Cancer Chemother Pharmacol (1989) 23: 323–328

Cancer Chemotherapy and Pharmacology

Phase II study of carboplatin in recurrent ovarian cancer: severe hematologic toxicity in previously treated patients*

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Summary. Carboplatin (CBDCA) is a second-generation cisplatin analog that has shown activity in early clinical trials. Its spectrum of toxicity is quantitatively and qualitatively different from that of the parent compound. Between November 1984 and September 1986 we conducted a phase II trial of CBDCA in 46 women wih epithelial ovarian cancer. All patients had undergone at least one prior chemotherapy regimen; 41 (89%) had previously received cisplatin (mean cumulative dose, 540 mg/m^2). The CBDCA dose was based on renal function and was injected i.v. once every 4 weeks. Patients were stratified on the basis of baseline creatinine clearance: those with a baseline creatinine clearance of $\geqslant$60 ml/min received 400 mg/m^2 CBDCA; those with a creatinine clearance between 30 and 60 ml/min received an initial dose calculated according to a previously published formula [2, 3] that corrected for renal insufficiency and projected nadir platelet counts of 75,000/mm^3. Of 41 evaluable patients, 6 (15%) had an objective response [2 complete responses (CRs); 4 partial responses (PRs)]; 5 of the 6 responders had previously responded to cisplatin treatment. No responses were observed in 12 patients who had not responded to prior cisplatin therapy. Significant hematologic toxicity was seen. Of 18 patients with a creatinine clearance of $\geqslant$60 ml/min (dose, 400 mg/m^2), 6 had nadir platelet counts of $<$25,000/mm^3, 4 with symptomatic bleeding. Of the 21 evaluable patients for whom the dose-modification formula was applied, 10 had nadir platelet counts of $<$75,000/mm^3; 5 had counts of $<$50,000/mm^3. CBDCA has activity even in patients who have previously undergone extensive cisplatin therapy; however, its toxicity is variable and thrombocytopenia is dose-limiting. We did not confirm the ability of the above-mentioned formula to calculate the CBDCA dose and accurately predict the nadir platelet count for all patients. Other factors, such as prior radiotherapy, may also be important in the dosing of CBDCA in pretreated patients.

* Supported in part by a grant from Bristol Myers Company Pharmaceutical Research and Development Division, CRU CA 16087 and CRU-96.

** N. Colombo is the recipient of a fellowship from the American Italian Foundation for Cancer Research

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Introduction

Major obstacles in the treatment of ovarian cancer include dose-limiting acute and cumulative toxicities from cisplatin-containing regimens and the lack of effective second-line therapies. Carboplatin (CBDCA) is an active second-generation cisplatin analog with quantitative and qualitative differences between its spectrum of toxicity and that of the parent compound. Its activity against epithelial ovarian cancer has been documented in phase I [1] and II [4, 5] studies. In its recent randomized comparison with cisplatin as the primary chemotherapy for ovarian cancer, equal activity was observed [10]. Furthermore, CBDCA may not be cross-resistant with cisplatin in ovarian cancer [4, 5], making it an attractive drug for second-line chemotherapy in patients previously treated with cisplatin. The dose-limiting toxicity for CBDCA is myelosuppression, particularly thrombocytopenia, whereas neurotoxicity, nephrotoxicity, and ototoxicity are commonly absent [1, 4, 5, 10]. This difference in the patterns of toxicity may permit CBDCA to be used in patients who have otherwise reached dose-limiting cisplatin toxicity.

CBDCA is eliminated primarily through the kidneys and its excretion can be related to the glomerular filtration rate. Patients with impaired renal function demonstrate slower clearance of CBDCA [8, 9] and increased myelosuppression [1], which is of particular importance in patients with cisplatin-induced renal insufficiency. A creatinine clearance of $<$60 ml/min is a common finding after aggressive platinum-containing therapy. In an attempt to maximize the therapeutic value of CBDCA without unacceptable toxicity, Egorin et al. [2, 3] have proposed and validated a formula for calculating CBDCA doses. This formula takes into consideration the slower clearance of drug by patients with renal impairment, hematopoietic status quantified by pretreatment platelet count, and desired platelet nadir [2, 3].

We conducted a phase II trial in patients with ovarian cancer; patients who had relapsed after prior cisplatin therapy and those who progressed while on cisplatin were eligible. Our objectives were to evaluate further the efficacy of CBDCA in this patient population. In addition, we prospectively evaluated the predictive dosing formula in patients with renal insufficiency.

