observed in both groups—with or without the use of amifostine. In both groups the elevation of urinary markers were rapidly reversible and values retained to baseline levels prior to the subsequent cycle of chemotherapy. Patients receiving amifostine at 1000 mg prior to cisplatin chemotherapy revealed a slightly lower increase of tubular urinary markers NAG and albumin. This observation corresponded to a lower incidence of hypomagnesemia in the amifostine group. The acute but reversible changes of urinary marker excretion had also not been significantly influenced by standard dose amifostine (910 mg/m^2). However, standard dose amifostine appears to be more effective to preserve glomerular kidney function compared to dose-reduced amifostine. There was no reduction of GFR values in patients treated with standard dose amifostine prior to cisplatin-based chemotherapy [122 (range 65–159) prior to and 132 (range 80–179) ml/min after chemotherapy].[12]

The use of amifostine at a absolute dosage of 1000 mg [corresponding to 540 (range 500–600) mg/m^2 for patients treated in this investigation] reduced the amount of tubular marker excretion, the degree of hypomagnesemia and, clinically most relevant, preserved the GFR almost completely in comparison ot control patients. It might therefore be appropriate to use the proposed lower dose of amifostine in patients with a restricted number of planned chemotherapy cycles (e.g. less than four cycles), a normal GFR at the start of treatment, no pre-existing factors for nephrotoxicity and a body surface area of 2 m^2 or less. In these patients amifostine at 1000 mg may result in a low rate of side effects, cost savings and sufficient nephroprotection.

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