Cancer Chemother Pharmacol (1994) 33: 340–346

Cancer Chemotherapy and Pharmacology

GM-CSF, carboplatin, doxorubicin: a phase I study

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Received: 29 December 1992/Accepted: 31 August 1993

Abstract. Dose intensification has the potential to increase the response frequency of chemosensitive tumors to chemotherapy. G-CSF and GM-CSF offer the possibility of dose-intensifying chemotherapy without prohibitive myelosuppression. A phase I study was undertaken to identify the maximum tolerated dose (MTD) of carboplatin that could be administered with a fixed dose of doxorubicin, 60 mg/m^2, administered every 28 days. Further escalation of the carboplatin dose was then attempted, with the concomitant addition of GM-CSF 10 mg/kg per day on days 1–21. We had 21 patients, 13 with prior therapy, who were eligible. In all, 60 courses of therapy were delivered, all with doxorubicin and with carboplatin doses of 250 mg/m^2, 325 mg/m^2 and 400 mg/m^2. At carboplatin 400 mg/m^2 and doxorubicin 60 mg/m^2, thrombocytopenia was dose limiting. The addition of GM-CSF did not allow further escalation. Of the 6 patients treated with carboplatin 400 mg/m^2, doxorubicin 60 mg/m^2, and GM-CSF, grade 4 granulocytopenia and thrombocytopenia were seen in 4 and 5 patients, respectively. The severity of thrombocytopenia was related to the calculated carboplatin AUC and also to baseline platelet count and prior therapy. In addition, the interaction of GM-CSF and chemotherapy, especially carboplatin-based, may be more complex than originally anticipated.

This investigation was supported in part by the following PHS Cooperative Agreement grant numbers awarded by the National Cancer Institute, DHHS: CA-14028, CA-28862, CA-12213, CA-13612, CA-32102

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Introduction

Dose intensification, defined as maximizing the amount of drug delivered per unit time [18], is now an important goal in cancer chemotherapy. Preclinical [33] and clinical data demonstrate that, over a broad range of drug doses, a dose-response curve exists for the successful treatment of chemotherapeutically sensitive cancers, with increasing log cell kill of cancer cells as the chemotherapy dose is escalated. In multiple trials in Hodgkin's disease [10], soft-tissue sarcoma [37], and breast [19], ovarian [7, 24], and colon cancer [20] there are data demonstrating that with increasing dose intensity the response rate also rises.

Doxorubicin has been used extensively in the treatment of a wide variety of solid tumor malignancies. Antitumor activity has been demonstrated in carcinomas of the breast [35], ovary [36], and endometrium [34], and small-cell lung cancer [9] and, in addition, soft-tissue sarcomas [15]. Dose escalation of doxorubicin, however, has been limited by the twin toxicities of mucositis and myelosuppression, and long-term treatment at therapeutic doses by concern about cardiotoxicity. Carboplatin is used in the treatment of lung [23], ovarian [31], endometrial [16], testicular [3], and head and neck [1] cancer. Its dose-limiting toxicity is myelosuppression.

The availability of cytokines capable of stimulating bone marrow myelopoiesis offers the possibility of employing dose intensifying chemotherapy while at the same time protecting the patient from severe myelosuppression. An early study of granulocyte-colony-stimulating factor (G-CSF) demonstrated its utility when added to the MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) regimen [14]. In that original study of patients with transitional cell bladder cancer, G-CSF administered concurrently with the MVAC regimen clearly reduced the number of days of severe myelosuppression and allowed delivery of full-dose chemotherapy without delays due to prolonged marrow recovery. Similar modification of toxicity was noted when granulocyte macrophage colony-stimulating factor (GM-CSF) was used in conjunction with

MAID (mesna, doxorubicin, ifosfamide, decarbazine) in the treatment of soft tissue sarcomas [2].

The broad-spectrum activity of carboplatin and doxorubicin makes them good candidates for use together, especially if their myelosuppressive toxicities can be avoided. Unfortunately, the potential for cardiotoxicity limits the possibility for dose intensification in the case of doxorubicin. On the other hand, carboplatin, with myelosuppression as its dose-limiting toxicity, is a very attractive candidate for dose escalation.

This trial was mounted by the Gynecologic Committee of the Southwest Oncology Group, with the goal of defining the optimal doses of doxorubicin and carboplatin, which when administered with GM-CSF support, could be used for the outpatient treatment of endometrial cancer, a cancer sensitive to both chemotherapy agents. However, a dose-intensive regimen of these two agents would have broad clinical applicability.

