Pharmacokinetics and Dosage Reduction of cis-Diammine(1,1-cyclobutanedicarboxylato)platinum in Patients with Impaired Renal Function[1]

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ABSTRACT

cis-Diammine(1,1-cyclobutanedicarboxylato)platinum (CBDCA) is a nonnephrotoxic but myelosuppressive analogue of cisplatin (DDP) with greatly reduced protein binding and greatly increased renal excretion. Thus, CBDCA might produce undue toxicity in patients with decreased renal function. Twenty-two patients [14 females and 8 males; median age, 66 (range, 35 to 83); median Karnofsky performance status, 70 (range, 40 to 90)] with refractory tumors and renal dysfunction [creatinine clearance (C_{Cr}) 6 to 83 ml/min] were treated with 31 courses of i.v. bolus CBDCA every 4 to 5 weeks. Dosages were determined by pretreatment C_{Cr}. Patients with $C_{Cr} \geq 40$ ml/min received 400 mg/sq m; patients with C_{Cr} 20 to 39 ml/min received 250 mg/sq m; and patients with C_{Cr} 0 to 19 ml/min received 150 mg/sq m. Toxicities were assessed by weekly clinical and laboratory assessment. Responses were assessed in patients with measurable disease. Plasma pharmacokinetics and urinary excretion of total and ultrafilterable platinum were measured with flameless atomic absorption spectrometry. Observed toxicities were similar to those in patients with normal renal function. Myelosuppression, especially thrombocytopenia, was the major toxicity. Nausea and vomiting were mild to moderate. There was no ototoxicity, neurotoxicity, or nephrotoxicity or reduction in C_{Cr} due to CBDCA. Total body clearance of ultrafilterable platinum correlated highly with C_{Cr}. The percentage of reduction in platelet count correlated highly and linearly with the area under the curve (AUC) of plasma-ultrafilterable platinum. However, for any AUC, there was 17% greater platelet reduction in patients who had previously received extensive myelosuppressive chemotherapy than in nonpretreated patients. Since total body clearance is proportional to C_{Cr}, platelet reduction is proportional to AUC, and total body clearance = dosage/AUC, we have derived an equation to calculate a dosage that will produce a desired reduction in platelet count. Calculations for theoretical patients (both pretreated and nonpretreated) with C_{Cr} of 100 ml/min produce dosages very close to maximum tolerated dosages derived in actual Phase I trials. The actual clinical utility of these predictive equations must await validation in prospective studies with larger numbers of patients.

INTRODUCTION

DDP[3] has become a major chemotherapeutic agent with established utility in the treatment of a number of solid tumors, including carcinomas of the testes, ovary, head and neck, bladder, and lung and certain lymphoproliferative disorders (32). However, the numerous and frequently severe toxicities, such as nausea and vomiting, nephrotoxicity, neurotoxicity, and ototoxicity, associated with the administration of DDP (32, 33) have spurred the search for maneuvers which might mitigate such toxicities (1, 14, 17, 18, 24, 25, 30, 35, 36). Another approach to this problem has been the development of DDP analogues with improved therapeutic indices (2, 6, 7, 13, 15, 28). One of these analogues, CBDCA, has already demonstrated activity against a wide variety of human tumors (3, 4, 8, 10, 12) and yet appears to have strikingly different toxicological and pharmacological properties when compared to DDP (3, 4, 8, 10, 12). In all clinical trials to date, the dose-limiting toxicity of CBDCA has been myelosuppression, with greater thrombocytopenia than leukopenia (3, 4, 8-10, 12, 19, 21, 22, 29, 31). Moreover, CBDCA has proved to be nonnephrotoxic, nonototoxic, and much less emetigenic than DDP (3, 4, 8-10, 12, 19, 21, 22, 29, 31). Unlike DDP, which is inactivated primarily by avid binding to plasma proteins (11, 16, 26, 27), CBDCA binds much less avidly to plasma proteins and finds its major route of excretion via the kidneys (4, 9). Between 55 and 70% of an administered dose of CBDCA platinum is excreted into the urine within the first 24 hr of administration (4, 9). Consideration of the reduced plasma protein binding and extensive renal elimination of CBDCA suggests that full doses of CBDCA might produce undue toxicity in patients with reduced renal function. However, such a population of patients might contain many individuals in whom CBDCA might have its greatest clinical utility. These would include patients whose renal function had been compromised by comorbid disease, by previous chemotherapy, or by neoplastic involvement such that they could no longer receive DDP and yet had tumors with a high probability of being platinum responsive. We therefore attempted to define the pharmacology of CBDCA in patients with reduced renal function and to utilize the information in the development of a rational, easily used scheme for CBDCA dosage modification in such patients.