Patients and methods

Between November 1984 and September 1986, 46 women with epithelial ovarian cancer recurrent or persistent after

conventional chemotherapy were entered in the study. Other eligibility criteria included: histologically proven epithelial ovarian cancer with measurable or evaluable disease, a WHO performance status of ≤ 3, adequate bone marrow function – defined by a baseline white blood count (WBC) of $>3{,}500$ cells/mm^3 and a platelet count of $>100{,}000$/mm^3 – and a 24-h creatinine clearance of >30 ml/min. Participation in the study was not restricted by the number of prior chemotherapy regimens or by prior radiotherapy. Written informed consent was obtained from all patients prior to study entry.

CBDCA was supplied in 150-mg vials by Bristol Myers Company, Pharmaceutical Research and Development Division. Each dose was injected i.v. in 500 ml 5% dextrose in water over 30 min with no added pre- or posthydration. The initial dose for patients with a creatinine clearance of >60 ml/min was 400 mg/m^2. Patients with a creatinine clearance of >30 ml/min and <60 ml/min received a starting dose calculated according to the following formula:

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

This formula includes a correction factor (-17) for previous extensive myelosuppressive therapy [2].

The target nadir platelet count was 75,000/mm^3. Subsequent CBDCA doses were adjusted to individual marrow tolerance as measured by peripheral blood counts. The CBDCA dose was escalated by 25% if the nadir platelet count was $>100{,}000$/mm^3 or the nadir WBC was $>2{,}500$/mm^3. It was reduced by 25% if the nadir platelet count was 50,000–75,000/mm^3 or the nadir WBC was 1,000–1,500/mm^3; the dose reduction was 50% for nadir platelet counts of $<50{,}000$/mm^3 and nadir WBCs of $<1{,}000$/mm^3. Treatment was repeated every 4 weeks, provided that peripheral blood counts were adequate on the treatment date (i.e., WBC of $>3{,}500$/mm^3 and platelet count of $>100{,}000$/mm^3). Otherwise, treatment was delayed until the recovery of counts to the above values.

A medical history and physical examination were carried out before each cycle of chemotherapy. Complete blood counts were obtained weekly, and creatinine clearance and serum chemistries were assessed at monthly intervals. To assess tumor response, appropriate radiologic studies and CA 125 tumor marker assays were carried out every 2–3 months.

Measurable disease was defined as a mass with clearly demarcated dimensions on physical examination, computerized axial tomography (CAT) scan, or ultrasonography. An evaluable tumor was defined as nonmeasurable disease that could be assessed for tumor response, i.e., pleural effusions, ascites, and pelvic or abdominal masses with ill-defined borders. A complete response (CR) was defined as the absence of any detectable disease for a minimum of 4 weeks, and a partial response (PR), as a reduction of $\geq 50\%$ in the sum of the products of the largest diameter and its perpendicular in all indicator lesions. A PR in patients with evaluable disease was defined as a 50% decrease in the square of the only measurable diameter or as an 80% decrease in the estimated volume of the pleural effusion or ascites. Progressive disease was defined as the appearance of new metastases, ascites, or pleural effusion or a 25% increase in the size of measurable lesions. The duration of response was measured from the data of the first CBDCA treatment until the time of progression.

Results

The characteristics of the 46 women who received CBDCA are shown in Table 1. In all, 25 patients had received 1 prior chemotherapy regimen, whereas 12 had received 2 prior regimens and 9 had undergone at least 3 (range, 3–5). Of the 46 treated patients, 41 (89%) had been previously treated with cisplatin. The mean total dose of prior cisplatin/patient was 540 mg/m^2 and the mean cisplatin dose/course was 90 mg/m^2. The previous chemotherapy in patients not treated with cisplatin-containing regimens included HEXA-CAF plus CMF, HEXA-CAF, melphalan, and melphalan and cyclophosphamide. Nine patients had also received prior abdominal radiotherapy with a mean total dose of 3800 rads.

