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Association of cisplatin nephrotoxicity with patient characteristics and cisplatin administration methods

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Abstract *Objective*: To assess factors that affect cisplatin nephrotoxicity. *Methods*: In 425 patients treated with cisplatin, we assessed the effect of pretreatment factors and treatment conditions on the rise in serum creatinine with the first course of cisplatin, on the maximum rise in serum creatinine over the entire course of the cisplatin therapy, and on residual nephrotoxicity after the last cisplatin treatment ended. (Because of the nature of the relationship between serum creatinine and creatinine clearance, rise in serum creatinine was divided by pretreatment creatinine squared.) Patients were dichotomized into the upper quartile versus the lower three quartiles of degree of nephrotoxicity. Multivariate analyses were based on logistic regression, controlling for cisplatin dose per course. *Results*: Controlling for cisplatin dose per course, factors most closely associated with nephrotoxicity during the first course of cisplatin were: serum albumin and potassium, body surface area, and administration of cisplatin over 2–5 days per course vs 1 day (negative associations). Controlling for cisplatin dose per course, the single factor most closely associated with maximum life-time cisplatin nephrotoxicity was concurrent use of a vinca alkaloid (negative association). Controlling for cisplatin dose per course, factors most closely associated with residual nephrotoxicity after the end of cisplatin therapy were cumulative dose of cisplatin, concurrent use of metoclopramide (positive associations), uric acid and concurrent use of phenytoin and a vinca alkaloid (negative associations). The association of nephrotoxicity with uric acid and with body surface area was felt to be an artifact resulting from its positive association with pretreatment serum creatinine. Nephrotoxicity during the first course of cisplatin also correlated significantly with autopsy kidney cortex platinum concentrations in 77 evaluable patients. *Conclusions*: (1) While several factors correlated with cisplatin nephrotoxicity, most of the observed nephrotoxicity was not explained by the variables identified. (2) While most patients received intravenous hydration, patients receiving high hydration volumes did not have significantly less nephrotoxicity than patients receiving lower hydration volumes. (3) Of the variables identified, serum albumin, metoclopramide and phenytoin may have affected nephrotoxicity by altering cisplatin uptake into or distribution within the kidney.

Key words Cisplatin · Nephrotoxicity · Administration

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Introduction

Cisplatin is active against several types of solid tumors, but nephrotoxicity is often dose-limiting. Vigorous hydration reduces nephrotoxicity [1], although the amount of hydration required for optimal nephroprotection remains poorly defined. In most series, mannitol with or without furosemide has been given along with cisplatin plus hydration. In animal studies, mannitol [2, 3] and acetazolamide [2, 4] have been shown to reduce cisplatin nephrotoxicity and to decrease kidney platinum concentrations. In randomized studies in humans, the

addition of mannitol to cisplatin plus hydration has been shown to reduce nephrotoxicity during the first treatment course when used with moderately high cisplatin doses, although it is less certain whether the protection continues to as great an extent with later cisplatin courses [5], and it has not yet been determined whether it would also offer an advantage with other dose schedules of cisplatin. Furosemide augments some aspects of cisplatin nephrotoxicity [3, 6] and actually augments kidney platinum concentrations [3, 7]. However, other studies have shown that furosemide reduces cisplatin nephrotoxicity [8].

Various other medications may also affect cisplatin nephrotoxicity. Various sulphur-containing compounds have been reported to reduce cisplatin nephrotoxicity in clinical or preclinical systems [9–13]. Nephrotoxicity is also reduced by various cations, such as copper [14], selenium [15–17], bismuth [18], calcium [19], and magnesium [20], and by other agents, such as prochlorperazine [21], procaine hydrochloride [22], captopril [23], verapamil plus cimetidine [24], buthionine sulfoximine [25, 26], probenecid [27], piperacillin [28], quinine and quinidine [29], ascorbic acid [10], and hypertonic saline solutions [30, 31]. Cisplatin nephrotoxicity has also been reported to be augmented by some medications, such as aminoglycosides [32, 33], and some medications which have been found to be protective in some studies have been found to augment cisplatin toxicity in others (e.g. probenecid [34] and buthionine sulfoximine [35]).

Several aspects of cisplatin administration affect the severity of cisplatin nephrotoxicity in humans and animals. For example, high peak plasma platinum concentrations may augment cisplatin nephrotoxicity [36–38], and steps that have been taken to reduce peak plasma platinum concentrations (such as slow as opposed to rapid administration [39–41], or multiple-day as opposed to single-day fractionation of a given total dose [42]) may reduce cisplatin nephrotoxicity [39–41]. The time of day of cisplatin administration also may be important: cisplatin administered in late afternoon (when urine production is maximal) has been reported to be less nephrotoxic than administration in the early morning (when urine production is least) [43, 44].

We have previously found that nephrotoxicity in patients treated with cisplatin may correlate with autopsy kidney platinum concentrations [45], and we concluded that cisplatin nephrotoxicity is at least partly directly attributable to the platinum concentrations attained. However, we also concluded that several other factors must be playing a role in the development of cisplatin nephrotoxicity. Moreover, we were interested in the degree to which factors that affected kidney platinum concentrations after cisplatin would also affect the severity of cisplatin nephrotoxicity. In this paper, we report the results of a retrospective assessment of patient characteristics, cisplatin administration methods, and concurrent medications that correlate with severity of cisplatin nephrotoxicity in a series of patients treated at the Ottawa Regional Cancer Centre.

Materials and methods

Patient population

We reviewed the inpatient and outpatient charts of 522 patients who had received cisplatin at the Ottawa Regional Cancer Centre between 1982 and 1990, and recorded various patient characteristics, blood test parameters, cisplatin treatment details, and details regarding clinical evidence of cisplatin nephrotoxicity. Of these 522 patients, 34 were excluded since they had preexisting renal dysfunction because of ureteric obstruction from bladder cancer. Of the remaining 488 patients, 57 were excluded from analysis since they received a total cumulative cisplatin dose or a dose per course of ≤ 15 mg/m^2 (often as part of voluntary pharmacology studies), which was not considered sufficient to cause nephrotoxicity. Of the remaining 431, two were excluded who had a baseline serum creatinine of 700 μmol/l or greater (and were not evaluable since they were being hemodialyzed), and four had missing values on this measure. To be evaluable for nephrotoxicity, a patient had to have had measurements of a pretreatment serum creatinine as well as at least one repeat serum creatinine between 1 and 3 weeks after their first cisplatin treatment.

Nephrotoxicity evaluation

Because we did not routinely repeat creatinine clearances on our patients, we used changes in serum creatinine instead of changes in creatinine clearance as a measure of nephrotoxicity. We assessed cisplatin nephrotoxicity in three ways: with the change following the *first* course of cisplatin, with the *maximum* rise in serum creatinine over the entire course of the cisplatin therapy and with *residual* nephrotoxicity after the *last* cisplatin treatment ended. For nephrotoxicity with the first course of cisplatin, pretreatment serum creatinine was subtracted from the highest serum creatinine value recorded between 1 and 3 weeks after the first cisplatin treatment. For maximum nephrotoxicity, pretreatment serum creatinine was subtracted from the highest serum creatinine value recorded at any time between the first treatment and 4 weeks after the last treatment. For residual nephrotoxicity after completion of cisplatin treatment, pretreatment serum creatinine was subtracted from the serum creatinine value recorded between 2.5 and 4 weeks after the last cisplatin treatment.