[3] The abbreviations used are: DDP, cisplatin; CBDCA, cis-diammine(1,1-cyclobutanedicarboxylato)platinum; AUC, area under the curve; CL_{TB}, total body clearance; C_{Cr}, creatinine clearance; LDH, lactate dehydrogenase.

MATERIALS AND METHODS

To be eligible for this protocol, patients had to fulfill the following criteria: histological proof of malignant disease which had failed conventional chemotherapy or for which no conventional therapy existed; a tumor type for which a Phase II trial with CBDCA was not active; recovery from all toxicities from prior treatments and passage of ≥4 weeks from any prior chemotherapy or radiotherapy; a minimum life expectancy of 12 weeks; a Karnofsky performance status ≥40%; adequate bone marrow function (WBC ≥3,500 cells/μl and platelet counts ≥100,000/μl); and adequate liver function (bilirubin ≤2.0 mg/dl). By definition, adequate renal function was not a prerequisite for entry into this study. Objective measurable disease was desirable but not required. Written, informed consent in accordance with federal and institutional policies was obtained from all patients prior to entrance into this study.

Before entry into study, each patient had a detailed history taken and a physical examination performed. Tumor measurements were made, and performance status was assessed. Pretreatment laboratory studies included complete and differential blood counts, platelet count, urinalysis, and serum electrolytes, urea nitrogen, glucose, and creatinine. Two 24-hr creatinine clearances were measured within 1 week prior to treatment, and their mean was used to determine CBDCA dosage as described below. If widely disparate values were obtained, a third 24-hr C_{Cr} was measured. Additional pretreatment blood studies included LDH, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, calcium, phosphorus, and magnesium. All patients had electrocardiograms and chest roentgenograms performed, and additional scans or roentgenograms were performed as appropriate for disease measurement.

After CBDCA treatment, patients had weekly clinic visits with assessment of performance status, weight, complete and differential blood counts, platelet count, and serum electrolytes, urea nitrogen, glucose, creatinine, calcium, phosphorus, magnesium, LDH, aspartate aminotransferase, and alanine aminotransferase. Before a patient received subsequent courses of chemotherapy, all pretreatment studies, with the exception of chest roentgenograms and electrocardiograms, were repeated. A Beltone 10D portable audiometer was used to obtain audiograms on each patient prior to his first course of CBDCA, after every 2 courses of treatment, or when the patient went off study.

CBDCA (NSC 241240) was supplied by the Investigational Drug Branch, National Cancer Institute, Bethesda, MD. The sterile, lyophilized powder was dissolved in sterile, distilled water to yield a solution containing CBDCA (15 mg/ml). CBDCA was administered as an i.v. bolus injection with dosages determined by C_{Cr} according to the following scheme: C_{Cr} ≥40 ml/min, CBDCA (400 mg/sq m); C_{Cr} 20 to 39 ml/min, CBDCA (250 mg/sq m); C_{Cr} 0 to 19 ml/min, CBDCA (150 mg/sq m). Those patients experiencing significant but not life-threatening toxicities were retreated at the next lowest dosage level or at 75 mg/sq m, if initially treated at 150 mg/sq m.

Each course of treatment was considered evaluable for toxicity if the patient was followed for 3 weeks after CBDCA administration. Toxicity criteria were those of Cancer and Acute Leukemia Group B (5), and standard response criteria were used to evaluate antitumor effect if measurable disease was present (5). Individual patients were removed from study when toxic effects were unacceptable or when objective tumor progression occurred.

