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Predicting genitourinary toxicity in patients receiving cisplatin-based combination chemotherapy: a Cancer and Leukemia Group B study*

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Summary. Assessment of renal function prior to cisplatin chemotherapy has long been based on measurement of creatinine clearance by 24-hour urine collection (CrC_{meas}). Estimated creatinine clearance (CrC_{est}) as calculated from the patient's age, weight, and serum creatinine level has been suggested as an adequate surrogate for CrC_{meas}, as it provides advantages of improved convenience, decreased cost, and possibly increased accuracy. We studied 847 patients receiving cisplatin-based chemotherapy on Cancer and Leukemia Group B (CALGB) protocols to determine whether the CrC_{meas}, CrC_{est}, or serum creatinine value or the age of the patient would predict the subsequent genitourinary (GU) toxicity. Both CrC_{meas} ($P = 0.001$) and CrC_{est} ($P = 0.02$) were predictive of subsequent grade 2+ GU toxicity, with CrC_{meas} being a slightly better predictor. Patient age also influenced subsequent GU toxicity, with the risk increasing with age ($P = 0.0008$). When patients were classified by age group and by CrC_{meas}, distinct subgroups were identified, with differences in the risk for grade 2+ GU toxicity ranging from 14% to 32%. Using a logistic model to assess the probability of grade 2+ GU toxicity, we found that an age of ≥ 60 years ($P = 0.005$), a CrC_{meas} value of <75 ml/min ($P = 0.004$), and the risk characteristics of the individual cisplatin trial were important, whereas CrC_{est} was not. Furthermore, CrC_{est} proved to be a poor predictor of a CrC_{meas} value of <75 ml/min, "misclassifying" nearly half of the patients to a "lower-risk" subgroup. In summary, both CrC_{meas} and the patient's age independently provided predictive information concerning cisplatin GU toxicity. Our data support the continued clinical usefulness of determining the CrC_{meas} value prior to the administration of cisplatin-based chemotherapy to most patients.

Introduction

Cisplatin is one of the most widely used and effective anticancer agents currently available. Since the first responses to cisplatin were noted in phase I clinical trials in the early 1970s, the most important toxic effect of this heavy-metal derivative has been renal insufficiency. The use of various hydration techniques has decreased the incidence of clinically significant cisplatin nephrotoxicity, but despite these preventative measures, nephrotoxicity continues to occur [11, 17].

As cisplatin pharmacokinetics are altered in patients with renal insufficiency [15], a normal or nearly normal (>50 ml/min) baseline creatinine clearance is believed to be necessary for the avoidance of nephrotoxicity [8]. Most clinical trials of cisplatin assess patient eligibility using a pretherapy 24-h urine collection for creatinine clearance. This test is done despite the scarcity of published information on the risk of cisplatin-induced nephrotoxicity in patients with preexistent renal insufficiency [3], the inconvenience of 24-h measurements of creatinine clearance, and the possibility of inaccurate sample collection.

The estimation of creatinine clearance using a formula derived by Cockroft and Gault [5] has been proposed as being more accurate, more reproducible, and less costly than measurement based on 24-h urine collection prior to cisplatin therapy [4, 6, 9]. Using a large group of patients treated with cisplatin in 13 Cancer and Leukemia Group B (CALGB) studies, we evaluated the usefulness of substituting estimation of the pretherapy creatinine clearance (CrC_{est}) using the Cockroft and Gault equation [5] for the measurement of creatinine clearance (CrC_{meas}) by 24-h urine collection. Previous investigators attempting to study this aspect based their conclusions on the question as to

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Table 1. Distribution of patients by study

Study number	Thoracic malignancy	Disease extent	Number of patients	Number of evaluable patients
8243	Non-small-cell	Advanced	171	77
8331	Non-small-cell	Advanced	42	24
8332	Small-cell	Extensive	32	18
8432	Small-cell	Limited	53	40
8433	Non-small-cell	Regional	83	37
8435	Mesothelioma	–	78	58
8531	Non-small-cell	Advanced	243	185
8532	Small-cell	Limited	66	49
8534	Small-cell	Limited	272	190
8631	Small-cell	Extensive	76	56
8632	Non-small-cell	Advanced	79	62
8634	Non-small-cell	Regional	45	30
8636	Non-small-cell	Regional	31	21
Totals	–	–	1271	847

