Prospective Validation of a Pharmacologically Based Dosing Scheme for the cis-Diamminedichloroplatinum(II) Analogue Diamminecyclobutanedicarboxylatoplatinum

Merrill J. Egorin, David A. Van Echo, Eve A. Olman, Margaret Y. Whitacre, Alan Forrest, and Joseph Aisner

ABSTRACT

We previously correlated both renal function and thrombocytopenia, the dose limiting toxicity of carboplatin, with the plasma pharmacokinetics of carboplatin. From these correlations, we developed equations to calculate carboplatin dosage for any patient based on that patient's creatinine clearance, body surface area, pretreatment platelet count, desired platelet nadir, and status of prior chemotherapy. We prospectively applied these equations in 44 courses of carboplatin given to 24 patients. There were 13 males and 11 females with median age 53 (range, 33-77), median Karnofsky performance status 80 (range, 50-100), and creatinine clearance 32 to 118 ml/min. Ten patients had creatinine clearances less than 60 ml/min. Precision of the equations used for dose calculation was evaluable in 38 courses administered to 23 patients. In 23 courses of carboplatin administered to 12 patients without extensive prior chemotherapy, the observed change in platelets = 1.04 x predicted change - 48,000 (r = 0.96). In the 15 courses of carboplatin administered to 11 heavily pretreated patients, the observed change in platelets = 1.13 x predicted change + 6,600 (r = 0.97). For the overall combined population, the observed change in platelets = 0.96 x predicted change - 7,000 (r = 0.94). These relationships which nearly define the line of identity (observed = expected) validate our initial observations. Only 2 patients developed WBC <2,000, but 12 patients developed hematocrit <29% and 8 required RBC transfusions. Fifteen patients had nausea and vomiting >grade 2. There were no other nonhematological toxicities observed. In view of continuing documentation of the antitumor activity of carboplatin, these equations allow safe and rational drug dosing of patients with potentially platinum-responsive tumors but with renal function too poor to receive cisplatin. Among the 9 patients in this study evaluable for response, there was 1 partial response in a patient with malignant melanoma and 1 objective response (<partial response) in a patient with adenocarcinoma of the cervix.

INTRODUCTION

Carboplatin is an analogue of cisplatin with documented activity against a number of human tumors and with toxicological properties very different from those of cisplatin (1-13). While carboplatin is neither nephrotoxic, neurotoxic, nor ototoxic, and is much less emetogenic than is cisplatin, it is myelosuppressive with thrombocytopenia being its dose limiting toxicity (1-13). These facts suggest the possibility of using carboplatin for platinum sensitive tumors in patients whose renal function has been impaired by neoplastic involvement, preexisting renal disease, or previous chemotherapy. Previous studies (2, 13-16) have shown that the kidney, and in particular glomerular filtration, is the major route of drug excretion and clearance. As might be expected, carboplatin is cleared from the body more slowly by patients with renal dysfunction (14, 15), and the usual dose of carboplatin produces undue toxicity in such individuals (2, 6, 15). These facts pointed to the need for a systematic dosing schema for carboplatin which would take into consideration the slower clearance of drug by patients with renal impairment, so that they would not be overdosed by "standard" therapy, and yet not be underdosed by an arbitrary dosage reduction. Our previous study yielded sufficient data on the pharmacodynamics and pharmacokinetics of carboplatin to generate a pair of equations for dosing such patients (14). Although based on the patient's renal function, quantified by creatinine clearance, and hematopoietic status, quantified by pretreatment platelet count, these equations also allow an element of judgment on the part of the physician who must enter a figure for acceptable platelet nadir. This allows the clinician to maximize the therapeutic value of carboplatin without unacceptable toxicity. Two equations are necessary because the myelotoxicity of carboplatin is systematically and measurably more profound in patients who have been heavily treated with myelosuppressive agents before receiving carboplatin (14). Apart from that single modification the equations are the same.