Pharmacokinetic Studies. Prior to and at specified times after CBDCA administration, blood samples were collected in heparinized tubes and centrifuged at 1000 × g for 10 min, and the plasma was removed. An aliquot of plasma was frozen at −20° until time of assay. Protein-free ultrafiltrates were prepared by centrifuging 3 ml of the remaining plasma in Centriflo CF 50A membranes (Amicon Corporation, Lexington, MA), at 1000 × g for 20 min at 4°. Urine samles were collected at the time of voiding, measured, and stored at −20° as pooled 4-hr collections.

Plasma, plasma ultrafiltrates, and urine samples were analyzed for platinum by flameless atomic absorption spectrometry, using the same instrumentation and methodology reported previously (23). Plasma pharmacokinetics were analyzed with the programs of MLAB (an on-line modeling laboratory, Division of Computer Resources and Technology, NIH, Bethesda, MD) (20). Curves were fit to the sum of 2 exponentials by a nonlinear technique with and without weighting by $1/SE^2$. The curve of concentration × time for ultrafilterable platinum in plasma was evaluated by calculating the AUC by means of the integral operator in MLAB and by the trapezoidal rule.

Statistical Methods. Regression and analysis of covariance models in this study were constructed using the method of least squares. Tests of overall model significance were accomplished using an *F*-test with appropriate degrees of freedom. For tests that a given parameter was equal to 0, a *t* test with appropriate degrees of freedom was utilized.

RESULTS

Patient Characteristics. The 22 consecutive, eligible patients entered into this study (Table 1) received 38 courses of CBDCA, 33 of which were evaluable for toxicity. The patients studied had a median age of 66 years and a median Karnofsky performance status of 70%. Two patients had not received prior therapy. Of the remaining 20 patients, 7 had been treated previously with chemotherapy, 5 with radiotherapy, 4 with a combination of chemotherapy and radiotherapy, 3 with combinations of chemotherapy, radiotherapy, and hormonal therapy, and 1 with a combination of immunotherapy and interferon. Among the 22 patients studied, there were a number of tumor types (Table 2), including 5 tumors of the head and neck, 4 ovarian carcinomas, 3 cervical carcinomas, 2 renal cell carcinomas, one endometrial carcinoma, one colon carcinoma, one adenocarcinoma of the urethra, one liposarcoma, and one adenocarcinoma of unknown origin. Three patients had 2 primary cancers: one with carcinomas of the breast and cervix, one with renal cell and prostatic carcinomas; and one with squamous cell carcinoma and soft tissue sarcoma of the pharynx.

In that a major goal of our study was to evaluate the pharmacokinetics and toxicities of CBDCA in patients with reduced renal function and to define an appropriate dosage reduction scheme in such patients, 13 of the 22 patients treated had creatinine clearances ≤60 ml/min, the lowest being 6 ml/min (Table 1; Chart 1). Among these 13 patients, 3 had preexisting renal disease, 5 had tumor-related renal dysfunction, and 5 had

Table 1
Patient characteristics

Patients	22
Courses	38
Evaluable courses	33
Median age (yr) (range, 35 to 83)	66
Median Karnofsky performance status (range, 40 to 90%)	70%
Sex (female:male)	14:8
Prior therapy	
None	2
Chemotherapy only	7
Radiotherapy only	5
Chemotherapy and radiotherapy	4
Chemotherapy, radiotherapy, and hormones	3
Immunotherapy and interferon	1
Renal function	
Patients with C_{Cr} <60 ml/min	13
Preexisting renal disease	3
Tumor-related	5
Cisplatin-induced	5

renal impairment secondary to prior DDP therapy.

Toxicities. As observed in phase I studies in patients with normal renal function (12–22), the dose-limiting toxicity of CBDCA in the present study was myelosuppression, with thrombocytopenia being more severe than leukopenia (Table 3). There were no WBC nadirs below 1000 cells/μl. Thrombocytopenia occurred in 14 of the 22 patients treated and in 23 of the 33 evaluable courses of CBDCA. Platelet counts below 30,000 cells/μl occurred in 10 courses given to 8 patients. The median day on which platelet nadirs occurred was 18 (range, 13 to 29), and the median day on which WBC nadirs occurred was 22 (11 to 36). These are similar to those reported for patients with normal renal function treated with CBDCA as an i.v. bolus every 4 to 5 weeks but are somewhat earlier than those reported by us (9) and Rozencweig et al. (31) in patients treated for 5 consecutive days with CBDCA. There were no episodes of bleeding or infection associated with CBDCA-induced myelosuppression.

