Effect of concurrent medications on cisplatin-induced nephrotoxicity in patients with head and neck cancer

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The goal of this study was to identify clinical characteristics and concurrent medications associated with an increased or decreased incidence of cisplatin-induced nephrotoxicity. The medical records for 62 subjects with head and neck cancer who received cisplatin 100 mg/m^2 (day 1) plus fluorouracil 1000 mg/m^2 (days 1–5) with or without radiation therapy were reviewed from three medical centers. The demographics, concurrent medication therapy, co-existing illnesses and clinical laboratory values were extracted from the medical records. Nephrotoxicity was defined as a minimum rise in serum creatinine of 0.5 mg/dl or above. The concurrent use of hydrochlorothiazide or multivitamins was associated with a higher incidence of nephrotoxicity after cycle 1. Use of albuterol, atenolol or hydrochlorothiazide was also associated with a higher incidence of nephrotoxicity after cycle 1 or 2. In contrast, subjects prescribed dexamethasone or ondansetron were less likely to experience nephrotoxicity. None of these medications affected treatment response. Race/ethnicity was independently correlated with the incidence of nephrotoxicity; African-American subjects were more likely to develop nephrotoxicity independent of the influence of these concurrent medications. Medications may modulate cisplatin-induced nephrotoxicity by altering the metabolic activation of cisplatin to a nephrotoxin. Genetic differences in the drug-metabolizing enzymes may contribute to the correlation with race. The results from this retrospective study provide data to support a larger prospective study to further investigate the associations between these concurrent medications and cisplatin-induced nephrotoxicity. *Anti-Cancer Drugs* **17:207–215**

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Introduction

Cisplatin is a platinum analog used to treat many malignancies, including head and neck cancer. One of the dose-limiting toxicities associated with cisplatin is nephrotoxicity. The primary site of the acute kidney damage is the distal segment of the proximal tubules. Acute renal failure occurs several days after cisplatin administration, resulting in decreased renal blood flow and glomerular flow rate due to impaired cellular sodium/potassium pumps, reduced water and sodium re-absorption, and increased renal vascular resistance [1,2]. Forced i.v. hydration with normal saline has been shown to reduce the incidence of nephrotoxicity [3]. Several independent factors have been reported to be associated with increased risk of cisplatin-induced nephrotoxicity. These factors include abnormal pre-treatment serum laboratories (such as low serum potassium and low serum albumin), concomitant administration of medications (such as metoclopramide and aminoglycosides) and prior treatment with cisplatin [4–7]. However, many patients with no known risk factors develop nephrotoxicity following administration of cisplatin with hydration. In one study, 32% of subjects developed nephrotoxicity following a single dose of 50–100 mg/m^2 cisplatin [1].

Cisplatin is metabolized *in vivo* to a glutathione conjugate that is metabolized to a nephrotoxin [8–12]. The glutathione–cisplatin conjugate is cleaved by the extracellular enzyme γ-glutamyl transpepidase (GGT) to a cysteinyl–glycine conjugate. The cysteinyl–glycine conjugate undergoes further metabolism to a cysteine-*S*-platinum conjugate that is taken up into the proximal tubule cells of the kidney. A cysteine-*S*-conjugate β-lyase found within the kidney converts the cysteine-*S*-platinum conjugate to a nephrotoxic thiol [13]. In animal models, inhibiting GGT or cysteine-*S*-conjugate β-lyase blocks cisplatin-induced renal failure [8–14]. Each of the steps in this metabolic pathway can be modulated. Medications administered with cisplatin may modulate these enzymes and alter the development of

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cisplatin-induced nephrotoxicity. Genetic variation of the enzymes involved in this pathway could explain the development of nephrotoxicity in subjects without known risk factors. Since the anti-tumor activity of cisplatin is a result of its DNA binding and does not require the biotransformation of cisplatin by the enzymes involved in the activation of cisplatin to a nephrotoxin, modifying this metabolic pathway should not alter the tumor response to cisplatin [15–17].

We propose that clinical characteristics or concurrent medications alter the development of cisplatin-induced nephrotoxicity independent of their effect on the anti-tumor activity of cisplatin. We conducted a retrospective cohort study at three medical centers in subjects with head and neck cancer who received cisplatin plus fluorouracil with or without radiation therapy to extract the clinical characteristics and concurrent medications. Individual factors that were associated with modulation of nephrotoxicity were further evaluated by a multivariable analysis to assess the independence of the association.

Methods

Study population

We reviewed the medical records from three medical centers: the University of Illinois Medical Center (UIMC; Chicago, Illinois, USA), the West Side Veterans' Affairs Hospital (WSVA; Chicago, Illinois, USA) and the University of Oklahoma Health Sciences Center (OUHSC; Oklahoma City, Oklahoma, USA). All subjects received treatment from January 1998 to December 2001 for histologically or cytologically proven head and neck cancer. The chemotherapy regimen for all subjects included in the study was cisplatin 100 mg/m^2 on day 1 plus fluorouracil 1000 mg/m^2 on days 1–5 with or without radiation therapy every 28 days for 1–8 cycles. All subjects received pre- and post-hydration. The Institutional Review Board at the UIMC and the OUHSC, and the Research and Development Committee at the WSVA approved the study. A waiver for written informed consent and authorization was granted from each review board.