The response to prior cisplatin therapy is shown in Table 1. Of the 17 patients who relapsed following CRs to cisplatin, 3 were unsuccessfully treated with other chemotherapy regimens before receiving CBDCA. Of the 11 patients who obtained PRs to cisplatin, 2 subsequently progressed while still on cisplatin therapy. The median

Table 1. Patient characteristics

Characteristic		Patients (*n*)
Entered in study		46
Median age in years (range)	60 (38–85)	
Performance status (WHO)		
0–1		32
2–3		14
Prior radiotherapy		9
Prior chemotherapy		
Cisplatin		41
Median mg/m^2 (range)	540 (150–1000)	
Median number of months	6 (2–12)	
Mean dose/course (mg/m^2)	90	
Number of prior regimens		
1	25	
2	12	
≥3	9	
Interval between last chemotherapy and CBDCA		
≤2 months	20	
>2 months	26	
Response to prior cisplatin		
Complete response (pathologic)		13
Complete response (clinical)		4
Partial response		11
No response		12
Not available		1
Creatinine clearance		
≤60 ml/min		28
≥60 ml/min		18
Baseline platelet count (mm^3)		
100,000–150,000		8
> 150,000		38

interval between the first dose of CBDCA and the last chemotherapy was 4.5 months. A total of 204 courses of CBDCA were given, with a median of 4 cycles/patient (range, 1–17).

Toxicity

All 46 treated patients were evaluable for toxicity. The analysis of thrombocytopenia and leukopenia refers only to the first cycle of treatment, since subsequent courses reflect dose adjustments based on nadir blood counts. In addition, cumulative hematologic toxicity may occur.

In all, 18 patients had a creatinine clearance of $\geqslant 60$ ml/min; 16 of these received an initial dose of 400 mg/m^2. Two patients received a dose of 325 and 360 mg/m^2 by error. Another patient was treated with 400 mg/m^2 despite a creatinine clearance of 56 ml/min. In all, 17 patients were treated at 400 mg/m^2. There were 27 patients with a creatinine clearance of 30–60 ml/min (median, 42; range, 32–57); their doses were calculated according to the predictive formula and ranged from 116 to 300 mg/m^2. As a result of this dose calculation, four different levels were identified for myelotoxicity analysis (Table 2): 200, 201–299, 300–399, and 400 mg/m^2.

We confirmed that thrombocytopenia is the dose-limiting toxicity of CBDCA, with nadir platelet counts occurring at a median of 21 days (range, 7–31) and recovery, at a median of 28 days (range, 19–48). However, we found that CBDCA-induced thrombocytopenia was variable and unpredictable. Of the 46 treated patients, 14 (30%) had nadir platelet counts of $<50{,}000/\text{mm}^3$; 6 (13%) had counts between 25,000 and 50,000/mm^3, and 8 (17%) had counts of $<25{,}000/\text{mm}^3$ (Fig. 1). Severe thrombocytopenia was observed at all dose levels and was related to neither dose nor baseline creatinine clearance. Of the 17 patients receiving 400 mg/m^2, 6 had nadir platelet counts of $<25{,}000/\text{mm}^3$; the creatinine clearances of these patients were 65, 70, 70, 75, 77, and 101 ml/min (all patients had a pretreatment platelet count of $>200{,}000/\text{mm}^3$). In four of these six patients, thrombocytopenia resulted in symptomatic bleeding including internal hematoma, hematemesis and rectal bleeding, hematemesis alone, ecchymosis, and vaginal bleeding.

Of the 27 patients for whom the predictive formula for dose calculation was applied, 21 were analyzed; 6 were nonevaluable due to errors in dose calculation. We compared the target nadir platelet count of 75,000/mm^3 with the observed values; using this desired platelet nadir, we considered counts of 50,000–100,000/mm^3 to be within the predicted range. Of the 21 patients, 15 (17%) had nadir

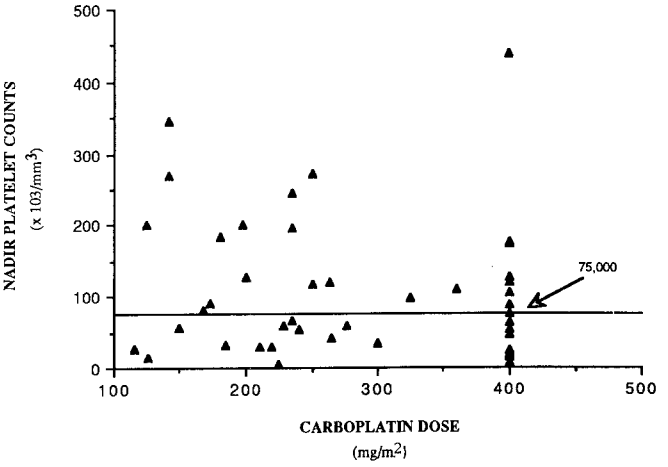

Fig. 1. The actual nadir platelet count observed for each patient according to the CBDCA dose received. The target platelet nadir of 75,000 is represented by the *horizontal line*