Moderate nausea and vomiting were the only nonhematological toxicities encountered in CBDCA-treated patients with reduced renal function. This is comparable to the spectrum of nonhematological toxicities encountered in CBDCA-treated patients with normal renal function. No CBDCA-induced musculoskeletal discomfort (9), was encountered in any patient in this study. No patient in this study developed evidence of ototoxicity, neurotoxicity, mucosal damage, or alteration in liver function tests. In addition, in no patient did CBDCA cause an elevation of serum creatinine or a reduction in C_{Cr}.

Responses. Although objective, measurable disease was not

a prerequisite for admission to this study, 12 patients were evaluable for response to CBDCA treatment. Among these patients, one partial response was observed in a patient with squamous cell carcinoma of the pharynx, and objective responses (less than partial) were observed in single patients with adenocarcinoma of the cervix and adenocarcinoma of the bulbous urethra (Table 2).

Pharmacokinetics. Previous studies in patients with normal renal function had demonstrated the major role played by the kidney and, in particular, glomerular filtration in CBDCA excretion (4, 9). We therefore examined the relationship between glomerular filtration rate, as assessed by C_{Cr}, and urinary excretion of platinum administered as CBDCA (Chart 1). As might be expected, reduced C_{Cr} correlated with decreased urinary excretion of CBDCA platinum, there being no other compensatory renal mechanisms, such as tubular secretion, which could maintain urinary clearance of the drug. In addition, C_{Cr} correlated highly with CL_{TB} of CBDCA ultrafilterable platinum (Chart 2), a fact not totally unexpected in view of the major role played by glomerular filtration in CBDCA excretion (4, 9) and the relatively slow binding of CBDCA to plasma proteins (4, 9). Examination of this relationship by linear regression analysis demonstrated a correlation coefficient of 0.82. This relationship of creatinine clearance to

Table 2
Tumor types and responses

Tumor type	No. of patients	No. of patients evaluable for response	No. of responses
Head and neck	5	3	1 PR[a] (duration, 3 mo)
Ovarian	4	2	NR
Cervical			
Adenocarcinoma	1	1	1 OR
Squamous carcinoma	1	0	
Mixed mesodermal	1	1	NR
Renal	2	0	
Endometrial	1	0	
Colon	1	1	NR
Liposarcoma	1	1	NR
Urethral (adenocarcinoma)	1	1	1 OR
Adenocarcinoma of unknown origin	1	0	
Cervix and breast	1	1	NR
Renal and prostate	1	0	
Pharyngeal: squamous carcinoma and sarcoma	1	1	NR

[a] PR, partial response; NR, no response; OR, objective response (less than partial).
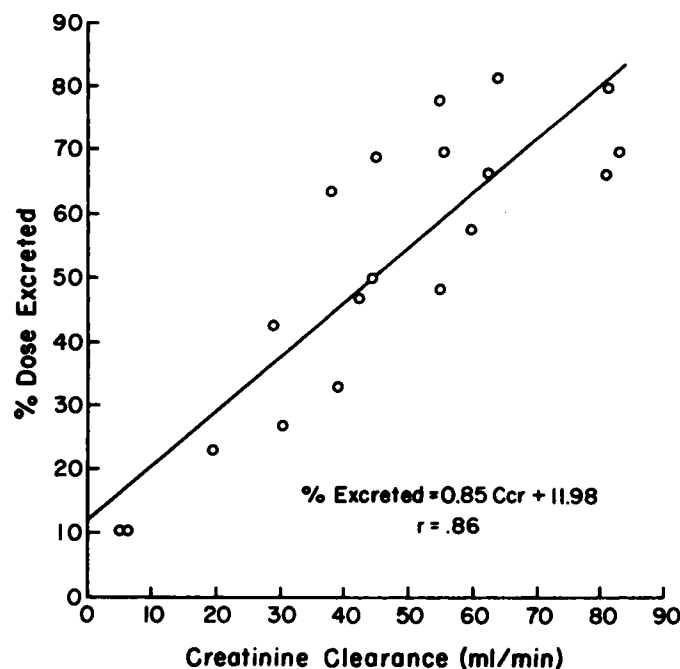