Study variables

The medical records were reviewed to collect subject demographics, medical history, laboratories and concurrent medication therapy. The medical history included co-existing illnesses, and the cancer diagnosis, treatment and adverse events. The treatment response was recorded as a complete response (a 100% decrease in the size of the tumor or extent of disease), partial response (a 30% decrease in the size of the tumor or extent of disease), stable disease (less than a 30% decrease or 20% increase in the size of the tumor or extent of disease) or progressive disease (at least a 20% increase in the size of the tumor or extent of disease or the appearance of new lesions) [18]. For each treatment cycle, concurrent medications and serial laboratories were recorded. Of note, not all values were available for each subject.

Pre-treatment creatinine clearance was calculated using the following equation: Cl_{cr} (ml/min) = [140 – age (years)] × total body weight (kg)/[0.8 × serum creatinine (mg/dl)]. Serum osmolalilty was calculated using the following equation: serum osmolality (mOsm/l) = [2 × sodium (mEq/l)] + [glucose (mg/dl)/18] + [blood urea nitrogen (mg/dl)/2.8].

Nephrotoxicity was defined as an increase in serum creatinine of greater than or equal to 0.5 mg/dl compared with pre-treatment serum creatinine measurements [19]. We assessed cisplatin-induced nephrotoxicity by identifying the *maximum rise* in serum creatinine during the entire treatment course. Creatinine clearance was not used to assess nephrotoxicity because the various methods used to calculate or measure creatinine clearance demonstrate significant intrasubject variability [20].

Subset analysis

Two subset analyses were completed after determining whether each subject developed nephrotoxicity according to the criteria defined above. For the first subset analysis, the demographic and clinical characteristics of the 21 subjects who developed nephrotoxicity following cycle 1 were compared with the characteristics of the 35 subjects who never developed nephrotoxicity. Four subjects who did not develop nephrotoxicity until cycle 2 were excluded from this analysis.

In the second subset analysis, the same variables were compared between the 25 subjects who developed nephrotoxicity after cycle 1 or 2 and the 29 subjects who were treated with at least 2 cycles of cisplatin and never developed nephrotoxicity. The six subjects that never developed nephrotoxicity, but only received 1 cycle of cisplatin, were excluded from this analysis.

Two subjects were excluded from both subset analyses. One subject was excluded, because he did not develop nephrotoxicity until cycle 5 and, therefore, he did not fit into any of the analysis groups. The second subject had a urinary obstruction that contributed to an increase in serum creatinine, making it unclear to the degree to which cisplatin compromised renal function.

Statistical analysis

This study explored the association between nephrotoxicity and multiple independent variables, and $P = 0.05$ was adopted as a benchmark for statistical significance. This P value does not represent a formal Bonferroni or other adjustment. Instead, it balances the need to adjust

for multiple comparisons with the study's goal of exploring associations between cisplatin-induced nephrotoxicity and several factors that have received little investigation.

The number and percentage were calculated for all nominal independent variables. The associations between nephrotoxicity and these variables were analyzed with the Fisher exact test (GraphPad Prism, version 4.0; GraphPad Software, San Diego, California, USA). The arithmetic mean and SD were calculated for continuous independent variables. The differences in mean values between the independent subject groups were analyzed using two-tailed Student's *t*-tests. Independent variables that were individually associated with nephrotoxicity were included in multivariable analyses with logistic regression (Statistical Analysis System, version 8.0; SAS Institute, Cary, North Carolina, USA).

Results

Subject demographics and clinical characteristics

The medical records for 62 subjects who received treatment with cisplatin plus fluorouracil for head and neck cancer between January 1998 and December 2001 at one of the three medical centers were reviewed. None of these subjects received prior treatment with cisplatin. The demographics and clinical characteristics of the study population are summarized in Table 1.

All subjects were treated with cisplatin 100 mg/m^2 on day 1 plus fluorouracil 1000 mg/m^2 on days 1–5 every 28 days for 1–8 cycles. Fifty-one (82%) subjects were treated with radiation. Most subjects received hydration with normal saline, whereas one subject received dextrose 5% with sodium chloride 0.45% supplemented with potassium chloride and magnesium sulfate.

Table 1 Demographics and clinical characteristics

	Study population
Gender [*n* (%)]	
men	59 (95)
women	3 (5)
Race [*n* (%)]	
African-American	46 (74)
Caucasian	13 (21)
other	3 (5)
Treatment center [*n* (%)]	
WSVA	47 (76)
UIMC	11 (18)
OUHSC	4 (6)
Diagnosis [*n* (%)]	
esophagus	24 (40)
hypopharynx	4 (6)
larynx	12 (19)
oral cavity	6 (10)
oropharynx	16 (25)
Stage [*n* (%)]	
II	4 (6)
III	9 (14)
IV	41 (66)
not specified	8 (14)
Social history [*n* (%)]	
smoking	57 (92)
drinking	52 (84)
Age [years (mean ± SD)]	62 ± 9
Weight [kg (mean ± SD)]	67 ± 15
Height [inch (mean ± SD)]	69 ± 3
Body surface area [m^2 (mean ± SD)]	1.8 ± 0.2

Factors affecting the development of nephrotoxicity after cycle 1

Demographics and clinical characteristics

Twenty-one subjects developed nephrotoxicity after cycle 1, whereas 35 subjects never developed nephrotoxicity after 1 or more cycles of cisplatin. The racial/ethnic distribution was the only demographic variable that differed between subjects with and without nephrotoxicity. African-American subjects were more likely to develop nephrotoxicity following cycle 1 ($P = 0.007$); 20 of the 21 subjects who developed nephrotoxicity following cycle 1 were African-American. Of the 35 subjects without nephrotoxicity, 22 subjects were African-American and 11 subjects were Caucasian.