platelet counts out of the predicted range: 10 had nadir platelet counts of $>100{,}000/\text{mm}^3$ and 5 had counts of $<50{,}000$. Six patients had counts between 50,000 and 100,000/mm^3; of these, only one had a nadir platelet count of $>75{,}000/\text{mm}^3$. In the six censored patients, doses ranged from 141 to 229 mg/m^2: four received $<70\%$ of the calculated dose (platelet nadir: 150,000, 200,000, 270,000, and 346,000/mm^3), and two had $>120\%$ of the calculated dose (platelet nadir: 6,000 and 60,000/mm^3).

Figure 1 represents the difference in percentage between the observed and expected nadir platelet counts compared with the baseline for all patients. The reduction in platelets was 15% greater than expected in 6 of the 21 patients for whom the formula was applied, whereas it was 15% lower than predicted in 8. For the 17 patients who received a dose of 400 mg/m^2 (that is, for whom the formula was not used), the reduction in nadir platelet counts was 15% greater than expected in 7 and 15% lower in 5.

Treatment after the first cycle produced severe thrombocytopenia in only 5 of 46 (11%) patients. In 2 of these 5, further toxicity occurred in the second cycle despite appropiate dose reduction; in addition 3 of 46 (7%) experienced grade 3–4 thrombocytopenia after the third cycle – in 2 of these, doses had been escalated to >400 mg/m^2.

Second to thrombocytopenia, anemia was the most frequently observed toxicity. A total of 23 patients (50%) required transfusions. The median decrease in hemoglobin from the baseline was 2.1 g/100 ml. Leukopenia was also seen and required 24 of the 204 treatment cycles to be

Table 2. Hematologic toxicity after the first cycle of CBDA

Dose (mg/m^2)	Evaluable patients (*n*)	Median nadir platelet count[a] (range)	Median nadir WBC count[a] (range)	Number of patients with platelet count of:	
				50[a]	25[a]
200	12	132 (15–346)	4.2 (1.5–6.4)	2 (17%)	1 (8%)
$\geq$200–300	14	62 (6–271)	4.3 (2.0–7.3)	4 (28%)	1 (7%)
$\geq$300–400	3	98 (35–110)	3.9 (1.6–6.1)	1 (33%)	0
400	17	63 (8–438)	3.2 (0.8–5.9)	7 (41%)	6 (35%)

[a] $\times 10^3/\text{mm}^3$

delayed. Five patients had nadir WBC counts of $<2{,}000/mm^3$ (three at a CBDCA dose of 400 mg/m^2 and one each at doses of 300–400 and 200 mg/m^2).

In all, 17 patients had preexisting peripheral neuropathy of median grade 2: 2 complained of increased neurological symptoms, 1 after the first cycle of CBDCA and 1 after the fifth. Nausea and vomiting was moderate in most cases, with only seven patients experiencing intractable vomiting. The antiemetics commonly used include lorazepam, diphenhydramine hydrochloride, dexamethasone, and prochlorperazine.

Response

In all, 41 patients were evaluable for response (Table 3); 6 (15%) achieved an objective response to CBDCA: 2 (5%) CRs and 4 (10%) PRs. One patient showed the complete disappearance of cytologically positive ascites after the first cycle of CBDCA; she received a total of nine cycles and remained disease-free for another 9 months without further treatment. Her disease recurred off therapy 17 months after the first CBDCA dose and is again responding to the drug. A second patient achieved a CR of an abdominal mass measuring 5×7 cm that was no longer detectable after the third course of CBDCA; her disease recurred 11 months after the start of therapy while she was still on treatment. The four PRs were observed in two patients with measurable disease in the inguinal lymph nodes and in two with pelvic and abdominal masses. The mean dose/cycle in responding patients was 343, 245, 185, 212, 400, and 130 mg/m^2, respectively, and the mean number of cycles/patient was 10.

Five patients were nonevaluable for response due to the absence of measurable or evaluable disease (two patients), the location of the only tumor in a previously irradiated area (one patient), and the presence of concomitant stage I endometrial cancer (two patients). Of the two patients without measurable disease, one showed a decrease in serum tumor marker CA 125 from 379 to 46 IU/ml and is still alive 6 months after the start of treatment. The other showed the complete disappearance of previously increasing irregularities on the surface of the residual uterus as documented by CAT scan; she is still alive 9 months after the beginning of treatment. The disease in the patient with the previously irradiated tumor remained stable throughout three cycles of CBDCA, and two patients with concomitant endometrial cancer failed to respond. Of the 35 treatment failures, 9 patients had only 1 course of CBDCA. Four of these showed rapidly progressive disease, two were removed from study due to persistent thrombocytopenia, one was removed due to worsening peripheral neuropathy, and two patients refused further treatment.