Chart 1. Relationship of C_{Cr} to urinary excretion of platinum in patients treated with CBDCA. CBDCA was administered as an i.v. bolus, and platinum concentrations were determined by flameless atomic absorption spectrometry as described in "Materials and Methods." Points represent individual courses of CBDCA therapy.

% Excreted = 0.85 Ccr + 11.98
r = .86

Table 3
Hematological toxicity encountered in carboplatin-treated patients with reduced renal function

Dosage (mg/sq m)	Evaluable		WBC (thousands of cells/μl)			Platelets		
	Patients	Courses	Pretreatment[c]	Nadir	Day of nadir	Pretreatment	Nadir	Day of nadir
150	3 (1)[a]	3	7.9[b] (6.3–8.3)[c]	2.6 (2.3–3.8)	25 (19–31)	259 (199–340)	88 (15–100)	23 (19–25)
250	8 (2)	10	5.6 (3.8–13.6)	2.5 (1.2–12)	22 (11–29)	276 (185–564)	71 (20–159)	16 (13–29)
400	13 (2)	20	6.0 (3.5–22.3)	3.1 (1.2–11.7)	20 (15–36)	354 (150–760)	63 (13–240)	18 (13–23)

[a] Heavily pretreated with chemotherapy.
[b] Median.
[c] Numbers in parentheses, range.

CL_{TB} implies that other means of drug elimination, such as enhanced protein binding or biliary excretion, are not activated to compensate for decreased renal function and to maintain CBDCA CL_{TB}.

Although the above-mentioned relationships between renal function and CBDCA platinum pharmacokinetics were demonstrated clearly in our population of patients with varying degrees of impaired renal function, the question remained as to whether any relationship existed between the CBDCA pharmacokinetics and the toxicities observed in individual patients. From our first several patients, it was apparent that peak plasma concentrations of ultrafilterable platinum bore no relationship to the myelosuppression produced by that course of therapy. Therefore, attempts were made to compare the AUC of plasma ultrafilterable platinum for each course of CBDCA with the platelet nadir observed in that course. Again, no good correlation was observed. However, it was apparent that individual patient's platelet counts, at the time of CBDCA administration, varied from 150,000 to 760,000 cells/μl and that a platelet nadir of 100,000 cells/μl produced in the former case might represent less myelosuppression than it would in the latter case. Subsequently, examinations focused on the relationship of AUC of plasma ultrafilterable platinum to the percentage of reduction in platelet count, the latter being defined as:

$$\left(\frac{\text{Pretreatment platelet count} - \text{platelet nadir}}{\text{Pretreatment platelet count}}\right) \times 100$$
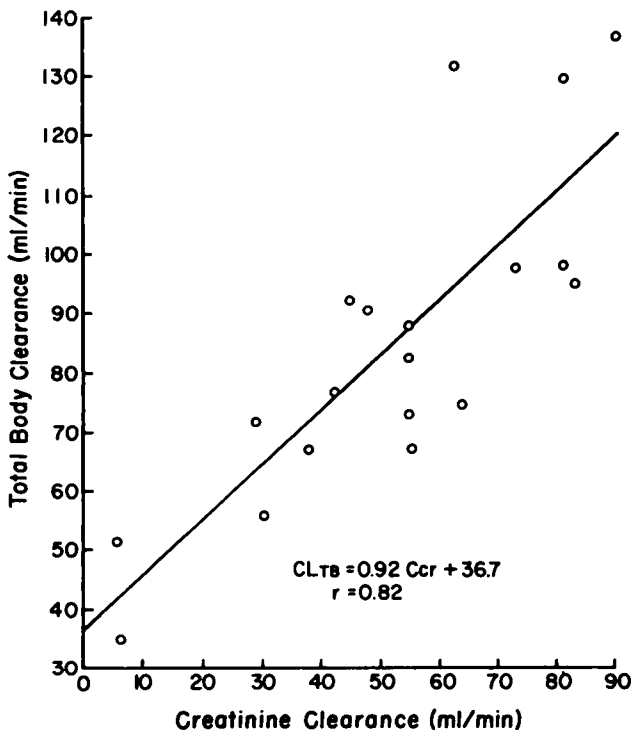
CL$_{TB}$ = 0.92 Ccr + 36.7
r = 0.82