None of the remaining demographic and clinical characteristics were associated with nephrotoxicity. Of note, the distributions of certain characteristics within this population were too unbalanced to determine if they significantly correlated with nephrotoxicity. For example, only four subjects in this study had diabetes mellitus (one with nephrotoxicity and three without nephrotoxicity) and only four subjects had hepatic dysfunction (one with nephrotoxicity and three without nephrotoxicity). The number of subjects with these co-existing illnesses was too small to determine whether they correlated with nephrotoxicity.

Laboratory parameter

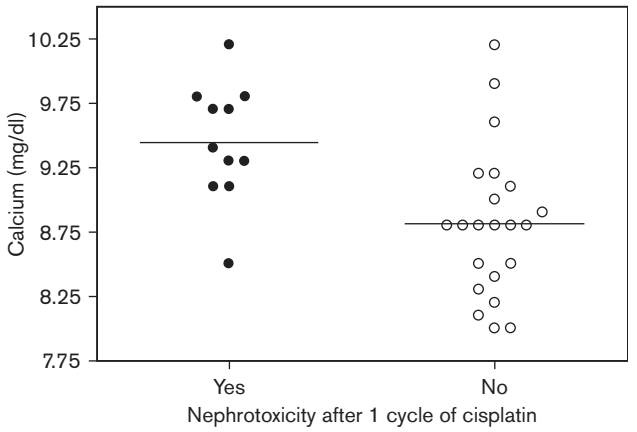
The pre-treatment serum laboratory values for subjects with and without nephrotoxicity after cycle 1 are shown in Table 2. The parameters are displayed in order of decreasing statistical significance based on the *P* value determined with a Student's *t*-test. The *t*-tests' underlying assumption of normality appeared to be valid for all laboratory parameters, except bicarbonate, blood urea nitrogen, glucose, aspartate transaminase and alkaline phosphatase. As the differences among these parameters were not significant with the *t*-test, the differences will not be significant with a non-parametric test.

The pre-treatment laboratory parameters that showed the strongest correlation with the development of nephrotoxicity were elevated serum calcium ($P = 0.004$), low serum chloride ($P = 0.024$) and elevated platelets ($P = 0.039$). The mean serum calcium and chloride levels did not differ among patients at the three institutions, indicating that laboratory standards and assays were equivalent among the institutions. In a multivariable model that examines serum values (chloride, calcium, and platelets) after cycle 1, elevated calcium is independently associated with nephrotoxicity ($P = 0.015$). However,

Table 2 Pre-treatment laboratory values in subjects with and without nephrotoxicity after cycle 1

Laboratory parameter	Nephrotoxicity after 1 cycle ($n=21$)			No nephrotoxicity after 1 cycle ($n=35$)			P
	Mean	SD	n	Mean	SD	n	
Calcium (mg/dl)	9.4	0.5	11	8.8	0.6	22	0.0036
Chloride (mmol/l)	100.2	4.5	20	102.8	3.8	34	0.0240
Platelet count (/mm^3)	362.7	118.1	19	283.7	130.8	29	0.0391
Glucose (mg/dl)	104.3	35.8	20	121.8	38.0	33	0.1021
Potassium (mmol/l)	4.4	0.6	21	4.1	0.4	34	0.1075
Blood urea nitrogen (mg/dl)	13.4	6.1	21	10.9	6.1	34	0.1337
Bicarbonate (mmol/l)	35.5	23.2	9	26.3	3.1	22	0.2647
Alkaline phosphatase (U/l)	155.0	85.0	4	96.7	26.8	11	0.2650
Creatinine clearance (ml/min)	76.3	26.9	21	84.8	31.4	32	0.3128
Creatinine (mg/dl)	1.0	0.2	21	0.9	0.2	35	0.3217
AST (U/l)	51.3	88.0	6	18.3	7.7	11	0.4004
ALT (U/l)	36.4	14.4	8	31.1	15.2	14	0.4322
White blood cell count (/mm^3)	8.1	2.1	19	7.6	2.9	29	0.4648
Magnesium (mEq/l)	1.7	0.3	11	1.8	0.2	25	0.5112
Sodium (mmol/l)	138.0	3.8	21	137.8	3.9	34	0.8474
Albumin (g/dl)	3.3	0.4	5	3.3	0.9	13	0.8816
Serum osmolality	286.3	8.0	21	286.1	8.2	32	0.9237
Hematocrit (%)	35.8	5.0	19	35.6	6.6	29	0.9331
Phosphorus (mg/dl)	3.5	0.7	8	3.5	0.7	21	0.9983

Fig. 1



Pre-treatment serum calcium in subjects with and without nephrotoxicity after 1 cycle of chemotherapy.

neither chloride ($P = 0.691$) nor platelets ($P = 0.333$) are independently associated with nephrotoxicity. The pre-treatment serum calcium concentrations for subjects with and without nephrotoxicity are shown in Fig. 1. Simple logistic regression analysis of the pre-treatment serum calcium levels predicts that subjects with pre-treatment serum calcium of 9.6 mg/dl have a 0.57 probability of developing nephrotoxicity after cycle 1. Subjects with pre-treatment serum calcium levels of 9.8 mg/dl have a 0.67 probability of developing nephrotoxicity.