Table 3. Response to CBDCA in 41 evaluable patients

Response (duration in months)	Patients (*n*)	%
Total responses	6	15
CR (11, 17)	2	5
PR (5, 12+, 17, 18+)	4	10
No response	35	85

CR, complete response; PR, partial response

Response was also analyzed in relation to prior cisplatin treatment: five of six (80%) patients responding to CBDCA had previously received cisplatin, and all of them underwent either a CR or PR. None of the 12 patients who progressed while on prior cisplatin therapy responded to CBDCA.

Discussion

The activity of CBDCA in refractory ovarian cancer has previously been documented [4, 5]. However, this phase II study contributes additional observations: (1) the efficacy of CBDCA in patients who had been previously treated with greater dose intensities of cisplatin (mean, 540 mg/m^2 over 6 months) than in previous studies, and (2) the prospective evaluation of a pharmacologically derived dosing formula in this specific clinical setting.

Evans et al. [5] have observed 7 responses in 28 pretreated patients, 4 of whom were resistant to cisplatin. Eisenhauer et al. [4] have recently reported a 28% response rate for CBDCA as a second-line therapy in ovarian cancer; of the 12 responses, 2 were observed in patients with progressive disease while on cisplatin. We observed 6 objective responses in 41 evaluable patients (15%). This lack of activity in cisplatin-refractory patients may be responsible for our slightly lower response rate compared with those of other phase II trials [4, 5]. Furthermore, no patient truly resistant to cisplatin showed a response to CBDCA in our study. This finding may be due to the fact that the majority of our patients had been treated in accordance with our current policy of using a medium-high dose intensity of cisplatin (100 mg/m^2 per cycle for 6 months) as a first-line treatment in ovarian cancer, which may, in turn, have selected a group of patients in whom the potential of responding to platinum analogs had been tested to a major extent. Moreover, in comparison to other trials, only 25 of 46 (54%) patients received CBDCA as therapy for first recurrence or progressive disease. If we considered only patients receiving the drug as a second-line treatment, our response rate would be 5 or 25, or 20%. Finally, it should be noted that 5 of the 41 patients included in the analysis of response could by some criteria have been considered to be nonevaluable (treatment stopped early due to toxicity or refusal); we consider the inability to give the drug to be a treatment failure.

In spite of these adverse factors, CBDCA showed activity in six of our patients, five of whom experienced disease recurrence after prior response to cisplatin. Although we cannot exclude that a similar response could have been achieved with the readministration of cisplatin, CBDCA's different spectrum of toxicity and, in particular, lack of nephrotoxicity may make it a more suitable drug for the treatment and long-term control of such recurrences. A CBDCA dose of 400 mg/m^2 produced a nadir platelet count of $<25{,}000/mm^3$ in 6 of 17 patients, indicating that this regimen may not be suitable in similarly pretreated patients. Furthermore, the occurrence of severe thrombocytopenia at each dose level, even at very low doses, suggests that CBDCA toxicity is highly variable in this group of patients. For better prediction of CBDCA-induced thrombocytopenia and leukopenia and further assessment of conditions for dose reduction, the identification of factors such as prior radiation therapy and prior response to cisplatin might be profitable.

Pharmacokinetic data indicate that differences in renal drug elimination by glomerular filtration play a major role in determining the high variability of CBDCA toxicity [2]. To determine a safe but effective dose for our patients with impaired renal function, we used the pharmacologically derived dosing scheme proposed by Egorin et al. [2, 3], corrected for previously treated patients. This formula-based dose is designed to insure the same area under the concentration-time curve (AUC) in all patients, despite differences in renal function, thereby predicting similar degrees of toxicity. We observed considerable variability in the severity of thrombocytopenia experienced by patients for whom the formula was applied. Only 6 of 21 (28%) patients had a nadir platelet count in the expected range (between 50,000 and 100,000/mm^3), whereas 5 of 21 (24%) had lower and 10 of 21 (48%), higher than predicted nadir platelet counts.