Patients and methods

Patients were being treated as the three participating cancer centers (Wayne State University, University of New Mexico and University of Arizona); they had documented solid tumors refractory to standard therapy or no standard therapy existed for them. Further inclusion criteria were: measurable or evaluable disease, Southwest Oncology Group performance status of 0–1, granulocyte count ≥1500/μl, platelet count ≥100,000/μl, creatinine clearance (calculated or measured) of ≥60 ml/min, and serum bilirubin ≤2.0 mg/dl. The results of all blood work and scans for disease measurement were obtained within 14 days of treatment registration. Patients were not included if they had a history of myocardial infarction or congestive heart failure, and had to have had a MMGA scan demonstrating an ejection fraction ≥50%. Patients were excluded if they had had prior chemotherapy with anthracyclines. Patients could have received prior cisplatin. Patients with concomitant serious medical illnesses and those who were pregnant were excluded. All patients were required to have signed an informed consent form reviewed and previously approved by the institutional investigational review board.

Initially, the trial was open both to previously untreated patients and to patients with prior therapy. However, after significant myelosuppression was identified at the entry level dose, prior treatment of patients could include no more than one non-nitrosourea-containing chemotherapy regimen, and no prior radiotherapy was permitted.

The study was designed for a standard dose of doxorubicin, 60 mg/m^2, and escalating doses of carboplatin, starting at 250 mg/m^2, with both drugs administered i.v. every 28 days. No attempt was made to base the initial dose on the patient's initial creatinine clearance. The dose of carboplatin was escalated in subsequent patient cohorts, and GM-CSF added at the maximally tolerated dose (MTD) of the combination of carboplatin and doxorubicin, for the final group of patients.

At least three patients were entered at each dose level. Complete blood counts were obtained three times weekly, starting the week following chemotherapy. The MTD for the two chemotherapy agent combination was defined as that dose causing grade III-IV granulocytopenia lasting >7 days or documented sepsis in at least 4 of 6 patients; grade IV thrombocytopenia in at least 3; and/or, grade III, nonhematologic toxicity, in at least 2 patients treated at a given dose level. The subsequent cohort of patients was to be treated with those doses of doxorubicin and carboplatin defined as the two-agent MTD, but with the addition of GM-CSF (Schering) 10 μg/kg per day administered s.c., initially days 1–21 in a 28-day cycle. Additional escalations of carboplatin were to follow. A second MTD was to be defined as that dose of carboplatin which when given with the same dose of doxorubicin but with GM-CSF support, generated the equivalent level of toxicity described for the two-agent combination.

Table 1. Characteristics of the 21 patients. Median performance status: 0 (range 0–2), Median age: 54 (range 34–69) years, 7 men, 14 women

Native background			
Caucasian	12		
Hispanic	7		
Afro-American	1		
Native American	1		
Prior therapy		**Tumor types**	
Chemotherapy	8	Lung	6
Radiotherapy	8	Sarcoma	5
Chemoradiotherapy	4	Cervix	2
Biologics	2	Ovary	2
None	8	Other	6

Dose reductions of both chemotherapy agents were mandatory for granulocyte count under 500/μl or platelet counts under 25,000/μl. The carboplatin dose was decreased by 50% if there was a fall in the creatinine clearance to 40–60 ml/min and halted if the creatinine clearance decreased below 40 ml/min. Chemotherapy was stopped if the serum bilirubin was >2 mg/dl or if the patient developed evidence of congestive heart failure or deteriorating function as manifested by MMGA scanning. GM-CSF was to be discontinued if grade >2 nonhematologic toxicities developed. It was reintroduced when toxicity resolved at a dose of 5 μg/kg per day. GM-CSF was halted whenever the WBC rose to >50,000/μl.

Platelets were transfused according to institutional norms and at the discretion of the treating physician. Platelet transfusions were prescribed at some institutions for platelet counts of 20,000/μl or lower and at others; for 10,000/μl or lower. Standard Southwest Oncology Group response criteria were utilized. Complete response required the disappearance of all measurable and evaluable disease as well as the normalization of serum tumor markers. A partial response required over 50% reduction in the sum of the products of all bidimensionally measured lesions without evidence of progression at any other site for at least 1 month. Progression was defined as a 25% increase in the size of any lesion or the development of new sites of disease. Patients completing 4 weeks of therapy were evaluable for response. All patients were evaluable for toxicity. Toxicity was graded with reference to the SWOG toxicity criteria.