Concurrent medications

The concurrent medications administered to subjects in our study population were evaluated to determine if any medications were associated with the development of nephrotoxicity. Table 3 summarizes the data for medications that were associated with nephrotoxicity after cycle 1. Albuterol, hydrochlorothiazide, multivitamins and thiamine were more commonly prescribed to subjects who developed nephrotoxicity. Seven of the 14 subjects prescribed multivitamins were also prescribed thiamine and seven of the nine subjects prescribed thiamine were also prescribed multivitamins. Multivitamins were independently associated with nephrotoxicity in a multivariable model that examined multivitamins, albuterol and thiamine ($P = 0.039$). However, neither thiamine ($P = 0.554$) nor albuterol ($P = 0.087$) are independently associated with nephrotoxicity. Hydrochlorothiazide could not be included in the multivariable analysis as all five subjects who received this medication developed nephrotoxicity.

Table 3 Concurrent medications that altered the incidence of nephrotoxicity after 1 cycle of cisplatin ($P<0.05$)

	Nephrotoxicity after 1 cycle ($n=21$)	No nephrotoxicity after 1 or more cycles ($n=35$)
Medications associated with an increased incidence [n (%)]		
albuterol	6 (29)	2 (6)
hydrochlorothiazide	5 (24)	–
multivitamin	10 (48)	4 (11)
thiamine	7 (33)	2 (6)
Medications associated with a decreased incidence [n (%)]		
dexamethasone	–	8 (23)
ondansetron	–	7 (20)

In contrast, none of the subjects who were treated with dexamethasone or ondansetron developed nephrotoxicity after cycle 1. Eight subjects received dexamethasone, with seven of these eight subjects receiving ondansetron. Since the administration of dexamethasone was strongly correlated with the administration of ondansetron ($P < 0.00001$), it was not possible to independently assess the effect of these medications on nephrotoxicity.

Multivariable analysis of dexamethasone or ondansetron could not be performed as the small number of subjects treated with these medications all experienced the same outcome.

Nephrotoxicity was not associated with other commonly prescribed medications including acetaminophen with or without codeine, docusate, magnesium oxide or prochlorperazine, each of which was prescribed for at least 12 of the subjects in this subset population.

Concurrent medications and treatment response

The treatment responses for the subjects prescribed albuterol, hydrochlorothiazide, multivitamins, thiamine, dexamethasone or ondansetron were analyzed to determine whether these medications correlated with treatment response. The treatment response was only available for 43 of the 56 subjects in this subset. Thirteen subjects had a complete response, three subjects had a partial response, seven subjects had stable disease and 20 subjects had progressive disease. There was no significant correlation between any of these medications and treatment response. Thirty-seven of these subjects had stage IV disease; there was no significant correlation between these medications and treatment response for these subjects with stage IV disease.

Factors affecting the development of nephrotoxicity after cycle 1 or 2

Demographics and clinical characteristics

Twenty-five subjects in this study population developed nephrotoxicity after cycle 1 or 2. The demographics, clinical characteristics and concurrent medications for these subjects were compared to the 29 subjects who received at least 2 cycles of cisplatin without developing nephrotoxicity. The variables associated with development of nephrotoxicity after cycle 1 were similar to those associated with development of toxicity after cycle 1 or 2. African-American subjects were more likely to develop nephrotoxicity ($P = 0.0006$). Twenty-four of the 25 subjects who developed nephrotoxicity following cycle 1 or 2 were African-American. Of the 29 subjects without nephrotoxicity, 16 subjects were African-American, 11 subjects were Caucasian and two were other races.

Laboratory parameters

The average pre-treatment serum chloride was lower, while the serum calcium and platelet count was higher in subjects who developed nephrotoxicity (Table 4). A multivariable analysis showed that high serum calcium is independently associated with nephrotoxicity ($P = 0.0196$). However, neither chloride ($P = 0.651$) nor platelets ($P = 0.346$) are independently associated with nephrotoxicity. The pre-treatment serum calcium concentrations are shown in Fig. 2.

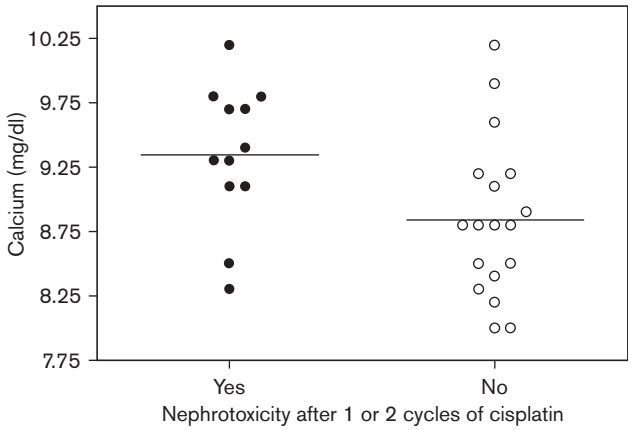
Concurrent medications

In addition to the concurrent medications that were associated with nephrotoxicity after cycle 1, atenolol was also prescribed to significantly more subjects who developed nephrotoxicity after 1 or 2 cycles of cisplatin ($P = 0.040$, Table 5). However, a multivariable analysis of multivitamins and thiamine showed that neither multivitamins ($P = 0.313$) nor thiamine ($P = 0.099$) are independently associated with nephrotoxicity. None of the five subjects who were prescribed dexamethasone and ondansetron developed nephrotoxicity ($P = 0.054$). Neither albuterol, atenolol, hydrochlorothiazide, dexamethasone or ondansetron could be included in a multivariable analysis as all subjects who received these medications experienced the same outcome.