Chart 2. Relationship of CL$_{TB}$ of ultrafilterable platinum to C$_{Cr}$. CBDCA was administered as an i.v. bolus, and ultrafilterable platinum concentrations in plasma were determined by flameless atomic absorption spectrometry as described in "Materials and Methods." AUC for plasma concentrations of ultrafilterable platinum were calculated by the trapezoidal rule. CL$_{TB}$ was determined from the equation:

$$CL_{TB} = \frac{\text{dosage}}{\text{AUC}}$$

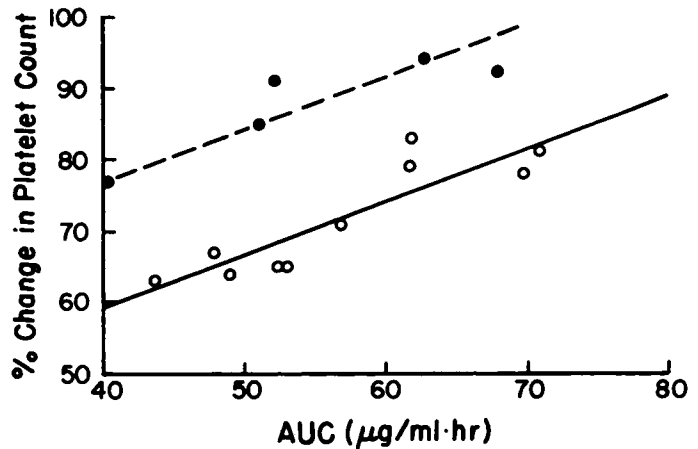*Points represent individual course of CBDCA.*

Chart 3. Relationship of the AUC of plasma ultrafilterable platinum and the percentage of reduction in platelet count. CBDCA was administered as an i.v. bolus, and ultrafilterable platinum concentrations in plasma were determined by flameless atomic absorption spectrometry as described in "Materials and Methods." AUC for plasma concentrations of ultrafilterable platinum were calculated by the trapezoidal rule, and the percentage of reduction in platelet count was calculated as

$$\frac{\text{Pretreatment platelet count} - \text{platelet nadir}}{\text{Pretreatment platelet count}} \times 100$$

Points represent individual courses of CBDCA therapy. O, patients without extensive prior chemotherapy; ●, heavily pretreated patients.

Such an analysis (Chart 3) produced 2 parallel regression lines, described by the equations:

Percentage of reduction in platelet count = 0.72 AUC + 48.5 and
Percentage of reduction in platelet count = 0.72 AUC + 31.2

These 2 relationships proved to be linear, with correlation coefficients of 0.73 and 0.89, respectively, and to be nonoverlapping ($p \leq 0.001$). Closer inspection revealed the first relationship to represent those patients who had been treated heavily with chemotherapy prior to receiving CBDCA and the second relationship to represent those patients without extensive prior chemotherapy. Therefore, it appeared that not only did a relationship exist between an easily determined pharmacokinetic parameter, i.e., AUC, and the pharmacodynamics resulting from drug therapy, but that, for any given AUC, heavily pretreated patients experienced 17% greater reduction in platelet count than did patients without extensive pretreatment.