Table 2. Cytotoxic agents given in the studies evaluated

Study number	Cisplatin dose/schedule	Other agents
8243	100 mg/m^2, q28d	AC, Vbl
8331	20 mg/m^2 daily × 5, q21d	E
8332	20 mg/m^2 daily × 5, q21d	C, A, E
8432	33 mg/m^2 daily × 3, q21d	C, A, E
8433	100 mg/m^2, q28d	Vbl
8435	75 mg/m^2, q28d	Mito, A
8531	100 mg/m^2, q28d	FU, Vbl
8532	33 mg/m^2 daily × 3, q28d	C, A, E
8534	33 mg/m^2 daily × 3, q28d	C, A, E
8631	35 mg/m^2 daily × 3, q28d	E
8632	50 mg/m^2, q28d	CBDCA
8634	100 mg/m^2, q28d	FU, Vbl
8636	100 mg/m^2, q28d	Vbl

AC, Cytosine arabinoside (ara-C); Vbl, vinblastine; C, cyclophosphamide; A, doxorubicin; E, etoposide; Mito, mitomycin; CBDCA, carboplatin; FU, 5-fluorouracil

whether a positive correlation existed between CrC_{est} and CrC_{meas} in the patient populations evaluated [4, 6, 9, 10]. Rather than using this approach, we chose to investigate the more clinically important question as to whether either CrC_{est} or CrC_{meas} would provide any predictive information concerning the patients' subsequent risk of developing nephrotoxicity.

Single-institution studies have suggested that older patients are not at increased risk of developing cisplatin-induced nephrotoxicity [1, 7]. The large number of older patients receiving cisplatin in these multi-institutional trials afforded an opportunity to confirm or refute this observation.

Patients and methods

Patients and study design. All patients entered in CALGB lung-cancer and mesothelioma series 82–86 who received cisplatin or cisplatin-containing combination regimens were analyzed. Overall, 13 studies enrolled a total of 1271 patients as shown in Table 1.

In all, 847 subjects were considered to be evaluable as based on adequate information concerning baseline renal function and subsequent genitourinary toxicity encountered while enrolled on study. All patients for whom complete data were available were considered; this means that some individuals who would normally have been excluded because they did not fulfill protocol eligibility requirements were included in the present evaluation. As a result, data obtained in some patients who were considered to be ineligible due to inappropriate renal function were included, and these provide information on the extremes of the range of data. A total of 424 patients were excluded from the evaluation due to missing data on either serum creatinine, CrC_{meas}, age, or genitourinary toxicity. To be eligible to participate in these lung cancer and mesothelioma trials, patients were required to have unresectable, measurable or evaluable disease, and a CALGB performance status of 0–2.

Table 2 shows the cisplatin dose and schedule and the other cytotoxic agents used in each of the treatment regimens. Study 8331 involved patients with small-cell lung cancer who had failed previous etoposide- or cisplatin-containing regimens. These 24 individuals were the only patients included in this evaluation who had received any prior chemotherapy. Each of the protocols required that the cisplatin be reconstituted in normal saline prior to its administration over 20–90 min. Of the 13 studies evaluated, 7 gave specific instructions concerning pre- and post-dosing hydration and mannitol diuresis. The other studies gave less specific guidelines, leaving the use of hydration and diuretics to the discretion of the treating physician. Chemotherapy was scheduled to be given for a minimum of two cycles and was continued in most studies until disease progression had been noted.

Genitourinary (GU) toxicity was based on that recorded by the treating physician while the patients were on study. In all trials, grading of GU toxicity was based on standard CALGB criteria (Table 3).

Table 3. CALGB GU toxicity grading

Category	Grade 0 (none)	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
BUN (mg%)	<20	21–30	31–50	>50	Uremic coma
Creatinine (mg%)	<1.2	1.21–2.0	2.1–4.0	>4.0	or
Creatinine clearance	Normal	75%–99%	50%–74%	<50%	Obstructive uropathy
Proteinuria	None	1+ <300 mg%	2–3+ 300–1000 mg%	4+ >1000 mg%	or
Hematuria	None	Microscopic, minimal	Microscopic, marked	Gross bleeding	Exsanguinating hemorrhage
Bladder function	Normal	Dysuria, no treatment	Dysuria, moderate	Dysuria, severe	
Patients (n)	431	247	127	31	10
% All evaluable patients	51%	29%	15%	4%	1%