Results

Seven men and 14 women were eligible and received chemotherapy (Table 1). The median age of the patients was 54 years (range 34–69). The median performance status was 0. Patients with lung cancer and sarcoma predominated. Only 8 patients had had no prior therapy.

Sixty courses of therapy were delivered, including: 13 at a carboplatin dose of 250 mg/m^2; 16 at 325 mg/m^2; six at 400 mg/m^2 without GM-CSF and 16 with GM-CSF supplementation. Nine additional doses were delivered at 188–200 mg/m^2, seven as a result of dose reductions and two as a result of dose miscalculation.

In courses without GM-CSF, myelosuppression was substantial at all carboplatin dose levels, even at the entry level (Table 2). Both neutropenia and thrombocytopenia were noted. Thrombocytopenia was deemed dose-limiting at a carboplatin dose of 400 mg/m^2. In 5 of 6 patients

Table 2. Myelotoxicity

Dose of carboplatin delivered with Doxorubicin 60 mg/m²	Number of patients (course)	Number of patients with grade III–IV toxicity during first course						Number of patients with grade III–IV toxicity Any course					
		Granulocytes (/mm³) <(1,000/mm³)			Platelets (,000/mm³)		Requiring platelet transfusions	Granulocytes (/mm³) <1000 for			Platelets (,000/mm³)		Requiring platelet transfusions
		500–999	<499	>7 days	25–49	<25		500–900	<499	>7 days	25–49	<25	
188–200	4 (09)	0	0	0	0	0	0	1	2	1	0	0	0
250	6 (13)	0	2	1	0	0	0	0	4	3	0	3	2
325	6 (16)	2	3	2	0	0	0	1	4	3	0	1	1
400	6 (06)	1	5	2	1	3	2	1	5	2	1	3	2
400 W/GMCSF	6 (16)	0	4	2	0	2	2	0	4	2	0	5	3

Table 3. Carboplatin plasma AUCs for each evaluable patient following the first course of chemotherapy

Carboplatin dose (mg/m²)	Initial PLT count (×10³)	Prior chemo/RT	Total carboplatin dose (mg)	Calculated creatinine clearance (ml/min)	AUC (mg/ml per h)	First course nadir WBC (×10³)	PLT(×10³)
250	1. 289	Yes	400	91	3.45	1.0	84
	2. 285	Yes	475	93	4.02	2.7	184
	3. 197	No	450	73	4.59	2.6	113
325[a]	1. 508	No	614	78	5.96	2.2	222
	2. 741	Yes	520	70	5.47	0.8	54
	3. 267	Yes	600	72	6.18	0.8	101
	4. 381	No	579	115	4.13	1.8	149
	5. 746	No	468	99	3.77	0.6	213
400	1. 549	Yes	660	93	5.59	0.8	22
No GM-CSF	2. 396	Yes	616	84	5.65	1.3	55
	3. 348	Yes	880	138	5.40	0.6	8
	4. 426	Yes	700	92	5.98	0.7	175
	5. 477	Yes	650	65	7.22	1.9	5
	6. 433	Yes	760	79	7.31	0.8	6
400	1. 448	Yes	744	146	4.35	0.7	106
+ GM-CSF	2. 862	No	588	83	5.44	0.4	119
	3. 313	Yes	620	77	6.07	0.5	8
	4. 369	No	756	129	4.91	2.6	77
	5. 388	No	584	105	4.49	4.9	157
	6. 101	No	632	80	6.02	0.1	11

PLT, platelet; Chemo, chemotherapy; RT, radiotherapy; WBC, white blood cells
[a] Dosing error precluded analysis of one patient

treated with 400 mg/m² carboplatin grade 3–4 myelosuppression was observed, and all 5 were withdrawn from the study after one cycle of chemotherapy because of disease progression. The 6th patient received two cycles, the second at a reduced dose, because of myelosuppression before disease progression occurred.

The addition of GM-CSF did not allow further escalation of carboplatin. The first 2 patients treated with carboplatin 400 mg/m² with doxorubicin 60 mg/m² plus GM-CSF 10 μg/kg per day had grade 4 neutropenia, lasting 4 and 7 days respectively. GM-CSF's initiation was delayed until the day after chemotherapy in the subsequent 4 patients. With this altered schedule, grade 4 granulocytopenia was seen in 2 of the 4 patients.