DISCUSSION

Carboplatin is an analogue of DDP which possesses a number of clinical features desirable in an analogue of a drug as clinically useful as is DDP. Not only does CBDCA have apparent activity against a wide variety of human solid tumors (3, 4, 8–10, 12, 19, 21, 22, 29, 31) but, to date, CBDCA appears to have activity equal to that of DDP against ovarian carcinoma (3). Moreover, the toxicities associated with administration of CBDCA are either qualitatively different or less severe than those resulting from DDP therapy. The dose-limiting toxicity of CBDCA is myelosuppression, especially thrombocytopenia (3, 4, 8–10, 12, 19, 21, 22, 29, 31), and the emesis occurring after injection of CBDCA is much less severe than the almost universal nausea

and vomiting produced by DDP (3, 4, 8–10, 12, 19, 21, 22, 29, 31, 32, 34). Furthermore, to date, CBDCA has proven devoid of nephrotoxicity and ototoxicity (3, 4, 8–10, 12, 19, 21, 22, 29, 31), and neurotoxicity secondary to CBDCA has only been reported in patients treated previously with DDP (4).

In addition to these promising clinical attributes, the pharmacokinetic behavior of CBDCA is strikingly different from that of DDP (4, 9, 11, 16, 26, 27). Specifically, CBDCA is relatively slowly bound to plasma proteins, and most of a dose is excreted in the urine during the first 24 hr after injection (4, 9). Although the relationship of the pharmacokinetics of the drug to the pharmacodynamic consequences resulting from drug therapy is apparent less often with antineoplastic agents than with classes of drugs such as antibiotics, antiasthmatics, and cardiovascular agents, the relatively minor role played by protein binding and the major role played by renal excretion in CBDCA elimination suggest that full doses of CBDCA would produce undue toxicities in patients with reduced renal function. This concept acquires more importance when one considers that such patients would include a large number of individuals who would benefit from CBDCA therapy.

Since all previous phase I and phase II studies had been restricted to patients with creatinine clearances ≥60 ml/min, our initial efforts were directed toward defining the urinary excretion and plasma pharmacokinetics of CBDCA in patients with impaired renal function. The high correlation between glomerular filtration rate and urinary excretion of CBDCA was observed at all C_{Cr} and implied little, if any, tubular secretory component to the renal excretion of CBDCA. Furthermore, CL_{TB} of CBDCA correlated highly with C_{Cr}, and this relationship argues against any compensatory mechanisms, such as increased protein binding or enhanced biliary excretion, being activated in the face of reduced renal function. If one applies the equation describing this relationship to a patient with a C_{Cr} of 100 ml/min, C_{Cr} would account for 92 of 129 or 71% of the CL_{TB}. This is very consistent with the reported urinary excretion of 55 to 70% of a dose of CBDCA (4, 9).

In addition to the observed strong correlation between the pharmacokinetics of CBDCA and renal function, there was a strong relationship, in individual patients, between the AUC of ultrafilterable platinum and the reduction in platelet count observed in those patients approximately 2 weeks after drug administration. As stated, this relationship of pharmacokinetics to pharmacodynamics is not commonly defined for antineoplastic drugs. In addition, our results document and mathematically describe a concept which is frequently observed and discussed in cancer chemotherapy but which is rarely characterized. That is the fact that certain drugs produce more severe myelosuppression in patients who have received extensive prior chemotherapy than they do in patients without prior chemotherapy. Our results not only demonstrate that similar doses of CBDCA produce increased myelosuppression in patients who have had prior chemotherapy, but go further and show that, for any given AUC, pretreated patients experience 17% greater reduction in platelet count than do nonpretreated patients. These observations are in keeping with the results of our institution's previous Phase I study with CBDCA which defined a maximum tolerated dosage of 77 mg/sq m/day × 5 for patients treated previously with chemotherapy but 99 mg/sq m/day × 5 for patients not treated previously (9).

Although all patients in this trial were treated with dosages of

CBDCA based on their C_{Cr} according to an empirical dosage reduction scheme, the results of this study (defining the relationships between C_{Cr} and CL_{TB} and between AUC and percentage reduction in platelet count), combined with the fact that $CL_{TB} =$ dosage/AUC raise the possibility of tailoring the dosage of CBDCA for any given patient based on that patient's C_{Cr}, pretreatment platelet count, desired platelet nadir, and prior chemotherapy status. When the equations relating CL_{TB} or dosage/AUC to creatinine clearance and relating percentage reduction in platelet count to AUC are rearranged, equations for dosage calculations for nonpretreated and pretreated patients result. These take the form of equations for a line, *i.e.*, $y = mx + b$, where y is the dosage or the dependent variable and x, the independent variable, reflects the patient's C_{Cr}, body surface area, and the percentage of reduction in platelet count desired. For previously untreated patients:

$$\text{Dosage (mg/sq m)} = (0.091)\frac{(\text{creatinine clearance})}{(\text{body surface area})}$$

$$\cdot\left[\frac{\left(\begin{array}{c}\text{pretreatment platelet count} \\ - \text{ platelet nadir desired}\end{array}\right)}{\text{pretreatment platelet count}} \times 100\right] + 86$$

In that our results for previously treated patients indicated that, for any AUC, previously treated patients experienced 17% greater reduction in platelet count than did previously untreated patients, the equation becomes:

$$\text{Dosage (mg/sq m)} = (0.091)\frac{(\text{creatinine clearance})}{(\text{body surface area})}$$

$$\cdot\left\{\left[\frac{\left(\begin{array}{c}\text{pretreatment platelet count} \\ - \text{ platelet nadir desired}\end{array}\right)}{\text{pretreatment platelet count}} \times 100\right] - 17\right\} + 86$$

To test the potential utility of these equations, calculations can be performed for theoretical nonpretreated and pretreated patients with C_{Cr} of 100 ml/min, body surface areas of 1.7 sq m, pretreatment platelet counts of 400,000 cells/μl, and a desired platelet nadir of 100,000 cells/μl. When these values are used, dosages of 488 mg/sq m and 396 mg/sq m are calculated for nonpretreated and pretreated patients, respectively. These values are remarkably similar to the maximum tolerated dosages of 495 mg/sq m (99 mg/sq m/day × 5) and 385 mg/sq m (77 mg/ sq m/day × 5), derived in the previous phase I trial conducted at our institution (9).

It was found subsequently that a better description of the linear relationship between the percentage of reduction in platelet count and dosage could be established while simultaneously adjusting for other variables, *e.g.*, C_{Cr}, body surface area, and pretreatment status. This was accomplished with analysis of covariance (33). Programs for this analysis were contained in the Statistical Analysis System on an IBM 4341 computer. The resulting model was highly statistically significant ($p = 0.00016$) and fit the data extremely well ($r^2 = 0.769$). The relationships defined by this model are:

For previously untreated patients

$$\% \text{ of platelet reduction} = 82.1 - 1.41 \times \left(\frac{C_{Cr}}{\text{body surface area}}\right)$$

$$+ 0.0031553 \left(\frac{C_{Cr}}{\text{body surface area}}\right) \times \text{dosage}$$

For previously treated patients

$$\% \text{ of platelet reduction} = 94.421 - 1.41 \left(\frac{C_{Cr}}{\text{body surface area}} \right)$$

$$+ \ 0.0031553 \left(\frac{C_{Cr}}{\text{body surface area}} \right) \times \text{dosage}$$

Rearrangement of these relationships yielded the following equations with which to calculate CBDCA dosages for patients with particular combinations of clinical variables.

For previously untreated patients

Dosage (mg/sq m) = 317

$$\cdot \left\{ \left[\left(\frac{\text{pretreatment platelet count} - \text{platelet nadir desired}}{\text{pretreatment platelet count}} \right) 100 - 82.1 \right] \cdot \frac{\text{body surface area}}{C_{Cr}} \right\} + 447$$

For previously treated patients

Dosage (mg/sq m) = 317

$$\cdot \left\{ \left[\left(\frac{\text{pretreatment platelet count} - \text{platelet nadir desired}}{\text{pretreatment platelet count}} \right) 100 - 92.4 \right] \cdot \frac{\text{body surface area}}{C_{Cr}} \right\} + 447$$

Retrospective application of these and the previous equations to patients treated in this study have shown that the latter 2 equations describe the actual clinical situation better than do the former equations. At present, the utility and applicability of these pharmacologically based dosage reduction schemes are being assessed through prospective studies comparing the actual reduction in platelet count with those anticipated from the dosage reduction calculations.

ACKNOWLEDGMENTS

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