Table 4 **Pre-treatment laboratory values in subjects with and without nephrotoxicity after cycle 1 or 2**

Laboratory parameter	Nephrotoxicity after 1 or 2 cycles ($n=25$)			No nephrotoxicity after 1 or 2 cycles ($n=29$)			*P*
	Mean	SD	*n*	Mean	SD	*n*	
Chloride (mmol/l)	100.4	4.7	25	103.1	3.8	28	0.0216
Calcium (mg/dl)	9.4	0.6	12	8.8	0.6	18	0.0292
Platelet count (/mm^3)	359.3	109.2	23	279.3	136.6	25	0.0308
Glucose (mg/dl)	103.9	32.6	25	119.4	30.1	27	0.0818
Potassium (mmol/l)	4.3	0.6	26	4.1	0.4	28	0.1064
Alkaline phosphatase (U/l)	155.4	73.6	5	96.7	26.8	11	0.1507
White blood cell count (/mm^3)	8.7	3.4	23	7.5	2.8	25	0.1876
AST (U/l)	70.4	94.9	7	18.3	7.7	11	0.1966
Bicarbonate (mmol/l)	33.8	20.1	12	26.4	3.4	18	0.2298
ALT (U/l)	59.7	75.7	10	31.0	15.8	13	0.2665
Magnesium (mEq/l)	1.7	0.2	13	1.8	0.2	21	0.3582
Blood urea nitrogen (mg/dl)	13.2	6.5	26	11.7	6.1	28	0.3952
Creatinine (mg/dl)	1.0	0.2	26	1.0	0.2	29	0.4444
Creatinine clearance (ml/min)	74.9	25.2	26	79.9	26.5	26	0.4907
Hematocrit (%)	35.1	4.9	23	36.2	6.7	25	0.5039
Serum osmolality	286.3	8.9	26	287.1	8.7	26	0.7625
Phosphorus (mg/dl)	3.5	0.7	9	3.5	0.7	18	0.7930
Albumin (g/dl)	3.3	0.4	5	3.3	0.9	13	0.8816
Sodium (mmol/l)	138.0	4.0	26	138.2	4.1	28	0.8994

Fig. 2



Pre-treatment serum calcium in subjects with and without nephrotoxicity after 1 or 2 cycles of chemotherapy.

Table 5 Concurrent medications that altered the incidence of nephrotoxicity after cycle 1 or 2 ($P<0.05$)

Medication	Nephrotoxicity after 1 or 2 cycles ($n=25$)	No nephrotoxicity after at least 2 cycles ($n=29$)
Medications associated with an increased incidence [*n* (%)]		
albuterol	6 (24)	–
atenolol	4 (16)	–
hydrochlorothiazide	5 (20)	–
multivitamin	11 (44)	4 (14)
thiamine	8 (32)	1 (3)
Medications associated with a decreased incidence [*n* (%)]		
dexamethasone	–	5 (17)
ondansetron	–	5 (17)

Concurrent medications and treatment response

Seven medications, including hydrochlorothiazide, multivitamin, thiamine, atenolol, albuterol, ondansetron and dexamethasone, were associated with either an increased or decreased incidence of nephrotoxicity after cycle 1 or 2. The data were analyzed to determine whether any of these medications correlated with the treatment response. The treatment response was only available for 45 of the 54 subjects in this subset. Fourteen subjects had a complete response, three a partial response, seven stable disease and 21 progressive disease. There was no significant correlation between these medications and treatment response. Thirty-five of the subjects had stage IV disease; there was no significant correlation between any of these medications and response in subjects with stage IV disease.

Discussion

In this retrospective cohort study, several novel factors were associated with cisplatin-induced nephrotoxicity. African-American subjects were more likely to develop nephrotoxicity in our study population. In addition, the concurrent administration of hydrochlorothiazide, multivitamins or atenolol was significantly correlated with an increased incidence of nephrotoxicity, while ondansetron and dexamethasone correlated with a decreased incidence of nephrotoxicity.

The incidence of nephrotoxicity in our study was higher than the incidence reported in previous clinical studies with similar doses of cisplatin [21]. Most studies define nephrotoxicity based on changes in creatinine clearance. However, creatinine clearance demonstrates significant intrasubject variability dependent on the method used to calculate clearance [20]. We defined nephrotoxicity based on changes in serum creatinine, and found 37% of the subjects developed nephrotoxicity after 1 cycle of chemotherapy and 46% of the subjects developed nephrotoxicity after 1 or 2 cycles of chemotherapy. If we defined nephrotoxicity based on a 50% reduction in creatinine clearance calculated with the Cockcroft–Gault equation, only 25% of our subjects developed nephrotoxicity. These data agree with the reported incidence from other studies among patients treated with 100 mg/m^2 or more of cisplatin [5,22]. Because the number of subjects who developed nephrotoxicity depends on the definition of nephrotoxicity, investigators need to standardize the definition of chemotherapy-induced nephrotoxicity based on a reproducible measurement.

The demographic and clinical characteristics were similar between the subjects with and without nephrotoxicity with the exception of race/ethnicity; African-Americans were more likely to develop nephrotoxicity than Caucasians and Hispanics included in the study. Race or ethnicity has not been previously identified as a predictive factor for cisplatin-induced nephrotoxicity; of note, previous studies failed to specify the racial or ethnic distribution of their study population [4,5,22]. Genetic variations in the enzymes that metabolize cisplatin to the nephrotoxin may be responsible for the differences we observed in the incidence of nephrotoxicity between African-Americans and other races.