Because of the nature of the mathematical relationship between serum creatinine and creatinine clearance, fairly large decrements in creatinine clearance can be accompanied by relatively small increases in serum creatinine when the baseline serum creatinine is low and the baseline creatinine clearance is high, while the opposite is the case when the baseline serum creatinine is high and the baseline creatinine clearance is low. Therefore, rather than testing an association of independent variables with change in serum creatinine per se or with change in serum creatinine as a percentage of pretreatment creatinine, we tested its association with change in serum creatinine as a percentage of pretreatment creatinine squared. (When there was no or zero change over a particular time period, the zero was recorded as 0.1 to avoid transformed variables equal to zero regardless of the denominator, i.e. creatinine squared.) We felt that transforming the change scores in this way would give a better indication of the extent of change in renal function. In fact, these "corrected values" correlated with uncorrected changes in serum creatinine levels with correlation coefficients > 0.90.

The number of evaluable patients for whom we had information on residual toxicity after the last cisplatin treatment was substantially lower than the number of patients for whom we had information on nephrotoxicity after the first cycle of cisplatin ($n = 242$ vs $n = 396$). The major reason for this was that patients who were completing a preplanned number of cisplatin treatments often did not return until more than 4 weeks after their last treatment, and a serum creatinine determination was often not repeated routinely after completion of planned therapy. Moreover, patients

who experienced tumor progression while on treatment were often admitted to a peripheral hospital without repeat serum creatinine determinations.

Cisplatin administration

Cisplatin administration methods varied considerably among patients. As a rule, cisplatin was mixed in normal or half-normal saline prior to administration. Individual doses greater than 25 mg/m^2 were usually accompanied by mannitol (250 ml of a 20% solution) plus at least an additional 750 ml of intravenous (i.v.) fluids, with the entire hydration and cisplatin administration procedure requiring a minimum of 1.5 h (most often as an outpatient). Patients were also encouraged to drink a minimum of six to eight glasses of fluid per day at home in the 2–3 days following treatment, although the amount of oral hydration was not monitored or recorded. Patients who were receiving a cisplatin dose of ≤ 75 mg/m^2 per course divided over 3 or more days (i.e. ≤ 25 mg/m^2 per day) were in some cases treated without mannitol and with only 300–550 ml total i.v. fluids per day. On the other hand, a small proportion of the patients receiving cisplatin 100–120 mg/m^2 as an inpatient received several litres of i.v. fluids. The total time over which cisplatin and hydration were infused was generally longer for patients receiving high doses of cisplatin and for patients with preexisting major renal or cardiac disease than for other patients. Patients who developed nephrotoxicity with their first course of cisplatin often had a reduction in their cisplatin dose with later courses, although the criteria for reducing the cisplatin dose and the amount of dose reduction varied between different Ottawa Regional Cancer Centre physicians.

Cisplatin was given either alone or as part of one of several different combination regimens. All patients were treated in the era prior to availability of 5-HT3 antagonist antiemetics. Hence, antiemetics generally consisted of low- to moderate-dose metoclopramide with or without dexamethasone, prochlorperazine, lorazepam, and various other agents.

Analyses

All statistical analyses were performed using SPSS-PC version 4.01 and BMDP/PC Release 7.01. Analyses were conducted on each of the three dependent measures: percent change (of baseline creatinine squared) in creatinine over the first course of cisplatin, maximum percent change in creatinine over all courses, and residual percent change in creatinine following the last cisplatin treatment. Predictor variables included physiological variables measured before the first cisplatin treatment, demographic factors, major concurrent illnesses, and details of cisplatin administration methodology (including concurrent use of other drugs and supportive care). For most of these variables, data recorded were pretreatment values (for patient characteristics) or values for the first course of cisplatin therapy (for treatment administration details). However, concurrent drugs were recorded if they were used at any point over the duration of cisplatin therapy.

Because the three dependent measures were not normally distributed and no transformation was successful in normalizing them, the decision was made to dichotomize each dependent measure into the upper quartile of nephrotoxicity versus the remainder. Cut points for the 75th percentile were selected individually for each of the three dependent measures. Logistic regression analysis (LR) using maximum likelihood estimation was used to develop the prediction models, i.e. to determine which factors were significantly associated with each outcome variable, controlling for other relevant factors. We recognize that the choice of alternative cut points could lead to identification of different sets of predictor variables. We chose to divide the population into upper quartile vs lower three quartiles since the upper quartile had a clinically significant creatinine rise. If, instead, we had just divided the population into upper half vs lower half, many patients in the upper half would have had a creatinine rise that was so small that it was clinically insignificant.

The number of predictor variables recorded for this study was too high to include all factors in a model. Selection of variables for entry depended, in part, upon results of univariate analyses of the association between each measure of nephrotoxicity (no/yes) and each factor. To avoid having to transform all non-normally distributed continuous variables in initial univariate analyses, nonparametric tests were used, including Kruskal-Wallis nonparametric analyses of variance or chi-squared, depending upon whether the variable was continuous or categorical. The decision was made to exclude supportive care drugs from multivariate analyses, regardless of univariate significance, if less than 10% or more than 90% of the patients received a particular drug.

Three criteria were used for inclusion of a variable in multivariate analyses: (1) dose per course (i.e. cisplatin dose with each 3-week course of chemotherapy in milligrams per metre squared) was always entered and could not be removed; (2) factors which had *P*-values less than 0.10 in the univariate analyses were then considered for entry; and finally (3) factors of potential biological importance, regardless of statistical significance in univariate analyses, were tested.

Once the sets of variables to be considered for entry were selected, continuous variables were examined for normality using the Kolmorgorov-Smirnov (K-S) test. Variables with a K-S test with $P < 0.01$ were examined. Any individual value with a positive or negative *z*-score > 3.5 was reduced to the next lowest observed value with a $\pm$ *z*-score < 3.5.

Other data transformations included dummy coding (e.g. 0 = none vs 1 = any or 0 = normal vs 1 = abnormal) for the dichotomous variables in multivariate analyses. The ordinal scale variables, patient performance status and time of day of administration of cisplatin (morning vs afternoon vs evening), were treated as categorical variables and coded accordingly. For ECOG performance status, levels 0 and 1 were combined into a single group. Given the large numbers of missing values for a number of factors, no attempt was made to impute means for missing values.

Prior to running the LRs, all the continuous variables to be entered into the models were examined for multivariate outliers (defined as Mahalanobis' Distance, chi-squared $P < 0.001$) using BMDP AM. Seven cases were identified as multivariate outliers for analyses of nephrotoxicity with first course of cisplatin, 11 for analyses of maximum nephrotoxicity over all courses of cisplatin, and none for analyses of residual nephrotoxicity post-cisplatin.

The rationale behind the analytic strategy was to identify all variables that might be associated with nephrotoxicity, controlling for other variables, including dose per course of cisplatin. Model building was undertaken in three stages for each of the three measures of nephrotoxicity. Stage 1 used hierarchical LR and default criteria for entry and removal of variables (i.e. chi-squared *P*-value to enter of 0.10 and *P*-value to remove of 0.15). First, dose per course was entered and could not be removed from the model. Then, all factors were entered that were associated with nephrotoxicity in univariate analyses, with $P < 0.10$, and for which there were fewer than 50 (12%) missing cases. Backwards stepping was used to eliminate any variable no longer in the model after controlling for other factors. The set of variables remaining were then used in the successive stages of model building.

At stage 2, biologically important variables that did not achieve the univariate $P < 0.10$ criterion were examined, as well as variables that had reached criterion, but for which there were ≥ 50 patients ($> 12\%$) with missing values. These factors were tested individually: each variable was entered into separate models after dose per course plus the final set of stage 1 variables. Backwards stepping, using default criteria, was used to determine which stage 2 variable remained in each model.

At the third and last stage, hierarchical forward (and backward) stepwise analysis was used. Dose per course of cisplatin was entered first and could not be removed. Then forward stepwise analysis was used to select among all remaining stage 1 and 2 factors. For stage 3, the default entry and removal criteria were changed, so that variables could enter and remain in the model only if they had a *P*-value to enter of ≤ 0.05. Results were confirmed using backward stepping procedures.