When analyzed retrospectively, the platelet count suppression predicted by these equations correlated well with the actual decreases in platelet counts observed in the 18 patients from whom the equations were developed (14). Also the dosages predicted for hypothetical patients with normal renal function and platelet counts were very close to the maximum tolerated dosages defined in actual phase I trials (2, 3, 6, 8, 9, 11-13). Still it remained to be shown whether the deductions drawn from that set of patients would apply to another set of patients evaluated prospectively. This paper presents the results of such an evaluation.

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, 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

Received 3/7/85; revised 9/9/85; accepted 9/9/85.

1 This work was supported in part by Contract N01CM27541 and USPHS Grant 1P50CA32107 awarded by the National Cancer Institute, Department of Health and Human Services.

2 To whom requests for reprints should be addressed.
CARBOPLATIN DOSAGE DETERMINATION

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. Patients with known tumor involvement of their bone marrow were excluded from 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 before they were entered onto this study.

Before entry onto study, each patient had a detailed history and physical examination performed. Tumor measurements were made and performance status was assessed. Pretreatment laboratory studies were unchanged from those performed in our previous Phase I study of carboplatin and assessed cardiac, marrow, hepatic, and renal function (5) as well as measurable disease when possible. Two 24-h creatinine clearances were measured within 1 week prior to treatment and their mean was used to determine carboplatin dosage as described below. No patient had pretreatment bone marrow biopsies done to assess marrow cellularity.

After carboplatin treatment patients had weekly clinic visits with assessment of performance status, weight, complete and differential blood counts, and platelet count. Before a patient received subsequent courses of chemotherapy all pretreatment studies with the exception of chest roentgenograms and electrocardiograms were repeated.

Carboplatin (NSC 241240) was supplied by the Investigational Drug Branch, National Cancer Institute, Bethesda, MD.

Carboplatin was administered as an i.v. bolus injection and dosage was calculated with the following formulae:

For previously untreated patients:

\[
\text{Dosage (mg/m}^2\) = \left(\frac{0.091}{\text{creatinine clearance/ body surface area}}\right) \left(\frac{\text{pretreatment platelet count} - \text{platelet nadir desired}}{\text{pretreated platelet count}} \times 100\right) + 86
\]

For patients heavily pretreated with myelosuppressive agents:

\[
\text{Dosage (mg/m}^2\) = \left(\frac{0.091}{\text{creatinine clearance/ body surface area}}\right) \left(\frac{\text{pretreatment platelet count} - \text{platelet nadir desired}}{\text{pretreated platelet count}} \times 100\right) - 17 + 86
\]

Patients were considered heavily pretreated if they had received any of the following: mitomycin C; a nitrosourea; combination chemotherapy with doxorubicin, cyclophosphamide, and cisplatin; chemotherapy with 5 or more different agents; or radiotherapy ≥4,500 rads to a single port 20 x 20 cm or more than one field of therapy.

Each course of treatment was considered evaluable for toxicity if the patient were followed for 3 weeks after carboplatin administration. Toxicity criteria were those of Cancer and Acute Leukemia Group B (17) and standard response criteria were used to evaluate antitumor effect if measurable disease were present (17). Individual patients were removed from study when toxic effects were unacceptable or when objective tumor progression occurred.

For each course of therapy the precision of the equations used to calculate carboplatin dosage was evaluated by comparing the observed platelet count decrease, i.e. (pretreatment platelet count – actual nadir), with that predicted based on the desired platelet nadir used in the dosage calculation, i.e. (pretreatment platelet count – desired nadir).

RESULTS

Patient Characteristics. Twenty-four consecutive patients were entered onto this study and they received 44 courses of carboplatin, 40 of which were evaluable for toxicity and 38 of which were assessable for efficacy of the dosing equations. One course was evaluable because the patient refused regular follow-up visits after treatment had been administered. The other evaluable course resulted from a patient’s failure to return to clinic during the week in which his nadir occurred. The 13 female and 11 male patients entered onto this study had a median age of 53 years (range, 33 to 77) and a median Karnofsky performance status of 80% (range, 50 to 100). Since one major goal of these studies was to evaluate the pharmacokinetics and toxicities of carboplatin in patients with reduced renal function, 10 of the 24 patients studied initially had creatinine clearances <60 ml/min, the lowest being 32 ml/min (Table 1). Among these 10 patients, 4 had preexisting renal disease, 4 had tumor-related renal dysfunction, and 2 had renal impairment secondary to prior cisplatin therapy. During the study a total of 20 courses of carboplatin was administered to patients with creatinine clearances 60 ml/min.