Thrombocytopenia was dose-limiting in patients treated with GM-CSF and carboplatin 400 mg/m² plus doxorubicin 60 mg/m². The toxicity was manifest more frequently in each patient's subsequent courses than in the initial course, suggesting cumulative toxicity. Of 5 patients receiving more than one course, grade IV thrombocytopenia was eventually seen after a median of three courses in 4 patients, none of whom had prior chemotherapy or radiotherapy. Dose reductions were necessary in 3 of 5 patients receiving more than one course of therapy.

Platelet transfusions were needed by five patients, two treated at carboplatin 400 mg/m² without GM-CSF and three at the same dose with GM-CSF. All required one or two transfusions. Interestingly, the two patients who received additional carboplatin with the dose reduced to 250 mg/m² also required platelet transfusions at the lower dose.

Chemotherapy delays were rare. There were only 3 patients, 1 receiving carboplatin 250 mg/m² and 2 receiving 400 mg/m² with GM-CSF, whose chemotherapy was delayed for up to 2 weeks until adequate peripheral blood counts were restored.

Six patients were hospitalized for neutropenic fever or sepsis: one patient receiving carboplatin 325 mg/m² re-

quired hospitalization for neutropenic fever during each of two courses and succumbed to *Klebsiella* sepsis. Before death, the patient had a WBC of 400/μl and a platelet count of 15,000/μl. Two patients being treated with 400 mg/m^2 carboplatin without GM-CSF were admitted for fever for 5 and 10 days, respectively. Three patients who received carboplatin 400 mg/m^2 plus GM-CSF required four admissions of 2, 5, 7, and 9 days' duration for febrile neutropenia.

GM-CSF caused occasional skin toxicity. The GM-CSF dose was reduced by 50% in one patient because of a severe skin reaction. Subsequent doses were well tolerated. A second patient was withdrawn from therapy because large skin welts developed at sites of GM-CSF injection.

Two patients were removed from the study because of toxicity. One patient being treated with 400 mg/m^2 carboplatin with GM-CSF was removed from study because of myelotoxicity. The patient became febrile, neutropenic and thrombocytopenic. She was refractory to platelet transfusions and only recovered a normal range platelet count 15 days, after a platelet nadir of 7000/μl. She received no further therapy. The second patient was withdrawn for GM-CSF skin toxicity as previously described.

The doxorubicin-carboplatin combination was active. The 2 patients removed early because of toxicity were not evaluated for response. The patient whose death was due to toxicity was not evaluable. Among the remaining 19 patients evaluable for response four responses were noted, all in patients with no prior therapy. A patient with breast cancer and chest wall metastases was treated with an original dose of 400 mg/m^2 carboplatin plus doxorubicin 60 mg/m^2 and GM-CSF. The patient's skin nodules disappeared within the first month and did not recur during the subsequent 4 months. Doses of both carboplatin and GM-CSF were reduced because of toxicity: progressive thrombocytopenia and, with the latter, fatigue, fever and skin toxicity. The patient's disease progressed 9 months after trial initiation. Partial responses were seen in 1 patient each with ovarian, small-cell lung cancer and sarcoma. The partial response in the patient with ovarian cancer occurred at a carboplatin dose level of 250 mg/m^2, and ultimately further dose reductions were required because myelotoxicity had developed. The response lasted at least 4 months, at which time the patient refused further follow up. The two other partial responses occurred in patients treated with doxorubicin 60 mg/m^2 plus carboplatin 400 mg/m^2 and GM-CSF. One patient, with a stromal carcinoma of ovarian origin with intraabdominal metastases, received six courses of therapy and achieved a stable partial response lasting at least 8 months. The second patient with small-cell lung cancer achieved a partial response after 2 months of treatment as measured by decreases in the sizes of liver and hilar metastases. A month later, the patient developed brain metastases and succumbed.

Discussion

The availability of G-CSF and GM-CSF and the early success of these compounds in abrogating myelosuppression has generated great enthusiasm for the use of these agents to permit safe dose intensification of chemotherapy. Among the original studies, G-CSF decreased the myelosuppression associated with MVAC [14] and the combination of doxorubicin, ifosfamide and mesna, and etoposide [5]. GM-CSF, similarly, was used to attenuate the myelosuppression associated with MAID [2] in patients with sarcomas, carboplatin and etoposide in patients with small cell lung cancer [26] and with MVAC in patients with urothelial tumors [25]. Both G-CSF and GM-CSF prompted earlier marrow recovery in patients with autologous transplants [4, 17, 32].