We evaluated the baseline laboratories to compare our findings to previous studies that found various pre-treatment laboratory parameters are correlated with nephrotoxicity following treatment with cisplatin [4,5,22]. We found that pre-treatment calcium and platelet count were significantly higher and serum chloride was significantly lower in subjects with nephrotoxicity. In the multivariable model, only calcium was independently associated with nephrotoxicity. Stewart *et al.* reported that serum albumin, serum potassium and body surface area predicted acute renal dysfunction [4]. Our data did not show an association between these parameters and cisplatin-induced nephrotoxicity. The apparent discrepancies may stem from differences in the underlying subject populations; Stewart *et al.* enrolled all

subjects receiving cisplatin regardless of their diagnosis or chemotherapy regimen [4], whereas we only reviewed the medical records of subjects with head and neck cancer who received a standard cisplatin plus fluorouracil regimen.

Subjects prescribed albuterol, hydrochlorothiazide, thiamine and multivitamins were more likely to develop nephrotoxicity after cycle 1. Additionally, subjects prescribed these medications, as well as atenolol, were more likely to develop nephrotoxicity after cycle 1 or 2. A multivariable analysis of patients who developed nephrotoxicity after cycle 1 showed that use of multivitamins was independently associated with nephrotoxicity.

Hydrochlorothiazide is a diuretic commonly prescribed to manage hypertension and congestive heart failure. Both hydrochlorothiazide and cisplatin cause the kidneys to waste magnesium, suggesting hydrochlorothiazide could increase the incidence of cisplatin-induced nephrotoxicity by causing similar damage to the renal proximal tubules [23]. Hydrochlorothizide also increases the urinary excretion of sodium, calcium, chloride and potassium. However, the diuresis and electrolyte depletion typically deteriorates with prolonged use [24]. Treatment with a thiazide diuretic excludes subjects from participation in an ongoing study at the National Institutes of Health (No. CDR0000068796), although no published preclinical or clinical studies report an interaction between these medications.

Multivitamins were also more frequently prescribed to our subjects who developed nephrotoxicity. Multivitamins are commonly self-administered and would not be included in medical charts; however, in this study most subjects received chemotherapy as hospital in-patients where all medications administered are noted in the charts. In addition, most subjects included in this study received Medicare or Medicaid benefits that require a prescription for vitamins. Our data indicates that multivitamin supplements are associated with increased incidence of nephrotoxicity. Jones *et al.* analyzed the effect of thiamine and other sulfur-containing compounds on cisplatin-induced nephrotoxicity in rats [25]. The serum creatinine levels in their study shows significantly more nephrotoxicity in rats treated with thiamine and cisplatin compared with those treated with cisplatin alone ($P = 0.03$). Thiamine also significantly enhanced cisplatin-induced renal swelling. Our clinical data showed that thiamine supplementation, the majority of which was administered to patients also prescribed multivitamins, was not independently associated with an increased incidence of nephrotoxicity. However, thiamine is a component of multivitamins. Thiamine may have contributed to nephrotoxicity, although it is not possible to independently assess the effect of the lower levels of thiamine contained in multivitamins. Individual vitamins that have antioxidant properties have been shown in animals to minimize side-effects associated with chemotherapy regimens that include cisplatin [26–29].

Atenolol is a β_1-receptor antagonist commonly used to manage hypertension and coronary artery disease. Atenolol is excreted in the urine and, thus, adverse reactions associated with atenolol are more common in subjects with renal dysfunction. A previous study indicated that subjects receiving atenolol experience an increased excretion of urinary proteins, including α-microglobulin during a 5-year period [30]. However, no prior reports indicate an increased incidence of renal toxicity due to the concurrent administration of atenolol and cisplatin. Of note, metoprolol, another β_1-receptor antagonist, was prescribed to one subject with nephrotoxicity and two subjects without nephrotoxicity. The small number of subjects receiving metoprolol prevented us from assessing a relationship between nephrotoxicity and metoprolol.

Based on previous retrospective cohort studies, other medications that may increase the risk of cisplatin-induced nephrotoxicity include metoclopramide and aminoglycosides [4]. Immunosuppresants (cyclosporine, tacrolimus), acyclic nucleotide phosphonates (cidofovir) and non-steroidal anti-inflammatory drugs (NSAIDs) may augment cisplatin-induced nephrotoxicity as these drugs are commonly associated with acute renal toxicity. NSAIDs inhibit the production of prostaglandin by blocking the enzyme cyclooxygenase, which subsequently reduces renal blood flow, whereas the nucleoside analogs cause direct damage to the renal proximal tubules [31,32].

Ondansetron and dexamethasone were associated with a reduced incidence of cisplatin-induced nephrotoxicity. These medications are routinely co-administered to patients receiving more than 20 mg of cisplatin to reduce the emesis that is experienced by more than 90% of patients treated with cisplatin [33]. The medications are generally prescribed for 1 or more days following cisplatin administration. Dexamethasone is a synthetic adrenocortical steroid and ondansetron is an inhibitor of the serotonin 5-HT_3 receptor. There are no mechanistic studies that provide information regarding an interaction between these medications and cisplatin.

This study identified several medications that appear to increase or decrease the onset of nephrotoxicity following treatment with cisplatin. Forced i.v. hydration can substantially minimize the risk of acute renal toxicity and other measures have been investigated to prevent acute renal toxicity. Diuretics, including furosemide, mannitol and acetazolamide, can potentially minimize toxicity by decreasing the contact time of cisplatin in the proximal tubules [34]. Renin angiotensin blockers and

calcium channel blockers may decrease acute renal toxicity by increasing the renal blood flow [35]. Other drugs, including amifostine, thiosulfate and mesna, may decrease nephrotoxicity by chelating platinum complexes [34]. Some drugs, such as steroids, might decrease toxicity by stabilizing the membrane of the proximal tubules. Antioxidants such as lycopene, vitamins and capsaicin are also being explored for their ability to minimize acute renal toxicity [36–38]. Other drugs, including probenecid and glutathione, may reduce cisplatin-induced nephrotoxicity by inhibiting the transport of cisplatin or the metabolism of cisplatin–glutathione conjugates [9,34]. However, none of these measures are the current standard of care. Treatment strategies remain limited to discontinuing platinum therapy or switching to carboplatin, which has lower renal toxicity, but higher hematologic toxicity. A decision to stop cisplatin therapy takes into account baseline kidney function, and the degree and duration of elevated serum creatinine following cisplatin treatment.