The accuracy with which we achieved a desired nadir platelet count is important since very low nadirs can lead to dangerous toxicity. We calculated the percentage of change from pretreatment platelet counts for both the expected and observed values. The difference in the percentage of decrease in platelet count between the expected and observed values is presented in Fig. 2 for all patients according to the CBDCA dose received. Although pharmacologic studies previously carried out in 11 of our patients [6] confirmed glomerular filtration as the main elimination route for CBDCA and demonstrated an inversely linear relationship between the mean residence time and creatinine clearance, renal function did not seem to be the only determinant of toxicity. These results do not exclude the value of the predictive formula in previously nontreated patients but document its limitation in heavily pretreated patients with a variety of other risk factors.

Previous phase I studies have suggested other possible co-determinants of toxicity, such as age, myelosuppression with previous therapy, performance status, existence of a third space, and bone metastases [1, 7]. We examined the pretreatment characteristics of all patients to evaluate the possible influence of these risk factors on hematologic toxicity; these are correlated with severe CBDCA-induced thrombocytopenia in Table 4. Although patient numbers are not adequate for statistical analysis, we observed a trend suggesting that prior radiation therapy enhanced drug-related thrombocytopenia. Severe thrombocytopenia occurred in eight of nine patients who had received prior radiotherapy. Until a better definition of important risk factors for CBDCA-induced myelosuppression is clarified by a cumulative analysis of the large number of cases now available, we recommend the use of a conservative starting dose (250–300 mg/m^2) in heavily pretreated patients with ovarian cancer.

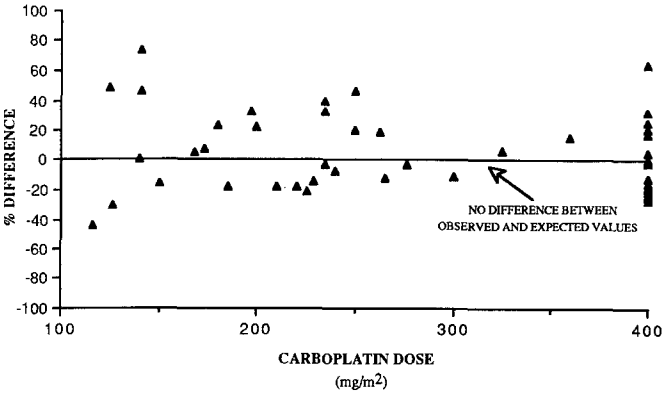

Fig. 2. The difference in percentage between the observed and expected decrease in platelet count for each patient. Patients receiving a dose of 400 mg/m^2 are also included in this analysis. The reduction in platelets was 15% greater than expected in 6 of 21 patients for whom the formula was applied, whereas it was 15% lower than predicted in 8 of these patients. For the 17 patients who received a dose of 400 mg/m^2, the reduction in nadir platelet counts was 15% greater than expected in 7 patients and 15% lower than expected in 5

Table 4. Relative risk factors for severe CBDCA-induced thrombocytopenia[a]

	Dose (mg/m^2)		Total (%)
	<400	400	
Number of patients with severe thrombocytopenia	7/29	7/17	14/46 (30)
Number of regimens			
1	4/16	3/9	7/25 (28)
>1	3/13	4/8	7/21 (33)
Prior radiotherapy			
yes	4/5	4/4	8/9 (89)
no	3/24	3/13	6/37 (16)
Performance status (WHO)			
0–1	2/19	6/13	8/32 (25)
2–3	5/10	1/4	6/14 (43)
Age (years)			
<65	4/13	6/12	10/25 (40)
≥65	3/16	1/5	4/21 (19)
Ascites			
present	4/12	2/6	6/18 (13)
absent	3/17	5/11	8/28 (28)

[a] Nadir platelet count, 50×10^3/mm^3

We conclude that the dose of CBDCA must be modified in heavily pretreated patients with impaired renal function. However, the toxicity can be quite variable, even after dose adjustment for creatinine clearance. Other factors, including prior radiation therapy, should also be considered. Current predictive formulas for CBDCA dosing do not in all cases yield accurate nadir platelet counts and should be applied with caution. Furthermore, CBDCA is effective in patients whose disease has progressed after a prior response to cisplatin treatment, although no response was observed in patients whose disease progressed during cisplatin therapy. Adequate regimens for patients resistant to adequate doses of cisplatin need to be developed.

Acknowledgement. We wish to acknowledge Margaret Nixdorf for her assistance in manuscript preparation and Dr. Ruth Oratz and Whitney Burrows for their helpful review.

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Received October 9, 1987/Accepted September 1, 1988