Table 4. Characteristics of patients at the time of protocol enrollment

	Number	Percentage
Sex:		
M	585	69%
F	262	31%
Age strata:		
<39 years	27	3%
40–49 years	114	13%
50–59 years	250	30%
60–70 years	366	43%
70+ years	90	11%
Performance status:		
Unknown	2	0
0	370	44%
1	357	42%
2	111	13%
3	7	1%
Serum creatinine strata:		
0.4–0.8 mg/dl	294	35%
0.9 mg/dl	170	20%
1.0–1.1 mg/dl	245	29%
1.2–2.0 mg/dl	138	16%
CrC_{est} strata:		
<75 ml/min	272	32%
75–84.9 ml/min	141	17%
85–99 ml/min	191	23%
100+ ml/min	243	29%
CrC_{meas} strata:		
<75 ml/min	243	29%
75–84.9 ml/min	146	17%
85–99.0 ml/min	154	18%
100+ ml/min	304	36%

Table 5. Distribution of GU toxicity according to protocol

Study number	GU toxicity of grades 2–4			Protocol GU toxicity classification
	Grade 2+ (*n*)	Total evaluable		
		n	%	
8243	22	77	29	High
8331	4	24	17	Moderate
8332	8	18	44	High
8432	4	40	10	Low
8433	4	37	11	Low
8435	16	58	28	High
8531	46	185	25	High
8532	5	49	10	Low
8534	31	190	16	Moderate
8631	16	56	29	High
8632	3	62	5	Low
8634	4	30	13	Low
8636	6	21	29	High
Totals	169	847	20	

Table 6. Grouping of studies by overall GU toxicity

Toxicity classification	Number of protocols	Grade 2 GU toxicity	
		Patients/total evaluable patients	Percentage
Low	5	20/218	9%
Moderate	2	35/214	16%
High	6	114/415	27%

The "measured" or laboratory-derived 24-h creatinine clearance (CrC_{meas}) was calculated as the mass of creatinine excreted per 24 h divided by the plasma creatinine concentration. This test was required prior to therapy in all patients. Individual institutions were responsible for instructing the patients on the method to be used for appropriate urine collections. Information concerning the "adequacy" of urine collections as based on the total amount of creatinine excreted per 24 h was not evaluated. The pretherapy estimated creatinine clearance (CrC_{est}) for each patient was calculated using the Cockroft and Gault [5] formula as follows:

$$CrC_{est} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{serum Cr} \times 72}.$$

Follow-up assessment of GU toxicity varied according to the individual study. At minimum, follow-up determinations of blood urea nitrogen (BUN) and serum creatinine levels were required after each cycle of therapy.

Statistical analysis. We assessed the association of various patient and study characteristics with the occurrence of GU toxicity using appropriate chi-square tests for contingency tables. The independent contribution of various characteristics to the prediction of the occurrence of GU toxicity was assessed using the logistic model.

Results

The characteristics of the patients are outlined in Table 4. The sample was stratified according to approximate quartiles of creatinine clearance, both measured and predicted, as follows: <75, 75–84.9, 85–99.9, and 100 + ml/min. The following mean values and standard deviations were observed for the study population as a whole: CrC_{meas}, 93.5 ± 30.1 ml/min; and CrC_{est}, 89.0 ± 28.3 ml/min.

As indicated above, the occurrence of GU toxicity at any time during the study was the primary outcome variable. In all, 416 of the 847 evaluable patients (49%) developed some degree of GU toxicity. For the purpose of this analysis, we chose to classify GU toxicity into two groups designated 0 (no toxicity) or 1 (mild toxicity) and 2+ (moderate or greater toxicity). We decided to focus our evaluation on the group of patients who developed grade 2+ toxicity because grade 1 toxicity (see Table 3) is of little clinical significance in the management of cancer patients receiving chemotherapy. Individual protocol charts were reviewed for all subjects who developed grade 2+ toxicity during 10 of the 13 trials evaluated. In 93% of cases (124/134), the grade 2+ GU toxicity encountered was attributed to rising BUN or creatinine levels or to a falling creatinine clearance.

The overall incidence of grade 2+ GU toxicity was 20%. Table 5 shows the distribution of toxicity rates by protocol. GU toxicity rates varied considerably according to the protocol involved, ranging from 5% (study 8632) to 44% (study 8332). This variability enabled the studies to be grouped according to the overall level of grade 2+ toxicity experienced (Table 6).