These analyses must be considered as exploratory only. Because of the number of variables and model-building strategies employed, *P*-values should only be taken as an indication of relative importance of factors in this particular data set. The family-wise error rate is considerably beyond 0.05.

We also assessed whether nephrotoxicity would correlate with autopsy kidney concentrations of platinum, as we had noted previously [45]. Autopsy kidney samples were available in 83 of the patients in this series. Platinum was assayed in kidney cortex and kidney medulla by flameless atomic absorption spectrophotometry, as previously described [46]. The association between nephrotoxicity and kidney platinum concentrations was examined using nonparametric correlations, i.e. Spearman's rank-order coefficients. Since the kidney cortex is the major site of cisplatin damage [47], we also used the kidney medulla as an "internal control" for unidentified factors that might affect kidney cortex platinum concentrations or cisplatin distribution within the kidney: we subtracted kidney medulla platinum concentration from kidney cortex concentration (to generate a variable designated COR-MEDPT), and correlated this difference with nephrotoxicity parameters. We also tested associations between dichotomized nephrotoxicity variables and kidney platinum concentration variables.

Results

Patient population

Patients in this study included 285 males and 140 females. Tumor types were non-small-cell lung cancer (104 patients), small-cell lung cancer (72 patients), gliomas (49 patients), head and neck cancer (33 patients), bladder cancer (29 patients), testicular cancer (22 patients), and other tumor types (95 patients), and tumor type was unknown in 21 patients. They had received life-time cumulative cisplatin doses of 30 to 1120 (median 220) mg/m^2, and received cisplatin 20 to 120 (median 75) mg/m^2 per course. Patients received a median of three courses (range 1–11) of cisplatin, and received a median of eight additional drugs concurrently with cisplatin.

Descriptive statistics of dependent measures

As would be expected, there was a positive correlation between change in serum creatinine with the first course of cisplatin and maximum rise in serum creatinine over the entire course of treatment (Spearman's $r = 0.63$, $P < 0.001$). There was a moderate correlation between change in serum creatinine with the first course of cisplatin and residual rise in nephrotoxicity following the last course of cisplatin ($r = 0.32$, $P < 0.001$).

Table 1 provides the median, minimum and maximum values of each of the three change in creatinine scores, both in the form of the original change scores and in the form of change as a percentage of creatinine squared. A total of ten patients (2.5%) had rises in serum creatinine with the first course of cisplatin of ≥100 μmol/l, of whom five had rises of ≥200 μmol/l. The cutoff value separating the upper quartile patients from the lower three quartiles for serum creatinine divided by creatinine squared was 0.3907. In a patient with a pretreatment serum creatinine of 80 μmol/l, this cutoff value for creatinine rise divided by pretreatment creatinine squared would translate into a creatinine rise of 25 μmol/l.

Total of 29 patients (7.1%) had maximum rises in serum creatinine of ≥100 μmol/l over the entire course of cisplatin treatment, of whom 14 had rises of ≥200 μmol/l. The cutoff value separating the upper quartile patients from the lower three quartiles of maximum rise was 0.7511. In a patient with a pretreatment serum creatinine of 80 μmol/l, this cutoff value for maximum creatinine rise divided by pretreatment creatinine squared would translate into a creatinine rise of 48 μmol/l. For 98 of the 319 patients who received more than one course of cisplatin (about 32%), the maximum rise in serum creatinine was identical to the change with the first course of cisplatin (i.e. the greatest rise in serum creatinine occurred with the first course of therapy).

Eight patients had residual rises in serum creatinine of ≥100 μmol/l from pretreatment to the period between 2.5 and 4 weeks after their last cisplatin, of whom three had rises of ≥200 μmol/l. The cutoff value separating the upper quartile patients from the lower three quartiles was 0.4815. In a patient with a pretreatment serum creatinine of 80 μmol/l, this cutoff value for creatinine rise divided by pretreatment creatinine squared would translate into a creatinine rise of 31 μmol/l.

Descriptive statistics of predictor variables

Table 2 provides statistics on the relationship between the three measures of nephrotoxicity and each continuous variable considered for entry in one of the logistic models. In Table 2, medians of the continuous variables

Table 1 Dependent variables: cisplatin nephrotoxicity

	Median	Minimum	Maximum
Change in creatinine with first course			
Raw score (μmol/l)	9.00	−51.00	681.00
Corrected[a]	0.14	−0.51	7.88
Maximum creatinine change for entire cisplatin course			
Raw score (μmol/l)	23.00	−35.00	754.00
Corrected[a]	0.36	−0.33	7.88
Residual creatinine change after last cisplatin			
Raw score (μmol/l)	8.00	−52.00	394.00
Corrected[a]	0.14	−0.72	4.95

[a]Raw score divided by baseline creatinine squared, then multiplied by 100

Table 2 Median values of continuous independent variables for patients in the upper vs lower three quartiles of creatinine change. Patient characteristics were assessed prior to the first cisplatin treatment. Drug administration variables (except for life-time cumulative cisplatin dose) applied to the first course of cisplatin

	First course change in creatinine[a]		Maximum change in creatinine[a]		Residual change in creatinine[a]	
	Lower 75%	Upper 25%	Lower 75%	Upper 25%	Lower 75%	Upper 25%
Cisplatin mg/m^2/course						
Median	75	80**	75	80**	75	80**
n	(297)	(99)	(308)	(102)	(182)	(60)
Total cumulative dose of cisplatin (mg/m^2)						
Median	225	150**	206	244*	200	240*
n	(297)	(99)	(308)	(102)	(182)	(60)
Age at initiation of treatment (years)						
Median	57	61*	58	59	58	58
n	(297)	(99)	(308)	(102)	(182)	(60)
Body surface area (m^2)						
Median	1.7	1.7**	1.7	1.7	1.7	1.7
n	(297)	(99)	(308)	(102)	(182)	(60)
Hemoglobin (g/l)						
Median	125	117**	124	122*	126	120*
n	(294)	(99)	(307)	(100)	(182)	(58)
Serum urea (mmol/l)						
Median	4.9	4.4	4.9	4.7	4.9	4.4
n	(295)	(98)	(306)	(101)	(182)	(60)
Serum uric acid (μmol/l)						
Median	293	279^{+}	290	296	304	292
n	(288)	(97)	(299)	(100)	(179)	(60)
Serum albumin (g/l)						
Median	39	37**	38	39	40	39
n	(291)	(98)	(302)	(101)	(179)	(60)
Serum total protein (g/l)						
Median	68	64**	67	68	67	68
n	(294)	(97)	(304)	(101)	(181)	(60)
Serum calcium (mmol/l)						
Median	2.33	2.25**	2.31	2.33	2.32	2.33
n	(290)	(98)	(301)	(101)	(177)	(60)
Serum magnesium (mmol/l)						
Median	0.76	0.74	0.76	0.74	0.75	0.74
n	(101)	(33)	(98)	(36)	(69)	(23)
Serum phosphorus (mmol/l)						
Median	1.18	1.19	1.16	1.19	1.16	1.17
n	(207)	(59)	(206)	(71)	(122)	(40)
Serum glucose (mmol/l)						
Median	6.0	5.9	5.9	6.0	6.0	6.1
n	(293)	(98)	(304)	(100)	(178)	(60)
Serum chloride (mmol/l)						
Median	101	99**	101	100^{+}	101	100
n	(295)	(99)	(306)	(102)	(181)	(60)
Serum CO_2 (mmol/l)						
Median	27	28	27	27	28	27
n	(286)	(96)	(296)	(99)	(176)	(58)
Serum sodium (mmol/l)						
Median	139	137*	139	138	139	139
n	(286)	(97)	(297)	(100)	(174)	(59)
Serum potassium (mmol/l)						
Median	4.3	4.2*	4.3	4.3	4.3	4.2
n	(291)	(97)	(302)	(100)	(179)	(59)
Serum bilirubin (μmol/l) (total)						
Median	6.0	6.8	6.8	7.0	6.9	6.0
n	(291)	(98)	(301)	(102)	(176)	(59)
Serum aspartane aminotransferase (U/l)						
Median	24	25	24	25^{+}	23	26
n	(285)	(96)	(296)	(99)	(175)	(58)
Serum alanine aminotransferase (U/l)						
Median	23	19^{+}	21	26	21	21
n	(211)	(89)	(220)	(83)	(144)	(51)

Table 2 (contd.)