Studies have involved G-CSF and GM-CSF to attain one of several different therapeutic goals. Originally, G-CSF and GM-CSF were used with standard regimens to decrease the myelotoxicity of these regimens and thereby improve the safety margin. Subsequent efforts have been directed at dose escalations beyond "standard" doses, using G-CSF and GM-CSF to make manageable what would otherwise have been a prohibitive toxicity. Acceptable toxicity in these latter regimens exceeds that of the former studies. This category is comprised of a variety of studies of different dose intensities, as the definition of acceptable toxicity varies from investigation to investigation. Some, such as our own, attempt to avoid prolonged granulocytopenia or the need for platelet transfusions. Others require only adequate and efficient restoration of counts and permit deep nadirs of both granulocytes and platelets as long as the nadirs are of short duration. A third category for the use of these cytokines is in support of marrow transplantation, to facilitate the rapid return of peripheral counts to acceptable levels after myeloablative therapy. Recently, GM-CSF has been used to promote the availability of peripheral blood stem cells for harvest and subsequent reinfusion after myeloablative therapy [17].

This study of escalating doses of carboplatin and fixed, standard-dose doxorubicin falls into the second category. Unexpectedly, the maximum tolerated dose without GM-CSF was 400 mg/m^2, and the addition of GM-CSF did not allow further dose escalation. At this dose level with GM-CSF, grade 4 granulocytopenia was seen in 4 and grade 4 thrombocytopenia in 5 of 6 patients so treated.

Our inability to escalate the dose of carboplatin was disappointing. In an attempt to explain the results of this study, we retrospectively evaluated patient laboratory and clinical characteristics potentially associated with severe leukopenia and/or thrombocytopenia. The severity of thrombocytopenia induced by carboplatin correlates with patient glomerular filtration rates (or its surrogate creatinine clearance) and carboplatin plasma AUC and is also influenced by a patient's pretreatment platelet count and prior therapy [8, 13, 21]. We calculated the carboplatin plasma AUC for the first course of treatment for each patient (Table 3). Using the Calvert equation, the median plasma AUC was 4.02 mg/ml per h at a carboplatin dose of 250 mg/m^2, 5.47 mg/ml per h at 325 mg/m^2 and 5.62 mg/ml per h for all patients receiving 400 mg/m^2 with or without GM-CSF. While grade 4 thrombocytopenia was seen in the 2 patients with an AUC >7 mg/ml per h and in 2 of the 3 patients with an AUC ≥ 6 mg/ml per h the occurrence of severe thrombocytopenia was more variable at an AUC of

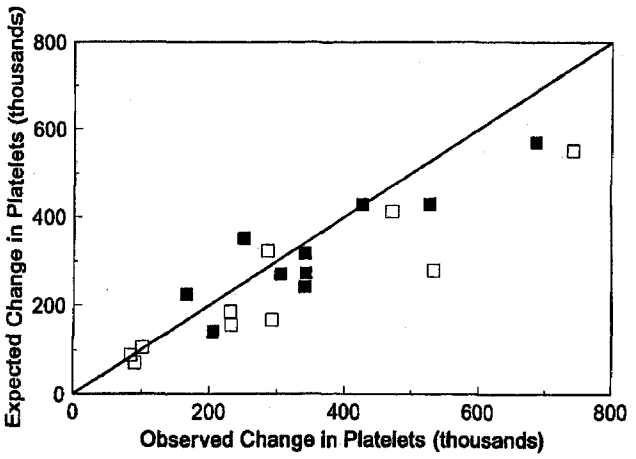

Fig. 1. Clinical platelet nadirs vs anticipated nadirs (Egorin formula). *Solid squares* reflect patients with extensive prior therapy

5 mg/ml per h and was mild or absent at an AUC <5 mg/ml per h. Further, the observed difference between initial platelet count and nadir platelet count conformed well to the Egorin formula [13] (△platelet = [(dose-86) (BSA) (initial platelet count)]/[(0.91) (creatinine clearance) (100)]) for anticipated platelet nadirs ($r = 0.91$; Fig. 1). Thus, the level of thrombocytopenia was appropriate for the dose, BSA, and renal function.