Table 7. Distribution of grade 2+ GU toxicity by age of the patient in decades

Age group (years)	Grade 2+ GU toxicity	
	Patients/total patients	Percentage
<40	1/27	4%
40–49	15/114	13%
50–59	42/250	17%
60–69	87/366	24%
70+	24/90	27%

Table 8. Distribution of grade 2+ GU toxicity by age risk group

Age group (years)	Grade 2+ GU toxicity	
	Patients/total patients	Percentage
<40	1/27	4%
40–59	57/364	16%
60+	111/456	24%
		($P = 0.0008$)

Table 9. Distribution of grade 2+ GU toxicity according to the parameters serum creatinine, CrC_{meas}, and CrC_{est}

Parameter	Grade 2+ GU toxicity	
	Patients/total patients	Percentage
Serum creatinine (mg/dl):		
0.4–0.8	53/294	18%
0.9	32/170	19%
1.0–1.1	54/245	22%
1.2–2.0	30/138	22%
		($P = 0.62$)
CrC_{meas} (ml/min):		
<75	69/243	28%
75– 85	21/146	14%
85–100	30/154	19%
100+	49/304	16%
		($P = 0.001$)
CrC_{est} (ml/min):		
<75	70/272	26%
75– 85	29/141	21%
85–100	32/191	17%
100+	38/243	16%
		($P = 0.02$)

Table 10. Distribution of grade 2+ GU toxicity by groups according to age and CrC_{meas}

Age (years)	CrC_{meas} (ml/min)	Grade 2+ GU toxicity	
		Patients/ total patients	Percentage
40–59	75+	38/280	14%
40–59	<75	19/84	23%
60+	75+	61/301	20%
60+	<75	50/155	32%
			($P = 0.00002$)

Table 11. Distribution of grade 2+ GU toxicities as estimated from logistic regression analysis and CrC_{meas} groups within groups defined by GU toxicity risk

Classification by		Studies classified by GU toxicity risk		
Age (years)	CrC_{meas} (ml/min)	Low	Moderate	High
40–59	75+	6%	11%	20%
40–59	<75	9%	18%	29%
60+	75+	9%	17%	29%
60+	<75	15%	26%	42%

The age of the patient clearly influenced the likelihood that grade 2+ GU toxicity would occur (Table 7). Because of the similarity of the risk for GU toxicity noted in the group aged 40–59 years and in patients aged ⩾60 years, three age groups could be formed (Table 8), showing a significant increase in the risk for toxicity with increasing age ($P = 0.0008$).

We investigated the extent to which serum creatinine, CrC_{meas}, and CrC_{est} predicted the occurrence of clinically significant (grade 2+) GU toxicity. The serum creatinine level, determined at the initiation of therapy had no predictive value ($P = 0.62$, Table 9). In contrast, both CrC_{meas} and CrC_{est} proved to be predictive of subsequent grade 2+ GU toxicity, with CrC_{meas} being a slightly better predictor ($P = 0.001$ vs $P = 0.02$, Table 9). Patients showing CrC_{meas} or CrC_{est} values of <75 ml/min were at highest risk. When patients were classified by age group (excluding those aged <40 years) and by CrC_{meas}, distinct subgroups were identified, with differences in the risk for significant (grade 2+) GU toxicity ranging from 14% to 32% ($P = 0.00002$, Table 10). As expected, the highest risk (>30%) was found for patients aged ⩾60 years who displayed CrC_{meas} values of <75 ml/min.

We next used a logistic model to predict the probability of the occurrence of grade 2+ toxicity as a function of patient and study characteristics. The analysis was restricted to the 820 patients aged 40 years or older, because the data obtained for individuals aged under 40 years indicated that they appeared to be at low risk for GU toxicity, irrespective of their baseline CrC_{meas} value or the study in which they were treated. This analysis showed that an age of ⩾60 years ($P = 0.005$), a baseline CrC_{meas} value of <75 ml/min ($P = 0.004$), and the indicators of GU toxicity risk for the cisplatin trial ($P = 0.02$, $P = 0.002$) were predictive of the occurrence of GU toxicity. The logistic model enabled the prediction of grade 2+ GU toxicity as a function of age, CrC_{meas}, and "study group" as shown in Table 11. There was no evidence that the GU toxicity risk differed among patients whose CrC_{meas} value was ⩾75 ml/min or among those whose CrC_{meas} value was <75 ml/min. We also found no evidence of an age effect following the stratification of patients into those aged <60 years and those aged ⩾60 years. Both an age of 60+ years and a CrC_{meas} value of <75 ml/min appeared to be predictive of a higher rate of grade 2+ GU toxicity, irrespective of the individual study's GU toxicity risk.