	First course change in creatinine[a]		Maximum change in creatinine[a]		Residual change in creatinine[a]	
	Lower 75%	Upper 25%	Lower 75%	Upper 25%	Lower 75%	Upper 25%
Serum lactate dehydrogenase (U/l)						
Median	221	232	219	261^{+}	227	232
n	(287)	(97)	(297)	(101)	(177)	(60)
Systolic blood pressure						
Median	126	122	126	122^{+}	127	124
n	(263)	(83)	(269)	(91)	(152)	(51)
Diastolic blood pressure						
Median	78	74	78	74	(79)	80
n	(263)	(83)	(269)	(91)	(152)	(51)
Urine volume 24 h						
Median	2100	2000	2100	2000	2150	2600
n	(57)	(19)	(60)	(16)	(44)	(13)
Total volume I.V. fluid (ml)						
Median	1350	1750	1400	1400	1405	1750
n	(257)	(80)	(269)	(81)	(160)	(50)
Duration of cisplatin infusion (h)						
Median	95	120**	100	120*	97	120**
n	(180)	(69)	(187)	(65)	(112)	(45)

[a]Divided by baseline creatinine squared
$^{+}0.05 < P < 0.10$, $^{*}P < 0.05$, $^{**}P < 0.01$

(and available sample sizes) are provided for patients in the lower three quartiles vs the upper quartile of each of the three nephrotoxicity measures. Table 3 provides the percentage distribution of each categorical variable within each of the low and high quartile groups of the three dependent measures. The level of significance of each association, based on Kruskal-Wallis nonparametric tests (Table 2) or chi-squared tests (Table 3), are also noted in these tables.

In addition to the concurrent medications included in Table 3, there were also many other drugs used concurrently with cisplatin in at least some patients. Too few patients received most of these drugs to adequately assess whether or not they had any impact on cisplatin nephrotoxicity. Based on the size of the differences in median serum creatinine changes, there is a possibility that significant effects might have been noted for some of these drugs if larger patient numbers had been studied. Patients who received any one of the following agents with their cisplatin had a $\geq 50\%$ *lower* median value for rise in serum creatinine (divided by baseline creatinine squared) than did patients who did not receive these agents (but $P > 0.05$): barbiturates, methylxanthines, H-2 blockers, calcium channel blockers, dipyridamole, and folic acid. Patients who received any one of the following agents with their cisplatin had a $\geq 50\%$ *higher* median value for rise in serum creatinine (divided by baseline creatinine squared) than did patients who did not receive these agents (but $P > 0.05$): H-1 blockers, beta blockers, nitroglycerin and related drugs, glycerol, amoxycillin or ampicillin, and iron replacement therapy.

For many of these agents, differences in creatinine changes may just have been from chance alone. Moreover, the patients included in our study received a median of eight drugs in addition to cisplatin, making it difficult to sort out any contribution to nephrotoxicity of any individual drug. However, there are possible mechanisms by which many of these agents could have decreased or augmented cisplatin nephrotoxicity. Additional medications that our patients received included 5-fluorouracil, cyclophosphamide, ifosphamide, mesna, nitrosoureas, methotrexate, corticosteroids, digoxin, loop diuretics (including furosemide), cephalosporins, cotrimoxazole, aminoglycosides (three patients only), nabilone, and others.

Results of logistic regression analyses

Tables 4–6 provide summaries of the variables tested as predictors in the series of LRs for each of the three dependent measures. Included in Tables 4–6 are the variables considered for entry at each stage and whether each variable remained in the model. Tables 7–9 provide details of the final model for each dependent measure.

After controlling for cisplatin dose per course, four variables were included in the final model for nephrotoxicity after the first course of cisplatin (goodness-of-fit $\chi^2 = 368$, DF = 366, $P = 0.453$, $n = 372$). These were serum albumin and potassium, body surface area, and number of days over which each cisplatin course was administered (≥ 2 vs 1) (negative associations). (Note that for goodness-of-fit tests, the higher the *P*-value, the better.)

After controlling for cisplatin dose per course, only one variable was included in the final model for maximum rise in serum creatinine over the entire course of cisplatin therapy (goodness-of-fit $\chi^2 = 408$, DF = 376,

Table 3 Cisplatin nephrotoxicity: baseline categorical independent variables. In each column is presented the number and per cent of patients to whom the characteristic applies. Patient characteristics were assessed prior to first cisplatin treatment. Drug administration variables (except for life-time cumulative cisplatin dose) applied to the first course of cisplatin. With respect to concurrent medications, concurrent chemotherapy drugs and antiemetics were given with first and later courses of cisplatin. In some cases, other medications varied from course to course of cisplatin therapy

	First course change in creatinine[a]				Maximum change in creatinine[a]				Residual change in creatinine[a]			
	Lower 75%		Upper 25%		Lower 75%		Upper 25%		Lower 75%		Upper 25%	
Gender												
Female	89	30%	42	42%*	94	31%	42	41%*	51	28%	24	40%+
Male	208	70%	57	58%	214	69%	60	59%	131	72%	36	60%
Ecog performance status												
0–1	145	51%	33	34%**	147	50%	40	40%	92	51%	27	47%
2	87	31%	28	29%	84	28%	34	34%	50	28%	20	34%
3	46	16%	26	27%	53	18%	20	20%	30	17%	9	16%
4	7	2%	10	10%	11	4%	6	6%	7	4%	2	3%
No. days cisplatin per course												
1	183	62%	81	82%**	200	66%	68	67%	135	75%	43	72%
2–5	112	38%	18	18%	105	34%	34	33%	46	25%	17	28%
Time of day of cisplatin administration												
8:00–12:00	115	42%	43	46%	120	43%	43	46%	76	47%	26	45%
12:00–16:00	136	50%	39	41%	138	49%	40	43%	74	46%	26	45%
16:00–24:00	21	8%	12	13%	24	9%	11	12%	11	7%	6	10%
Total volume of I.V. hydration												
< 1 litre	94	32%	34	35%	96	31%	34	34%	60	33%	19	32%
1–2 litres	182	62%	59	61%	192	63%	59	60%	107	59%	37	63%
> 2 litres	19	6%	4	4%	19	6%	6	6%	14	8%	3	5%
Route of administration												
Intraarterial	50	17%	14	14%	51	17%	12	12%	35	19%	4	7%*
Intravenous	247	83%	85	86%	257	83%	90	88%	147	81%	56	93%
History of diabetes												
No	277	94%	88	89%	287	93%	92	91%	167	92%	55	93%
Yes	19	6%	11	11%	21	7%	9	9%	15	8%	4	7%
History of hypertension												
No	241	82%	85	86%	250	81%	88	88%	153	85%	50	86%
Yes	53	18%	14	14%	57	19%	12	12%	28	15%	8	14%
History of atherosclerosis												
No	228	77%	75	76%	238	77%	73	73%	143	79%	48	83%
Yes	67	23%	24	24%	70	23%	27	27%	39	21%	10	17%
History of alcohol abuse												
No	224	81%	84	88%+	241	83%	77	79%	143	84%	46	82%
Yes	53	19%	11	12%	48	17%	20	21%	27	16%	10	18%
Mannitol												
No	17	8%	10	13%	18	9%	9	12%	13	9%	5	11%
Yes	184	92%	70	88%	190	91%	68	88%	129	91%	40	89%
Corticosteroids												
No	9	3%	3	3%	13	4%	1	1%	10	6%	0	0%+
Yes	287	97%	95	97%	294	96%	100	99%	171	94%	59	100%
Benzodiazepines												
No	119	40%	48	48%	125	41%	43	42%	81	45%	27	45%
Yes	178	60%	51	52%	183	59%	59	58%	101	55%	33	55%
Metoclopramide												
No	61	21%	20	20%	67	22%	18	18%	49	27%	8	13%*
Yes	236	79%	79	80%	241	78%	84	82%	133	73%	52	87%
Prochlorperazine												
No	125	42%	51	52%	131	43%	51	50%	85	47%	25	42%
Yes	171	58%	48	48%	176	57%	51	50%	96	53%	35	58%
Vinca alkaloids												
No	218	73%	89	90%**	228	74%	91	89%**	139	76%	55	92%**
Yes	79	27%	10	10%	80	26%	11	11%	43	24%	5	8%
Doxorubicin												
No	220	74%	74	75%	223	72%	84	82%*	138	76%	43	72%
Yes	77	26%	25	25%	85	28%	18	18%	44	24%	17	28%
Bleomycin												
No	234	79%	88	89%*	245	80%	86	84%	149	82%	55	92%+
Yes	63	21%	11	11%	63	20%	16	16%	33	18%	5	8%