None of the concurrent medications that altered the incidence of nephrotoxicity affected treatment response. These data agree with preclinical studies that demonstrate that the metabolic pathway responsible for producing the nephrotoxic form of cisplatin is independent of the anti-tumor activity. Expression of GGT is essential for the nephrotoxicity of cisplatin [10]. Yet, expression of GGT by tumor cells increases their resistance to cisplatin toxicity [39].

In summary, this study is the first to report that patients treated with atenolol, hydrochlorothiazide or multivitamins have a significantly increased incidence of cisplatin-induced nephrotoxicity, whereas patients prescribed ondansetron and dexamethasone have a lower incidence of cisplatin-induced nephrotoxicity. Our data show that none of these medications alter the tumor response to cisplatin-containing chemotherapy. They may modulate cisplatin-induced nephrotoxicity by altering the metabolic activation of cisplatin to its nephrotoxin. In addition, African-American subjects in this study population were more likely to develop nephrotoxicity. Genetic differences in medication metabolizing enzymes may contribute to this association.

Despite hydration and other supportive measures, many of the subjects treated with cisplatin experienced nephrotoxicity. The results from this retrospective study provide data for larger prospective studies to further investigate and confirm the associations between concurrent medications and cisplatin-induced nephrotoxicity. We are currently investigating the mechanism by which these medications alter cisplatin-induced nephrotoxicity. This study demonstrates that analysis of a small, but a tightly controlled, study population can lead to important new insights into medication interactions.

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References

1 Daugaard G, Abildgaard U, Holstein-Rathlou NH, Amtorp O, Leyssac PP. Effect of cisplatin on renal haemodynamics and tubular function in the dog kidney. *Int J Androl* 1987; **10**:347–351.
2 Jones BR, Bhalla RB, Mladek J, Kaleya RN, Gralla RJ, Alcock NW, *et al.* Comparison of methods of evaluating nephrotoxicity of *cis*-platinum. *Clin Pharmacol Ther* 1980; **27**:557–562.
3 Santoso JT, Lucci JA, III Coleman RL, Schafer I, Hannigan EV. Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. *Cancer Chemother Pharmacol* 2003; **52**:13–18.
4 Stewart DJ, Dulberg CS, Mikhael NZ, Redmond MD, Montpetit VA, Goel R. Association of cisplatin nephrotoxicity with patient characteristics and cisplatin administration methods. *Cancer Chemother Pharmacol* 1997; **40**:293–308.
5 Lagrange JL, Medecin B, Etienne MC, Pivot X, Cassuto-Viguier E, Renee N, *et al.* Cisplatin nephrotoxicity: a multivariate analysis of potential predisposing factors. *Pharmacotherapy* 1997; **17**:1246–1253.
6 Salem PA, Jabboury KW, Khalil MF. Severe nephrotoxicity: a probable complication of *cis*-dichlorodiammineplatinum (II) and cephalothin–gentamicin therapy. *Oncology* 1982; **39**:31–32.
7 Jongejan HT, Provoost AP, Molenaar JC. Potentiation of *cis*-diamminedichloroplatinum nephrotoxicity by amikacin in rats. *Cancer Chemother Pharmacol* 1988; **22**:178–180.
8 Hanigan MH, Gallagher BC, Taylor Jr PT. Cisplatin nephrotoxicity: inhibition of gamma-glutamyl transpeptidase blocks the nephrotoxicity of cisplatin without reducing platinum concentrations in the kidney. *Am J Obstet Gynecol* 1996; **175**:270–273.
9 Hanigan MH, Gallagher BC, Taylor Jr PT, Large MK. Inhibition of gamma-glutamyl transpeptidase activity by acivicin *in vivo* protects the kidney from cisplatin-induced toxicity. *Cancer Res* 1994; **54**:5925–5929.
10 Hanigan MH, Lykissa ED, Townsend DM, Ou CN, Barrios R, Lieberman MW. Gamma-glutamyl transpeptidase-deficient mice are resistant to the nephrotoxic effects of cisplatin. *Am J Pathol* 2001; **159**:1889–1894.
11 Townsend DM, Hanigan MH. Inhibition of gamma-glutamyl transpeptidase or cysteine S-conjugate beta-lyase activity blocks the nephrotoxicity of cisplatin in mice. *J Pharmacol Exp Ther* 2002; **300**:142–148.
12 Townsend DM, Deng M, Zhang L, Lapus MG, Hanigan MH. Metabolism of Cisplatin to a nephrotoxin in proximal tubule cells. *J Am Soc Nephrol* 2003; **14**:1–10.
13 Zhang L, Hanigan MH. Role of cysteine S-conjugate beta-lyase in the metabolism of cisplatin. *J Pharmacol Exp Ther* 2003; **306**:988–994.
14 Townsend DM, Marto JA, Deng M, Macdonald TJ, Hanigan MH. High pressure liquid chromatography and mass spectrometry characterization of the nephrotoxic biotransformation products of cisplatin. *Drug Metab Dispos* 2003; **31**:705–713.
15 Fuertesa MA, Castillab J, Alonsoa C, Perez JM. Cisplatin biochemical mechanism of action: from cytotoxicity to induction of cell death through interconnections between apoptotic and necrotic pathways. *Curr Med Chem* 2003; **10**:257–266.
16 Hanigan MH, Frierson Jr HF, Taylor Jr PT. Expression of gamma-glutamyl transpeptidase in stage III and IV ovarian surface epithelial carcinomas does not alter response to primary cisplatin-based chemotherapy. *Am J Obstet Gynecol* 1998; **179**:363–367.
17 Nakamura M, Imaoka S, Tanaka E, Misawa S, Funae Y. *cis*-Diamminedichloroplatinum induces peroxisomes as well as CYP4A1 in rat kidney. *Res Commun Mol Pathol Pharmacol* 1998; **99**:23–32.
18 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al.* New guidelines to evaluate the response to treatment