We refitted the logistic model, replacing CrC_{meas} with CrC_{est} to assess which of these measures would better

Table 12. Ability of CrC_{est} to predict a CrC_{meas} value of <75 ml/min

Age group (years)	Total number of patients	Number of patients with a CrC_{meas} of <75 ml/min	Number of these patients with a CrC_{est} of <75 ml/min
40–49	114	18	5 (28%)
50–59	250	66	26 (39%)
60–69	366	116	67 (58%)
70+	90	39	31 (79%)
Totals	820	239	129 (54%)

predict grade 2+ GU toxicity. We found that CrC_{meas} was a significant predictor of GU toxicity following adjustment for age and "study GU toxicity risk," whereas CrC_{est} was not ($P = 0.09$).

Given that a CrC_{meas} value of <75 ml/min is the "standard" pretherapy parameter used to predict high risk for GU toxicity, it is important that any surrogate be capable of accurately and appropriately "classifying" patients. We found that CrC_{est} was a poor predictor of a CrC_{meas} value of <75 ml/min. Of the 239 patients aged 40+ years who showed a CrC_{meas} value of <75 ml/min, a CrC_{est} value of <75 ml/min identified only 129 (54%) (Table 12). The sensitivity of a CrC_{est} value of <75 ml/min in predicting the same measured value was especially poor in patients aged <60 years.

Discussion

Cisplatin is a crucial ingredient in the most effective regimens used to treat cancer of the testis, ovary, lung, head and neck, bladder, uterine cervix, and endometrium. Recent studies suggest that its use in breast cancer [17], gastric carcinoma [13], and lymphomas [12] may be increasing. The use of 24-h urine collections for determination of creatinine clearance in the assessment of renal function has been widely adopted as a prerequisite to the administration of cisplatin.

The CrC_{est} determined using Cockroft and Gault's [5] formula was originally derived from a group of hospitalized male veterans with a variety of medical problems. Several groups have suggested that CrC_{est} is an adequate substitute for 24-h urine collection in cancer patients scheduled to receive cisplatin-based chemotherapy [4, 6, 9]. Davila and Gardner [6] looked at 24-h urine collections in 19 consecutive patients receiving cisplatin-based chemotherapy and found a significant correlation ($r = 0.922$, $P<0.001$) between "accurately" collected 24-h urine specimens (CrC_{meas}) and the CrC_{est} value determined using Cockroft and Gault's equation. They concluded that CrC_{meas} was more variable, less reliable, and of little clinical usefulness as compared with CrC_{est}. Ignoffo et al. [9] also found that CrC_{est} and CrC_{meas} "correlated" ($r = 0.88$, $P = 0.02$) in their 100 cisplatin-treated patients and concluded that CrC_{est} was not only an adequate surrogate for 24-h urine collection, but also a cost-effective alternative. Chambers et al. [4], who evaluated 84 patients with ovarian cancer who were scheduled to receive cisplatin, found a significant "correlation" ($r = 0.508$, $P<0.000001$) between the two methods of determining creatinine clearance and concluded that CrC_{est} alone was sufficient prior to chemotherapy.

In each of these studies, which primarily investigated the substitution of CrC_{est} for 24-h CrC_{meas}, the authors found CrC_{est} to be an adequate surrogate for CrC_{meas} by demonstrating the existence of a statistical correlation between the two clearance measures. However, the use of correlation to assess the ability of CrC_{est} to predict CrC_{meas} may be based on a statistical artifact. The value of the correlation coefficient for these measures is a function of age, weight, and serum creatinine level, and it can be shown that even in the absence of a true association, the correlation coefficient must be positive [14].

Given the potential statistical problems and the limited size of the previous studies, we again decided to study the possibility of substituting CrC_{est} as determined using Cockroft and Gault's formula for the standard 24-h urine collection. We evaluated a large group of patients from recent CALGB studies who were at moderate to high risk for cisplatin-induced renal toxicity. Rather than again simply addressing the question as to whether CrC_{est} could be substituted for CrC_{meas}, we chose to investigate a clinically more important issue: whether pretherapy CrC_{est} or CrC_{meas} would provide any predictive information concerning the patients' subsequent risk of developing nephrotoxicity. The routinely acquired pretherapy serum creatinine value was also studied for comparison.