Table 3 (contd.)

	First course change in creatinine[a]				Maximum change in creatinine[a]				Residual change in creatinine[a]			
	Lower 75%		Upper 25%		Lower 75%		Upper 25%		Lower 75%		Upper 25%	
Cytosine arabinoside												
No	267	90%	86	87%	281	91%	84	82%*	155	85%	54	90%
Yes	30	10%	13	13%	27	9%	18	18%	27	15%	6	10%
Phenytoin												
No	235	79%	87	88%+	249	81%	84	82%	134	74%	55	92%**
Yes	61	21%	12	12%	58	19%	18	18%	47	26%	5	8%
Non-steroidal antiinflammatories												
No	268	90%	89	90%	283	92%	89	87%	167	92%	52	87%
Yes	29	10%	10	10%	25	8%	13	13%	15	8%	8	13%
Acetaminophen												
No	240	81%	81	82%	253	82%	79	77%	148	81%	47	78%
Yes	57	19%	18	18%	55	18%	23	23%	34	19%	13	22%
Narcotics												
No	199	67%	55	56%*	198	64%	67	66%	110	60%	38	63%
Yes	98	33%	44	44%	110	36%	35	34%	72	40%	22	37%
Digoxin												
No	286	96%	91	92%+	292	95%	97	95%	172	95%	54	90%
Yes	11	4%	8	8%	16	5%	5	5%	10	5%	6	10%

[a]Change in creatinine divided by baseline creatinine squared
+$0.05 < P < 0.10$, *$P < 0.05$, **$P < 0.01$

Table 4 Variables considered for entry at each stage of the analysis of cisplatin nephrotoxicity during the first course of cisplatin

Variables entered at each stage of logistic regression analysis		
Stage 1 P to enter = 0.10 P to remove = 0.15	Stage 2 P to enter = 0.10 P to remove = 0.15	Stage 3 P to enter = 0.050 P to remove = 0.051
Forced in model: Dose/course	Forced in model: Dose/course Hemoglobin Albumin Chloride Potassium Body surface area No. days/course Vinca alkaloids	Forced in model: Dose/course
Evaluated via backwards stepping:[a] Age Uric acid *Hemoglobin *Albumin Total protein Calcium *Chloride Sodium *Potassium *Body surface area Gender *No.Days/Course Bleomycin *Vinca alkaloids Phenytoin	Individual variables evaluated via backwards stepping:[b] Bilirubin Performance status Time of day Route Diabetes Alcohol abuse Prochlorperazine Metoclopramide Nonsteroidals Narcotics Magnesium[d] *ALT[d] Mannitol[d] Hydration volume[d] Infusion duration[d]	Evaluated via forward and backward stepping:[c] Hemoglobin *Albumin Chloride *Potassium *Body surface area *No. days/course Vinca alkaloids

[a]These variables were associated with nephrotoxicity in univariate analyses, with $P < 0.10$, and had fewer than 50 missing cases
[b]Stage 2 factors are biologically important variables, but with univariate $P > 0.10$, as well as variables that had reached the statistical criterion, but for which there were 50 or more patients with missing values
[c]Variables meeting statistical criteria at stages 1 and 2
[d]Factor has too many missing cases (> 50) to be considered in later stages of model building
*Variables meeting default criteria of P to enter and remove

Table 5 Variables considered for entry at each stage of analysis of maximum cisplatin nephrotoxicity over the entire course of cisplatin. Model building was performed as in Table 4

Variables entered at each stage of logistic regression analysis		
Stage 1 *P* to enter = 0.10 *P* to remove = 0.15	Stage 2 *P* to enter = 0.10 *P* to remove = 0.15	Stage 3 *P* to enter = 0.050 *P* to remove = 0.051
Forced in model: Dose/course	Forced in model: Dose/course Cumulatative dose Hemoglobin Cytosine arabinoside Vinca alkaloids	Forced in model: Dose/course
Evaluated via backwards stepping: *Cumulatative dose *Hemoglobin Chloride AST LDH Gender *Cytosine arabinoside Doxorubicin *Vinca alkaloids	Individual variables evaluated via backward stepping: Age Uric acid Albumin Potassium Bilirubin Body surface area Performance status No. days/course Route Diabetes Prochlorperazine *Metoclopramide Phenytoin Nonsteroidals Narcotics Magnesium[a] Systolic blood pressure[a] Mannitol[a] Hydration volume[a] Infusion duration[a]	Evaluated via forward and backward stepping: Cumulatative dose Hemoglobin Cytosine arabinoside *Vinca alkaloids Metoclopramide

[a]Factor has too many missing cases (> 50) to be considered in later stages of model building
*Variables meeting default criteria of *P* to enter and remove

$P = 0.121$, $n = 396$). This was concurrent use of vinca alkaloids (negative association). After controlling for cisplatin dose per course, five variables were included in the final model for residual nephrotoxicity as assessed 2.5–4 weeks after the last course of cisplatin (goodness-of-fit $\chi^2 = 236$, DF = 230, $P = 0.390$, $n = 238$). The factors were cumulative dose of cisplatin, concurrent administration of metoclopramide (positive associations), uric acid, and concurrent administration of vinca alkaloids and phenytoin (negative associations).

Mannitol use, hydration volume, and cisplatin infusion duration were not tested in the final stage 3 models since there were more than 50 cases with missing values for these variables. Furthermore, in general, these variables did not significantly correlate with nephrotoxicity when tested in Stage 2 of the modelling, that is when their effect was tested (in the subpopulation of patients for which values were available) after correcting for the effect of factors achieving statistical significance in stage 1 of the LR analyses. In stage 2 of the modelling, cisplatin infusion duration was positively associated with residual nephrotoxicity. When each of these three variables was tested for its effect on nephrotoxicity after controlling for the effects of the variables entering the final models, the only association that was statistically significant was a positive correlation between cisplatin infusion duration and residual nephrotoxicity.