One patient had received no prior therapy. Of the remaining 23 patients, 7 had been treated previously with chemotherapy, 4 with radiotherapy, 8 with combinations of chemotherapy and radiation therapy, and 4 with combinations of chemotherapy, radiation therapy, hormonal therapy, interferon, and biological response modifiers. Twelve patients were classified as heavily pretreated before receiving carboplatin. Six of these patients had received prior therapy with mitomycin C or a nitrosourea. One patient each had received 5 and 1 courses of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (740 and 180 mg total dose, respectively). One patient had received two courses of mitomycin C at a dose of 20 mg/course, and the final patient had been previously treated with both mitomycin C and methyl 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea. Of the remaining 6 patients classified as heavily pretreated, one had received radiation therapy only. The other 5 heavily pretreated patients had had both radiotherapy plus chemotherapy with from 1 to 5 agents including 5-fluorouracil, doxorubicin, methotrexate, cisplatin, vincristine, vinblastine, dihydroxyanthracenedione, spiromustine, cyclophosphamide, etoposide, and mitotane. Among the 24 patients studied, there were multiple tumor types.

Responses. Although objective measurable disease was not a prerequisite for admission to this study, 9 patients’ disease was evaluable for response to carboplatin treatment in that they had measurable disease and received at least 2 courses of carboplatin. Among these patients one partial response was

<table>
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<tr>
<th>Av. pretreatment creatinine clearance (ml/min)</th>
<th>No. of patients</th>
<th>No. of courses</th>
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<tr>
<td>≤29</td>
<td>0</td>
<td>0</td>
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<tr>
<td>30–39</td>
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<td>5</td>
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<tr>
<td>40–49</td>
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<td>50–59</td>
<td>2</td>
<td>9</td>
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<td>60–69</td>
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<tr>
<td>70–79</td>
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<td>80–89</td>
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<td>90–99</td>
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<td>3</td>
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<tr>
<td>≥100</td>
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Cause of decreased renal function

- (creatinine clearance <60 ml/min)
- Preexisting renal disease: 4
- Tumor related: 4
- Cisplatin induced: 2

Table 1

Renal function in evaluable patients and courses

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observed in a patient with malignant melanoma, and an objective response (less than partial) was observed in 1 patient with adenocarcinoma of the cervix. No responses were observed in remaining 7 patients; these included 1 with squamous carcinoma of the bladder, 2 with colorectal carcinoma, 1 with head and neck adenocarcinoma, 2 with renal cell carcinoma, and 1 with adenocarcinoma of unknown primary. The other patients who were not evaluable for response all developed evidence of progressive disease in new sites.

**Toxicities and Evaluation of Dosing Equations.** Nonhematological toxicity resulting from carboplatin therapy was limited to grade 2 or greater nausea and vomiting which occurred in 15 of 24 patients during 25 of 44 courses. This problem was controlled in all cases with antiemetics. There was no evidence of nephrotoxicity in any patient, nor was there any symptomatic or physical examination evidence of ototoxicity or neurotoxicity.

Hematological toxicity was the major adverse manifestation of carboplatin therapy. The median decrease in hematocrit was 5%, with a range of 0–12%. Twelve of 24 patients on study had a hematocrit which decreased to ≤29% during at least one course of carboplatin therapy. Eight of these patients received a total of 18 units of RBC transfusions while on study. Five patients each received 2 units of packed RBC after their first course of therapy. Two patients each received 2 units of packed RBC after their second course, and 1 patient received 4 units after his fourth course. Leukopenia was mild with only 2 patients developing WBC ≤2,000/µl. There were no episodes of leukopenia related sepsis in any patient during this study.