Thrombocytopenia, which was dose-limiting in our study, is a common problem and defines the MTD in other such studies where grade 4 thrombocytopenia is considered dose-limiting. The data, however, are not entirely consistent. In a randomized trial, de Vries utilized carboplatin, 300 mg/m^2, and cyclophosphamide, 750 mg/m^2, on day 1 with GM-CSF O (placebo), 1.5, 3 and 6 μg/kg per day given s.c. on days 6–12. Increased levels of neutrophils, at most cycle time points, were noted in the GM-CSF treated patients, most particularly those treated with the highest dose of GM-CSF. Platelet decrements following chemotherapy were clinically acceptable and more modest in patients treated with GM-CSF, 3 and 6 μg/kg per day than in the placebo controls. There was no apparent cumulative toxicity [11]. On the other hand, Edmonson administered carboplatin 300 mg/m^2 and cyclophosphamide 1000 mg/m^2 on day 1 and GM-CSF 10 μg/kg per day s.c. on days 3–22 and found dose-limiting thrombocytopenia, which was only ameliorated by altering the dose of GM-CSF to 10 μg/kg/every 12 h on days 2–15 [12]. Similar schedule dependency was also noted when carboplatin was combined with etoposide [25].

Other explanations might be proposed for the neutropenia with GM-CSF. In this phase II study, GM-CSF was initiated on day 1 after the chemotherapy in the first 2 patients and in the next 4, on day 2. The vast majority (i.e. approximately 70%) of carboplatin should have been excreted within the first 24 h after administration [29], while most of the doxorubicin remains for more than 30 h [28]. In retrospect, GM-CSF may have been promoting myelopoiesis in the presence of doxorubicin, thus augmenting rather than attenuating the myelotoxicity of this regimen. A similar observation was made in another study using fluorouracil with leucovorin daily for 5 days with GM-CSF added on days 1–14. Unexpectedly, severe neutropenia was noted with this regimen. When GM-CSF's initiation was delayed until the day after chemotherapy was concluded, neutropenia was not seen [26]. Thus, a later starting day, i.e. day 4, as used in many other studies, would have been a more judicious choice for our study.

The contribution of doxorubicin to the development of severe myelosuppression cannot be readily determined. In a recent study, patients received treatment with doxorubicin 75 or 100 mg/m^2 every other week with G-CSF. In these patients no platelet transfusions were required though the precise level of platelet suppression was not indicated. Neutropenia was severe but quite brief. However, higher doses of doxorubicin, 125 and 150 mg/m^2, did generate severe thrombocytopenia requiring transfusions and severe but short duration neutropenia [6].

A curious pair of recent observations further emphasizes the complexity of G-CSF/GM-CSF/cancer therapy interactions. A SWOG study of patients with small-cell lung cancer was designed to explore the benefit of GM-CSF in a combined modality treatment regimen of etoposide 60 mg/m^2 on days 1–3 and cisplatin 25 mg/m^2 on days 1–3, along with chest radiotherapy 45 Gy/25 fractions. GM-CSF was administered at a dose of 250 μg/m^2 twice daily s.c. Among the 213 patients entered onto the trial, significantly more thrombocytopenia and anemia were seen in patients treated with GM-CSF [7]. Similarly, 40 patients with non-small-cell lung cancer were treated with etoposide, cisplatin, and mitomycin along with chest radiotherapy. Seven additional patients receive G-CSF 5 μg/kg per day along with the therapy. Consistent thrombocytopenia was observed in those patients receiving G-CSF, which was not seen in patients not so treated. The difference in first course nadirs was statistically significant, despite the small number of patients [27].

In our trial, the combination of carboplatin and doxorubicin was active with four responses noted, three at the highest level of carboplatin with adjunctive GM-CSF. It might be speculated that use of the higher dose of carboplatin and the addition of GM-CSF contributed to the notable activity of the combination. However, despite GM-CSF, carboplatin had to be reduced in 3 of 6 patients because of myelosuppression. Therefore, a more likely explanation for the activity of the combination is that these drugs were given to previously untreated patients whose tumor types had known sensitivity to either carboplatin or doxorubicin and were more likely to respond.

The addition of GM-CSF to the combination of carboplatin and doxorubicin did not allow dose escalation of these two chemotherapy agents in our trial. However, because this is an active combination of agents, alternative schedules of GM-CSF or the use of other cytokines should be explored.

Acknowledgements. The secretarial support from Cheryl Gunnells, statistical support from Glenn Cummings and data management support from Gayle Kusch are much appreciated. Dr. M. Egorin's assistance and guidance is also greatly appreciated.

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