Kidney platinum concentrations and nephrotoxicity

Kidney cortex (but not kidney medulla) platinum concentrations were significantly ($P < 0.05$) higher in the patients in the upper quartile for nephrotoxicity with the first course of therapy than in patients in the lower three quartiles. However, neither kidney cortex nor kidney medulla platinum concentrations correlated significantly with maximum nephrotoxicity nor with residual nephrotoxicity. As in our earlier studies [45], when we subtracted kidney medulla platinum concentrations from kidney cortex platinum concentrations (to use kidney medulla as an internal control for unidentified factors that affect cisplatin uptake into kidney cortex or that affect cisplatin distribution within the kidney), the resulting value (designated COR-MEDPT) was significantly higher in patients in the upper quartile than in patients in the lower three quartiles but, again, only for nephrotoxicity with the first course of cisplatin ($P = 0.007$). If nephrotoxicity was treated as a continuous variable, rather than being dichotomized (Table 10), neither kidney cortex nor kidney medulla platinum concentrations correlated with nephrotoxicity, but COR-MEDPT correlated significantly with both nephrotoxicity after the first course of cisplatin and with maximum nephrotoxicity over the entire course of therapy.

Table 6 Variables considered for entry at each stage of analysis of residual nephrotoxicity after the end of cisplatin therapy. Model building was performed as in Table 4

Variables entered at each stage of logistic regression analysis		
Stage 1 *P* to enter = 0.10 *P* to remove = 0.15	Stage 2 *P* to enter = 0.10 *P* to remove = 0.15	Stage 3 *P* to enter = 0.050 *P* to remove = 0.051
Forced in model: Dose/course	Forced in model: Dose/course Cumulative dose Gender Vinca alkaloids Metoclopramide Phenytoin	Forced in model: Dose/course
Evaluated via backwards stepping: *Cumulatative dose Hemoglobin *Gender Route Bleomycin *Vinca alkaloids *Metoclopramide *Phenytoin	Individual variables evaluated via backwards stepping: Age *Uric acid Albumin Chloride Potassium Bilirubin LDH Body surface area Performance status No. days/course Diabetes Cytosine arabinoside Prochlorperazine Nonsteroidals Narcotics Magnesium[a] *ALT[a] Mannitol[a] Hydration volume[a] *Infusion duration[a]	Evaluated via forward and backward stepping: *Cumulatative dose Gender *Vinca alkaloids *Metoclopramide *Phenytoin *Uric acid

[a]Factor has too many missing cases (> 50) to be considered in later stages of model building
*Variables meeting default criteria of *P* to enter and remove

Table 7 Results of hierarchical logistic regression analysis of cisplatin nephrotoxicity during the first course of cisplatin ($n = 372$). Dose per course forced first in model

Variable	Results of final model			
	Coefficient	Standard error	$e^{(coeff)}$	95% CI of $e^{(coeff)}$
Dose/course	0.0168	0.007	1.02	1.00–1.03
Albumin	−0.1053	0.026	0.90	0.85–0.95
Potassium	−0.5933	0.279	0.55	0.32–0.96
Body surface area	−1.4121	0.653	0.24	0.07–0.88
No. days/course (1 vs 2–5)	−0.9392	0.313	0.39	0.21–0.72
Constant	6.7396	1.833		

Goodness of fit chi-squared (2*o*ln(o/e)) = 368.505, DF = 366, *P*-value = 0.453
Goodness of fit chi-squared (Hosmer-Lemeshow) = 4.613, DF = 8, *P*-value = 0.798

Table 8 Results of hierarchical logistic regression analysis of maximum cisplatin nephrotoxicity over the entire course of cisplatin ($n = 396$). Dose per course forced first in model

Variable	Results of final model			
	Coefficient	Standard error	$e^{(coeff)}$	95% CI of $e^{(coeff)}$
Dose/course	0.0136	0.006	1.01	1.00–1.03
Vinca alkaloids	−1.0921	0.360	0.34	0.17–0.68
Constant	−2.0247	0.512		

Goodness of fit chi-squared (2*o*ln(o/e)) = 408.331, DF = 376, *P*-value = 0.121
Goodness of fit chi-squared (Hosmer-Lemeshow) = 8.188, DF = 8, *P*-value = 0.415

Table 9 Results of hierarchical logistic regression analysis of residual cisplatin nephrotoxicity after the end of cisplatin therapy ($n = 238$). Dose per course forced first in model

Variable	Results of final model			
	Coefficient	Standard error	$e^{(coeff)}$	95% CI of $e^{(coeff)}$
Dose/course	0.0031	0.009	1.00	0.99–1.02
Cumulative dose	0.0025	0.001	1.00	1.00–1.00
Vinca alkaloids	−1.3324	0.526	0.26	0.09–0.74
Metoclopramide	0.8600	0.435	2.70	1.00–5.57
Phenytoin	−1.4106	0.532	0.24	0.09–0.70
Uric acid	−0.0034	0.002	1.00	0.99–1.00
Constant	−1.2403	0.949		

Goodness of fit chi-squared (2*o*ln(o/e)) = 235.362, DF = 230, *P*-value = 0.390
Goodness of fit chi-squared (Hosmer-Lemeshow) = 9.810, DF = 8, *P*-value = 0.279

Table 10 Correlations between nephrotoxicity[a] and kidney platinum concentrations. Values are Spearman's coefficients (number of evaluable patients)

	Cortex	Medulla	COR-MEDPT[b]
First course	0.19[c] (77)	0.06 (73)	0.30** (73)
Maximal	0.13 (78)	0.10 (74)	0.24* (74)
Residual	0.09 (47)	0.15 (43)	0.18 (43)

[a]Rise in creatinine divided by baseline creatinine squared
[b]Kidney cortex minus kidney medulla platinum concentration (using kidney medulla as an "internal control")
[c]Not significant for nephrotoxicity as a continuous variable, but $P < 0.05$ if nephrotoxicity is dichotomized, and the upper quartile is compared with the bottom three quartiles
*$P < 0.05$, **$P < 0.001$

As we have previously reported for this patient population [46], kidney cortex and medulla platinum concentrations each correlated significantly ($P < 0.05$) with cisplatin dose per course and with concurrent metoclopramide use (positive correlations) and with time from last cisplatin treatment to death and with concurrent phenytoin use (negative correlations) in multivariate analysis. We did not examine COR-MEDPT in that earlier study. Factors that correlated significantly ($P < 0.05$) with COR-MEDPT in the present study were poor ECOG performance status (positive correlation) and cumulative cisplatin dose, serum albumin and total protein, systolic blood pressure, and concurrent metoclopramide (negative correlations).

We then ran hierarchical, stepwise LRs, in which the outcomes were dichotomized nephrotoxicity variables, to assess whether kidney platinum concentrations added anything further to the ability to predict nephrotoxicity after correcting for the effect of cisplatin dose. In each LR, cumulative cisplatin dose and cisplatin dose per course were evaluated first for stepwise entry and could not be removed. Then, each of the three autopsy variables (kidney cortex platinum concentration, kidney medulla platinum concentration, COR-MEDPT) was evaluated (in different analyses). Out of nine LRs (three autopsy variables vs three nephrotoxicity variables), in only one did an autopsy variable approach statistical significance after correcting for both cumulative cisplatin dose and cisplatin dose per course: for nephrotoxicity during the first course of cisplatin, $P = 0.058$ for COR-MEDPT.

Discussion

When we embarked on this study, we had four main goals. The first was to better understand the biology of cisplatin nephrotoxicity by identifying factors that correlated with it. The second goal was to develop models that would enable us to predict which patients treated in the future would be at highest risk of developing cisplatin nephrotoxicity. The third goal was to attempt to identify specific strategies that might decrease cisplatin nephrotoxicity. The fourth goal was to determine whether factors that correlated with human autopsy kidney cortex platinum concentrations also correlated with cisplatin nephrotoxicity. It is stressed that, since we examined a large number of variables, at least some of the statistically significant associations reported in this paper almost certainly arose by chance alone. However, our observations do suggest some specific future studies that could potentially facilitate the safe administration of cisplatin.