in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**:205–216.
19 Thadhani R, Pascual M, Bonventre JV. Acute renal failure. *N Engl J Med* 1996; **334**:1448–1460.
20 Donahue A, McCune JS, Faucette S, Gillenwater HH, Kowalski RJ, Socinski MA, *et al.* Measured versus estimated glomerular filtration rate in the Calvert equation: influence on carboplatin dosing. *Cancer Chemother Pharmacol* 2001; **47**:373–379.
21 Daugaard G. Renal morbidity. In: Plowman PN, Meadows AJ (editors): *Complications of cancer management*. Oxford: Butterworth-Heinemann; 1991, pp. 213–231.
22 Comis RL. Cisplatin nephrotoxicity: the effect of dose, schedule and hydration scheme. In: Prestako AW (editor): *Cisplatin: current status and new developments*. Orlando: Academic Press; 1980, pp. 485–494.
23 al Ghamdi SM, Cameron EC, Sutton RA. Magnesium deficiency: pathophysiologic and clinical overview. *Am J Kidney Dis* 1994; **24**: 737–752.
24 Yu T, Berger L, Sarkozi L, Kaung C. Effects of diuretics on urate and calcium excretion. *Arch Intern Med* 1981; **141**:915–919.
25 Jones MM, Basinger MA, Holscher MA. Control of the nephrotoxicity of cisplatin by clinically used sulfur-containing compounds. *Fundam Appl Toxicol* 1992; **18**:181–188.
26 Durak I, Ozbek H, Karaayvaz M, Ozturk HS. Cisplatin induces acute renal failure by impairing antioxidant system in guinea pigs: effects of antioxidant supplementation on the cisplatin nephrotoxicity. *Drug Chem Toxicol* 2002; **25**:1–8.
27 Appenroth D, Frob S, Kersten L, Splinter FK, Winnefeld K. Protective effects of vitamin E and C on cisplatin nephrotoxicity in developing rats. *Arch Toxicol* 1997; **71**:677–683.
28 Greggi Antunes LM, Darin JD, Bianchi MD. Protective effects of vitamin c against cisplatin-induced nephrotoxicity and lipid peroxidation in adult rats: a dose-dependent study. *Pharmacol Res* 2000; **41**: 405–411.
29 Naziroglu M, Karaoglu A, Aksoy AO. Selenium and high dose vitamin E administration protects cisplatin-induced oxidative damage to renal, liver and lens tissues in rats. *Toxicology* 2004; **195**:221–230.
30 Suwelack B, Kobelt V, Erfmann M, Hausberg M, Gerhardt U, Rahn KH, *et al.* Long-term follow-up of ACE-inhibitor versus beta-blocker treatment and their effects on blood pressure and kidney function in renal transplant recipients. *Transplant Int* 2003; **16**:313–320.
31 Perazella MA. Drug-induced renal failure: update on new medications and unique mechanisms of nephrotoxicity. *Am J Med Sci* 2003; **325**:349–362.
32 Cheng HF, Harris RC. Renal effects of non-steroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors. *Curr Pharm Des* 2005; **11**:1795–1804.
33 Grunberg SM, Osoba D, Hesketh PJ, Gralla RJ, Borjeson S, Rapoport BL, *et al.* Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity – an update. *Support Care Cancer* 2005; **13**:80–84.
34 Ries F, Klastersky J. Nephrotoxicity induced by cancer chemotherapy with special emphasis on cisplatin toxicity. *Am J Kidney Dis* 1986; **8**:368–379.
35 Pinzani V, Bressolle F, Haug IJ, Galtier M, Blayac JP, Balmes P. Cisplatin-induced renal toxicity and toxicity-modulating strategies: a review. *Cancer Chemother Pharmacol* 1994; **35**:1–9.
36 Atessahin A, Yilmaz S, Karahan I, Ceribasi AO, Karaoglu A. Effects of lycopene against cisplatin-induced nephrotoxicity and oxidative stress in rats. *Toxicology* 2005; **212**:116–123.
37 Weijl NI, Elsendoorn TJ, Lentjes EG, Hopman GD, Wipkink-Bakker A, Zwinderman AH, *et al.* Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study. *Eur J Cancer* 2004; **40**:1713–1723.
38 Shimeda Y, Hirotani Y, Akimoto Y, Shindou K, Ijiri Y, Nishihori T, *et al.* Protective effects of capsaicin against cisplatin-induced nephrotoxicity in rats. *Biol Pharm Bull* 2005; **28**:1635–1638.
39 Hanigan MH, Gallagher BC, Townsend DM, Gabarra V. gamma-glutamyl transpeptidase accelerates tumor growth and increases the resistance of tumors to cisplatin *in vivo*. *Carcinogenesis* 1999; **20**:553–559.