As previously described (1–13), the major manifestation of myelotoxicity due to carboplatin was a reduction in platelet count. However, this toxicity proved manageable in view of the excellent performance of the equations used to tailor carboplatin dosages for each patient. More specifically, when the actual decrease in platelet count was compared with that predicted in calculating the dosage of carboplatin for that same course, excellent correlations, approaching the line of identity, were observed (Charts 1–3). When all administered courses of carboplatin were considered, there was a linear and almost perfect fit between the predicted change in platelet count and that observed (Chart 1). This relationship was defined by the equation: observed change in platelet count = 0.96 x predicted change in platelet count – 7,000 (r = 0.94). However, such an analysis could be unduly simplistic and also misleading since two dosing equations were used, i.e., one for patients who had been heavily treated previously, and one for patients who had not been heavily pretreated. In fact, closer inspection of the pooled data revealed that most previously treated patients fell above both the line of identity and that describing the behavior of the population as a whole, whereas most patients without previous extensive myelosuppressive therapy fell below the two lines (Chart 1). When the two populations were analyzed separately, excellent correlations were again seen between observed and predicted changes in platelet counts, although the two populations clearly behaved differently (Charts 2 and 3). The relationship in patients without previous heavy myelosuppressive therapy was again linear and close to the line of identity. This relationship was defined by the equation: observed change of platelet count = 1.04 x predicted change in platelet count – 48,000 (r = 0.96), and held true over a wide range of predicted changes in counts (Chart 2). In the 15 courses of carboplatin administered to patients who had been heavily pretreated before therapy with carboplatin, the relationship between observed changes in platelet counts and those predicted deviated from the line of identity, but did so in a consistent fashion (Chart 3). There was a highly linear relationship between observed and predicted changes in platelet counts defined by the equation: observed change in platelet count = 1.13 x the predicted change in platelet count + 6,600 (r = 0.97), implying a consistently observed reduction in platelet count of approximately 10% more than that predicted. Still no patient in either group required platelet transfusions and there were no episodes of bleeding related to thrombocytopenia. When these relationships between predicted and observed reductions in platelet count were investigated in the subset of patients with reduced renal function similar results were obtained. Specifically
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administration of carboplatin is much less severe than the

especially thrombocytopenia (1-13), and the emesis resulting

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that of cisplatin (16). Moreover the toxicities associated with the

activities against ovarian carcinoma equivalent to

Carboplatin has activity against a wide variety of human tumors

in the seven courses of carboplatin administered to patients with

creatinine clearances <60 ml/min who were classified as not

being heavily pretreated: observed change in platelet count =

0.57 x predicted change in platelet count + 27,940 (r = 0.97).

The analogous relationship for the courses courses of carboplatin

administered to heavily pretreated patients with creatinine clear-

ances <60 ml/min was: observed change in platelet count =

1.17 x predicted change in platelet count + 14,320 (r = 0.99).

DISCUSSION

Carboplatin is a cisplatin analogue which possesses a number of

features desirable in an analogue of a clinically active drug. 

Carboplatin has activity against a wide variety of human tumors

(1-13), including activity against ovarian carcinoma equivalent to

that of cisplatin (16). Moreover the toxicities associated with the

administration of carboplatin are either qualitatively different or

are less severe than those resulting from cisplatin therapy (1-

13). The dose limiting toxicity of carboplatin is myelosuppression,

especially thrombocytopenia (1-13), and the emesis resulting from

administration of carboplatin is much less severe than the

nearly universal nausea and vomiting produced by cisplatin (1-

13). Furthermore to date carboplatin has proven devoid of neph-

rotoxicity and ototoxicity (1-13), and neurotoxicity after treat-

ment with carboplatin has only been reported in patients treated

previously with cisplatin (2, 4).

In addition to these promising clinical attributes, the pharma-

cokinetic behavior of carboplatin is quite different from that of

cisplatin (2, 13, 15, 16). Specifically carboplatin is relatively slowly

bound to plasma proteins and most of the dose is excreted in

the urine during the first 24 h after injection (2, 13, 15, 16).