With respect to our first goal, we identified several factors that correlated with nephrotoxicity. Risk factors differed somewhat for first course nephrotoxicity, maximal nephrotoxicity, and residual nephrotoxicity. Of these, the most "accurate" were probably those for first course nephrotoxicity, since most of the patient characteristics tested were ones that were present at the time of the first cisplatin treatment, and many would have changed somewhat over the course of treatment. In addition, the fact that data on residual nephrotoxicity were missing in several patients suggests that particular

caution must be exercised in interpreting the data for this dependent variable.

The negative correlation of nephrotoxicity with serum albumin confirms an earlier association we reported based on a preliminary analysis of an initial subset of this patient population [48]. This association could possibly be explained by the fact that cisplatin is rapidly and virtually irreversibly bound to plasma albumin and other proteins [49]. In earlier studies, we had found that serum albumin levels correlated inversely with kidney cortex platinum concentrations in univariate analysis [46] (Spearman's $r = -23$, $P < 0.05$), and in the present analysis, we also found that it correlated inversely with COR-MEDPT ($r = -0.30$, $P < 0.01$). This suggests that cisplatin, binding to albumin may sequester the cisplatin, thereby reducing kidney uptake. Alternatively, the possible effect of albumin on platinum distribution in the kidney and its effect on cisplatin nephrotoxicity could be mediated through its effect on peritubular capillary resorption and intrarenal hemodynamics [50].

Serum potassium levels also correlated inversely with nephrotoxicity from the first course of cisplatin. Cisplatin administration may itself result in hypokalemia in some patients [51]. We are unaware of any prior reports suggesting that serum potassium levels might influence the development of cisplatin nephrotoxicity, although the risk of cisplatin nephrotoxicity may be related to urinary potassium excretion [44]. In addition, hypokalemia itself may result in renal tubular damage [52], and it is possible that this could potentiate cisplatin nephrotoxicity. Furthermore, a variety of other cations have been reported to reduce cisplatin nephrotoxicity through uncertain mechanisms [14–20], and it is possible that potassium acts in a similar manner. Calcium levels were negatively associated with nephrotoxicity in our univariate analysis. We have also found that some cations may affect cisplatin uptake into tumor cell lines [53] and human tumors [54]. In those earlier studies, potassium reduced both cisplatin uptake and cytotoxicity in a human lung cancer cell line [53]. However, potassium showed little correlation with human autopsy kidney cortex platinum concentrations in our earlier studies [46], nor with COR-MEDPT in this study, suggesting that any effect of potassium on cisplatin nephrotoxicity is not mediated through an effect on kidney uptake of cisplatin. Overall, the negative correlation of cisplatin nephrotoxicity with serum potassium levels suggests that it might be best to avoid loop diuretics in patients receiving cisplatin and that aggressive supplementation with potassium chloride might be beneficial in hypokalemic patients.

A preliminary analysis done on an early subpopulation of the data set had suggested a significant positive correlation between serum uric acid levels and cisplatin nephrotoxicity [48], but this final analysis did not confirm this association. In fact, there was a significant *negative* correlation between serum uric acid and residual nephrotoxicity in the present study. This negative association between serum uric acid and residual nephrotoxicity was probably an artifact. Serum uric acid correlated significantly with pretreatment serum creatinine ($r = 0.46$, $P < 0.001$), while it did not correlate significantly with actual residual rise in serum creatinine. Since our nephrotoxicity variables were derived by dividing rise in serum creatinine by pretreatment creatinine squared, anything that was associated with pretreatment serum creatinine could also potentially affect the nephrotoxicity variables without actually affecting nephrotoxicity itself. Similarly, the association we noted between high body surface area and nephrotoxicity was probably an artifact arising out of the correlation between body size and serum creatinine.

A given cisplatin dose was less nephrotoxic when spread over 2–5 days than when all the drug was administered on a single day. Our autopsy studies did not indicate that this was a result of alteration of kidney cortex platinum concentrations, although the impact of multiple-day administration on cisplatin pharmacology may nevertheless be an important contributing factor: multiple-day fractionation of a dose reduces peak plasma platinum concentrations [42], and high peak plasma platinum concentrations may augment cisplatin nephrotoxicity [36–38]. It is possible that the relationship between peak concentrations and nephrotoxicity may arise as a result of the high peak drug concentrations temporarily overwhelming a potential tissue protective mechanism, such as glutathione [35].

Other steps that reduce peak plasma platinum concentrations, such as slow as opposed to rapid administration, have also been reported to reduce cisplatin nephrotoxicity [39–41]. However, in our study, there was no significant association between cisplatin infusion duration and cisplatin nephrotoxicity, and the lack of such an association may have been an artifact related to the fact that patients receiving higher cisplatin doses and patients with preexisting major renal or cardiac dysfunction received longer cisplatin infusions, as per our institutional policy.

Three concurrent medications correlated with nephrotoxicity. Concurrent phenytoin administration correlated inversely with residual nephrotoxicity. Similarly, in our tissue pharmacology studies, kidney cortex platinum concentrations correlated inversely with phenytoin use in both univariate and multivariate analyses [46]. The reasons for this association are unclear. However, phenytoin alters the flux of cations across cell membranes [55], and it is possible that the mechanism by which it does this is the same mechanism by which it affects cisplatin kidney uptake and nephrotoxicity.

Metoclopramide use was associated with increased residual nephrotoxicity, and also correlated significantly with human autopsy kidney cortex platinum concentrations in univariate and multivariate analyses in our earlier studies [46]. We are unaware of any other data linking metoclopramide to cisplatin nephrotoxicity clinically, and there is also no evidence in rats that it augments cisplatin nephrotoxicity [56]. However, metoclopramide antagonizes renovascular dopamine receptors [56], reduces renal blood flow [57], and augments

cisplatin antitumor efficacy in preclinical systems, possibly through inhibition of the DNA repair enzyme polyadenosine-diphosphoribosyl-transferase [58]. In mice, when metoclopramide is given after cisplatin, it is associated with augmented antitumor efficacy, increased serum platinum concentrations, increased cisplatin-DNA adducts in tumors, and there is a tendency towards increased cisplatin-DNA adducts in the kidneys [59].

Since all of our data were based on patients treated in the era prior to availability of the 5-HT3 antagonists, we have no data on the effect of 5-HT3 antagonists on cisplatin nephrotoxicity, and are not aware of any data indicating that there is less cisplatin nephrotoxicity with 5-HT3 antagonists than with metoclopramide. Nevertheless, in light of our observations on the apparent effect of metoclopramide on cisplatin nephrotoxicity, we feel that it would be worthwhile testing whether higher doses of cisplatin can be achieved safely with the 5-HT3 antagonists than was previously possible with metoclopramide.

Concurrent administration of vinca alkaloid chemotherapeutic agents was associated with reduced maximal and residual nephrotoxicity. The reason for this is unclear, but this association suggests that it may be reasonable to attempt to administer higher cisplatin doses when vinca alkaloids are being administered concurrently.

Hydration and mannitol are routinely used with cisplatin to reduce nephrotoxicity [1, 5], and 91% of evaluable patients in our study did receive mannitol with their cisplatin. However, in our earlier studies, neither hydration volume nor mannitol use correlated with a reduction in human autopsy kidney cortex platinum concentrations [46], and kidney platinum concentrations actually correlated positively with 24-h urine output (Spearman's $r = 0.67$, $P < 0.05$) in the 12 patients who were evaluable. Prior randomized studies have indicated that the addition of mannitol to hydration does help reduce cisplatin nephrotoxicity [5]. Patients receiving mannitol in our study had the same median cisplatin doses per course as patients not receiving mannitol (75 mg/m^2), but the cumulative cisplatin dose was significantly higher among those who received mannitol in comparison to those who did not (200 mg/m^2 vs 100 mg/m^2, $P < 0.01$). The lack of correlation between mannitol use and nephrotoxicity in this study may also have been largely because only 9% of evaluable patients did not receive mannitol with their cisplatin, and this 9% would have been a subpopulation felt to be at particularly low risk of nephrotoxicity.