In our large group of patients, both CrC_{est} (determined using Cockroft and Gault's equation) and 24-h urine collection for determination of CrC_{meas} were predictive of subsequent GU toxicity, with CrC_{meas} showing a slightly higher predictive value. Using a logistic model to predict the probability of grade 2+ GU toxicity, we found that a CrC_{meas} value of <75 ml/min predicted an increased risk ($P = 0.004$). No similar statistically increased risk was seen using CrC_{est} values following adjustment for age and "study GU toxicity risk." Furthermore, a CrC_{est} value of <75 ml/min was a poor predictor of a CrC_{meas} value of <75 ml/min, exhibiting a sensitivity of only 54%. This observation means that if used exclusively, CrC_{est} would independently provide little predictive information and would "misclassify" nearly half of the patients identified by a CrC_{meas} value of <75 ml/min as being at higher risk of developing GU toxicity. Taken together, these data do not support the abandonment of CrC_{meas} in the assessment of nephrotoxicity risk prior to the initiation of cisplatin treatment.

We did not investigate whether the 24-h urine collections evaluated in our study met standard definitions of adequacy based on the total amount of creatinine excreted in 24 h. Total excreted creatinine is related in a linear fashion to both age [5] and the fat-free body mass [16]. A "normal" level usually represents a minimal value, such as 15 mg kg^{-1} 24 h^{-1} for men, determined by calculating the mean for a population of patients in the sixth or seventh decade of life who presumably exhibit average amounts of fat per kilogram of body mass. The value that would be considered to represent normal total creatinine excretion in the present study population of patients with lung cancer remains unknown, as it is unclear exactly how the abrupt

loss of muscle mass that is often associated with malignancy might impact on the expected relationship between age, fat-free body mass, and total excreted creatinine. Pretherapy evaluation of our patients was done at cancer research centers in which patients were presumably carefully instructed concerning the method to be used for urine collections. Because accuracy could not be guaranteed, some of the CrC_{meas} values obtained may be incorrect.

We also chose to evaluate the role of age as a potential risk factor for cisplatin-induced nephrotoxicity. In other toxic nephropathies, such as those related to aminoglycosides and radiographic contrast agents, advanced age is a risk factor [8]. Aging is associated with increased toxicity secondary to cytotoxic chemotherapy in the cardiovascular, gastrointestinal, respiratory, hematopoietic, and central nervous systems [2]. It is noteworthy that despite the known deterioration of renal function with age, the published cancer chemotherapy literature provides no evidence suggesting an increased risk for nephrotoxicity with age [2]. Two studies, each involving a limited number of patients, have supported age not being a risk factor for the development of excessive nephrotoxicity during cisplatin chemotherapy given at either standard [7] or "high" [1] doses. Hrushesky et al. [7] studied only 24 patients aged over 60 years and found that after multiple courses of cisplatin-based chemotherapy, the mean decrease in creatinine clearance noted in these individuals differed little from that observed in the 19 younger patients they evaluated. On the basis of this information, they concluded a "lack of age-dependent cisplatin nephrotoxicity." Bajorin et al. [1] concluded that "elderly patients easily tolerated the treatment without [developing] excessive toxicity" in a phase I dose-escalation trial of cisplatin involving 47 patients whose median age was only 53 years.

In the present study, which included over 450 evaluable patients aged 60 years or older, we found that age was an important risk factor for the development of significant GU toxicity during cisplatin treatment. Patients aged less than 40 years were at negligible risk of developing significant GU toxicity, regardless of either the measured baseline creatinine clearance or the estimated value. A significant risk increase was noted with progressive age; thus, regardless of the baseline creatinine clearance or the study GU toxicity risk, patients over the age of 60 years were at higher risk than younger individuals.

We also found that the risk characteristics of the individual CALGB studies in which patients were enrolled were important to the prediction of significant GU toxicity. Although the retrospective nature of our study did not enable detailed analysis that would supply definitive conclusions, neither the planned cisplatin regimen nor the concomitant administration of other cytotoxic agents offered a ready explanation. Factors possibly contributing to the "high-risk" nature of a study, such as the use of nephrotoxic antibiotics, were not evaluated. Unfortunately, these factors do not allow the clinician to predict in advance the GU toxicity "risk" associated with a particular cisplatin-based therapy regimen.

In cancer patients who are scheduled to receive cisplatin-based chemotherapy, the necessary pretherapy evaluation of renal function remains uncertain. Our data suggest that the risk in patients under the age of 40 years is sufficiently low that neither CrC_{meas} determined by 24-h urine collections nor CrC_{est} provides important additional information, although the number of such patients evaluated in the present study was small. In older patients, a CrC_{meas} of >75 ml/min indicates a significantly lower risk for GU toxicity and appears to be a reasonable pretherapy requirement if excessive GU toxicity is to be avoided. Our data support a continued role for the measurement of creatinine clearance using 24-h urine collections prior to the administration of cisplatin in most clinical settings.

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