The combination of the pharmacokinetic behavior of carbopla-

tin and its dose-limiting toxicity of myelosuppression implied that

this drug might be given safely to patients with reduced renal

function; however, dosage reduction would be required to avoid

undue myelosuppression. This concept has been demonstrated

previously by Calvert et al. (2) and Rosencweig et al. (15). It was

further extended by our center which defined a relationship not

only between an individual patient’s renal function and the phar-

macokinetics of carboplatin in that patient, but also between

those pharmacokinetics and the subsequent degree of throm-

bocytopenia observed in that same patient (14). We utilized

these relationships and other pharmacological principles to de-

vice equations for calculating carboplatin dosage. When these

equations were applied to hypothetical, normal patients, the

dosages calculated agreed very closely with those determined

in actual phase I trials performed at our institution and others

(2-6, 8, 9, 11-13). However, validation of our proposed dosing

schema required prospective evaluation. Our current data dem-

onstrate the applicability of these dosing equations and validate

their use. Each analysis, whether of the total population or the

individual analyses of pretreated and nonpretreated patient pop-

ulations, demonstrates a high correlation between the predicted

and observed reductions in platelet count. Moreover in each

case the actual data define a line very close to the line of identity.

The one exception involves those patients who had been heavily

pretreated with chemotherapy in which the precision of fit, while

very good, is not perfect. In a practical sense this is the popula-

tion in whom the least perfect fit would be expected, since

differences with regard to previous treatment and actual degree

of previous exposure to the chemotherapy make this a rather

heterogeneous group as compared to patients with little or no

prior exposure to antineoplastic chemotherapy.

We feel that this prospective demonstration and validation of

pharmacologically based dosing schema for carboplatin is im-

portant in at least two respects. First, when combined with the

evolving demonstration of antitumor activity of carboplatin

against multiple cancers, it provides increased impetus for con-

sidering carboplatin therapy in patients with reduced renal func-

tion who normally would be treated with cisplatin, but whose

renal function precludes such treatment. The ability to calculate

rationally a fully therapeutic but not unduly toxic dose of drug is

reinforced by this prospective validation of our method. Second,

the relationship documented between the pharmacokinetics and

pharmacodynamics of carboplatin and the ability to use this

pharmacologically based dosing schema required prospective evalua-

tion. Our current data demonstrate the applicability of these dosing equations and validate their use. Each analysis, whether of the total population or the individual analyses of pretreated and nonpretreated patient populations, demonstrates a high correlation between the predicted and observed reductions in platelet count. Moreover in each case the actual data define a line very close to the line of identity. The one exception involves those patients who had been heavily pretreated with chemotherapy in which the precision of fit, while very good, is not perfect. In a practical sense this is the population in whom the least perfect fit would be expected, since differences with regard to previous treatment and actual degree of previous exposure to the chemotherapy make this a rather heterogeneous group as compared to patients with little or no prior exposure to antineoplastic chemotherapy.

We feel that this prospective demonstration and validation of pharmacologically based dosing schema for carboplatin is important in at least two respects. First, when combined with the evolving demonstration of antitumor activity of carboplatin against multiple cancers, it provides increased impetus for considering carboplatin therapy in patients with reduced renal function who normally would be treated with cisplatin, but whose renal function precludes such treatment. The ability to calculate rationally a fully therapeutic but not unduly toxic dose of drug is reinforced by this prospective validation of our method. Second, the relationship documented between the pharmacokinetics and pharmacodynamics of carboplatin and the ability to use this toward patient benefit should provide impetus for further studies attempting to document such relationships for other antitumor agents. These studies need not necessarily be restricted to investigational drugs during initial studies, as occurred with carboplatin, but in theory would be most beneficial if extended to more commonly used antitumor drugs.

ACKNOWLEDGMENTS

We thank H. Chlewicki and B. Knickman for their assistance in preparation of this manuscript, and Keith Kalmbach whose ministrations to our atomic absorption spectrometer allowed this work to come to fruition.

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