Data on hydration volume were also missing in too many of our patients to permit us to draw firm conclusions. However, it did not correlate significantly with any measure of nephrotoxicity, even after controlling for the effects of other stage 3 model variables. The lack of definite benefit for high hydration volume could not be explained on the basis of an association between hydration volume and cisplatin dose, as hydration volume did not correlate with cisplatin dose per course (Spearman's $r = 0.05$, $P > 0.10$). Somewhat complicating interpretation of the role of hydration is the fact that we had no data on the volume of oral fluids ingested by our patients, although they were generally instructed to drink a minimum of six to eight glasses of fluid per day for the first several days after cisplatin treatment. While there is general agreement that generous hydration is important to decrease the risk of cisplatin nephrotoxicity, there is little data on the fluid volume that is optimal nor on the minimum fluid volume that is required. In light of the relatively modest impact of hydration volume in this nephrotoxicity study and in our previous studies of human kidney cortex platinum concentrations, it is possible that the minimum required fluid volume may be somewhat less than that used routinely by many groups. Further study of this is warranted, since it could potentially facilitate administration of cisplatin on an outpatient basis. Our usual practice for the past few years (spanning the last half of the data acquisition period for this study) with cisplatin doses up to and including 100 mg/m^2 is to administer the cisplatin on an outpatient basis in 500 ml normal saline over 1–2 h concurrently with mannitol (250 ml of a 20% solution), and preceded by 250 ml dextrose 5% in normal saline or half-normal saline over 30 min. Prehydration is omitted if the patient is also receiving a chemotherapeutic agent that requires ≥ 250 ml of fluid for administration (e.g. i.v. etoposide). While modest rises in serum creatinine values are common, severe nephrotoxicity is distinctly uncommon.

It has previously been reported that time of day of cisplatin administration affects nephrotoxicity [43, 44]. However, in our study, we could detect no major effect of time of day of cisplatin administration on cisplatin nephrotoxicity, even after using multivariate analysis to correct for the effect of other variables. While in studies claiming an effect of time of day, the morning cisplatin dose was given earlier and the evening cisplatin dose was given later than the usual time range in our patients, we conclude that time of administration of cisplatin within the usual outpatient work day does not appear to have any major impact on degree of cisplatin nephrotoxicity.

With respect to preexisting diseases that might affect risk of cisplatin nephrotoxicity, nephrotoxicity was not correlated with a history of hypertension and atherosclerosis, with blood pressure at the time of first treatment, or with a history of diabetes.

With respect to our second main goal of being able to predict which patients would be at highest risk of cisplatin nephrotoxicity, our study indicates that knowledge of factors associated with cisplatin nephrotoxicity provides us with a very imperfect method of predicting nephrotoxicity in individual patients. The predictive value positive and predictive value negative were not helpful, using a probability cutoff of 0.5 of being in the upper quartile. The imprecision of our models indicates that there are several important factors that we failed to identify despite the large number of variables tested. Despite the relative imprecision of our predictive models,

our data suggest that hypoalbuminemic, hypokalemic patients may be at highest risk, and that particular caution should be used in this group.

With respect to our third goal, our data suggest that there may be some strategies that could be tested to reduce cisplatin nephrotoxicity. These include infusion of albumin in hypoalbuminemic patients, correction of electrolyte disturbances, and administration of cisplatin over multiple days per course (instead of on a single day). Our data also suggest that patients who are receiving vinca alkaloids concurrently with cisplatin may possibly tolerate higher doses of cisplatin than would other patients, that new antiemetic agents may possibly be accompanied by less cisplatin nephrotoxicity than with metoclopramide, and that phenytoin may reduce nephrotoxicity. As noted previously, however, for many of these, there are other possible explanations besides true associations or cause and effect relationships with nephrotoxicity. Therefore, each will need to be tested in further studies.

With respect to our fourth goal, we did confirm that factors that correlated with kidney cortex platinum concentrations (cisplatin dose per course and concurrent use of phenytoin or metoclopramide [46]) were correlated with development of cisplatin nephrotoxicity. This suggests that each of these three factors may have exerted their effect on cisplatin nephrotoxicity by altering renal cortex uptake of cisplatin.

The kidney cortex and corticomedullary junction are the sites of the major histopathological evidence of kidney damage following cisplatin administration [3, 47, 60, 61], with fewer changes in the kidney medulla. In our first study of cisplatin concentrations in autopsy kidneys from 35 patients, we found a significant correlation between kidney cortex platinum concentrations and cisplatin nephrotoxicity [45]. In the current series, in which the original population of 35 patients was expanded to 83 for whom we have data on autopsy kidney platinum concentrations, patients in the upper quartile for nephrotoxicity with the first course of cisplatin had significantly higher kidney cortex platinum concentrations than did those in the lower three quartiles. This association was found despite the fact that the median time from last cisplatin exposure to death was 38 days (range < 1 to 609 days) [46]. We had also found that cisplatin peripheral sensory neuropathy correlates with dorsal root ganglion platinum concentrations [62], that many chemotherapeutic agents are retained in human tissues for prolonged periods of time, that tissue distribution patterns may correlate with toxicity (reviewed in reference 46), and that the propensity of chemotherapeutic agents to cause long-term toxicity may in some cases be related to the time that they are retained in tissues [46, 63].

When multivariate analyses were used to correct for the effect of cisplatin dose, there was no longer a significant association between nephrotoxicity and kidney cortex platinum concentration. This is not surprising, since, as would be expected, kidney platinum concentration correlates with cisplatin dose [46].

In our original series, we had also done further analyses in which we used the kidney medulla as an "internal control" for the effect of various factors on kidney cortex platinum concentrations. When kidney medulla platinum concentration was subtracted from kidney cortex platinum concentration, the resulting value (designated COR-MEDPT) correlated significantly with cisplatin nephrotoxicity in both our initial series [45], and in this expanded study. Factors that correlated most strongly with COR-MEDPT were ECOG performance status (positive association), serum albumin and total protein levels, and systolic blood pressure during treatment (negative associations), while the factors that correlated most strongly with kidney cortex platinum concentrations (after correcting for the effects of cisplatin dose and time from treatment to death) were concurrent use of phenytoin (negative association) and metoclopramide (positive association). Together, these data suggest that serum albumin levels and concurrent use of phenytoin and metoclopramide each may have affected cisplatin nephrotoxicity by modulating cisplatin uptake into, retention in, or redistribution in the kidney. On the other hand, the fact that the number of days of cisplatin administration per course, serum potassium levels, and concurrent vinca alkaloids did not significantly correlate with kidney platinum content or with COR-MEDPT suggests that they modulated nephrotoxicity by a mechanism that was independent of an effect on kidney cisplatin uptake or retention.

In summary, we identified several factors that correlated with cisplatin nephrotoxicity. For some of these factors, the effect on nephrotoxicity appeared to be mediated through an effect on kidney cortex platinum concentrations, while it is less certain how some others were exerting their effect. For at least some of these factors, specific therapeutic manipulations could be tested for their effect on nephrotoxicity. Since only a small portion of the observed nephrotoxicity was predicted by our models, there must also be several other still unrecognized factors affecting cisplatin nephrotoxicity. In addition, our models are too inexact to permit us to accurately predict the degree of nephrotoxicity in individual patients. Nevertheless, they may permit identification of patients at particularly high risk of nephrotoxicity, as well as patients who might potentially tolerate higher than standard cisplatin doses. Our results support the concept that multiple-day cisplatin administration is less nephrotoxic than single-day administration. They also suggest that it might prove feasible to safely administer higher cisplatin doses accompanied by new 5-HT3 antiemetics than was possible with older antiemetics.

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