Randomized Trial of Carboplatin plus Amifostine versus Carboplatin Alone in Patients with Advanced Solid Tumors

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BACKGROUND. To test the hypothesis that the cytoprotectant amifostine attenuates the thrombocytopenia produced by carboplatin, the authors performed a randomized trial comparing treatment with carboplatin alone versus the combination of amifostine and carboplatin.

METHODS. Patients with refractory or carboplatin-sensitive malignancies were randomized to receive either carboplatin, 500 mg/m^2 alone or carboplatin, 500 mg/m^2 in conjunction with 2 doses of amifostine of 910 mg/m^2 each.

RESULTS. Fifty-five patients with a variety of malignancies were entered on this study. One patient withdrew from each arm prior to the administration of any therapy, leaving 30 evaluable patients treated with carboplatin alone and 23 treated with the combination of amifostine and carboplatin. For 82 cycles of therapy with amifostine plus carboplatin, the median platelet nadir was 127×10^9/L while the median platelet nadir was 88×10^9/L over the 80 courses of therapy with carboplatin alone ($P = 0.023$). The median platelet nadir after the first cycle of therapy was 144×10^9/L for patients treated with amifostine plus carboplatin and 85×10^9/L for patients treated with carboplatin alone ($P = 0.24$). The median survival for 9 patients with advanced nonsmall cell lung carcinoma treated with carboplatin alone was 39 weeks whereas the median survival for 12 such patients treated with amifostine plus carboplatin was 52 weeks ($P = 0.116$).

CONCLUSIONS. These data support the hypothesis that amifostine attenuates the myelosuppression of carboplatin. Additional studies of amifostine in combination with carboplatin-containing chemotherapy regimens are warranted. ***Cancer* 1997;80:1134–40.** © *1997 American Cancer Society.*

KEYWORDS: amifostine, carboplatin, thrombocytopenia, cytoprotection.

Amifostine, the compound formerly known as WR-2721, was developed by the U.S. Defense Department as a potential radioprotectant.[1] Preclinical studies demonstrated that this agent acted not only to protect normal tissues from radiation damage but also to attenuate the effects on normal cells of cytotoxic agents of the alkyating, platinating, and other classes.[2–6] Moreover, this protection was found to be relatively specific for normal tissues, whereas implanted tumors were not protected.[2,4–6] Further studies indicated that amifostine was a pro-drug that was metabolized by alkaline phosphatases to the active thiol WR-1065, which was transported intracellularly.[7–9] The specificity for normal as opposed to malignant tissues has been hypothesized to be due to differences in membrane alkaline phosphatase activity, with this activity higher in normal compared with tumor cells.[7–9] Because a chemoprotectant compound such as amifostine could increase the therapeutic index of a variety of cytotoxic agents,

clinical trials were undertaken. Phase I trials demonstrated that amifostine was tolerable, although it produced nausea, emesis, hiccoughs, and rapidly reversible hypotension.[1,10] Further studies indicated that amifostine could reduce the myelosuppression produced by cyclophosphamide and the hematopoietic and renal toxicities of the combination of cyclophosphamide and cisplatin.[11–13]

The authors studied the combination of carboplatin and amifostine, based first on the observation that amifostine was found to protect against the toxic effects of cisplatin in preclinical and clinical trials. Because cisplatin and carboplatin yield the same platinating species,[14,15] it was hypothesized that amifostine would reduce the toxicity of carboplatin. In addition, thrombocytopenia is the dose-limiting toxicity of carboplatin and the bone marrow is an organ protected by amifostine.[2–4] Therefore, investigation of the combination of amifostine and carboplatin appeared logical. Preclinical studies indicated that amifostine could reduce the hematologic toxicity of carboplatin in mice, whereas the antitumor effects of carboplatin against the OVCAR-3 cell line were not only maintained, but enhanced.[16] Based on this rationale, the authors performed a Phase I trial of two doses of amifostine, given in conjunction with carboplatin.[17] The initial dose of amifostine was given just prior to carboplatin, whereas the second was given 2 hours afterward. The second dose of amifostine was given because the plasma half-life of carboplatin is long relative to that of amifostine.[1,14,15] In this trial, it was demonstrated that 1) 2 doses of amifostine of 740 mg/m^2 each could be given safely with carboplatin, and 2) the maximum tolerated dose of carboplatin that could be given with 2 doses of amifostine in a population comprised largely of previously treated patients was 500 mg/m^2.[17] The magnitude of change in the platelet count after the first cycle of therapy was generally less than would have been predicted, based on a formula derived from patients receiving carboplatin alone.[18] These observations were consistent with the hypothesis that amifostine could reduce the thrombocytopenia produced by carboplatin. To further explore this hypothesis, the authors performed a randomized trial comparing the toxicity of therapy with the combination of amifostine and carboplatin with that of therapy with carboplatin alone.

MATERIALS AND METHODS

Eligibility

This trial was open to patients age $\geq$ 18 years with a histologically verified diagnosis of advanced malignancy that was refractory to standard treatment or for which single agent carboplatin was appropriate therapy. Patients were entered on this trial only after written informed consent to participate was obtained. Participants were required to have an Eastern Cooperative Oncology Group performance status of 0–2 and to meet the following laboratory criteria: leukocyte $\geq$ 3.5 $\times$ 10^9/L, platelet count $\geq$100 $\times$ 10^9/L, hemoglobin $\geq$8.5 gm/dL, total bilirubin $\leq$1.5 mg/dL, and either a serum creatinine $\leq$1.5 mg/dL, a 24-hour creatinine clearance $\geq$60 mL/min, or an iothalamate clearance $\geq$60 mL/min. Patients were allowed to have received up to one prior chemotherapy regimen, including adjuvant therapy, and were not permitted to have received prior radiotherapy to the spine, pelvis, or chest. At least 3 weeks were required to have elapsed since the last surgery, chemotherapy, or radiation treatment. Patients who had received prior nitrosoureas, cisplatin, carboplatin, or intravenous mitomycin C were excluded from entry, as were pregnant women, sexually active patients not practicing contraception, and patients with active coronary artery disease (New York Heart Association Class $\geq$3). Patients who were suspected to have bone marrow involvement by malignancy were excluded unless bone marrow aspirate and biopsy were negative within 4 weeks of study entry; all patients with a diagnosis of breast carcinoma were required to have negative bone marrow studies. Patients were not required to have measurable disease. Informed consent to participation was required of all patients entered on this trial, and neurologic or psychologic ability to give such consent was necessary.

Treatment

Patients were entered on this trial after informed consent to participate was obtained and after they underwent the following assessments: history and physical examination, performance status determination, tumor measurement (if measurable disease was present), chest X-ray, complete blood count with differential, serum multichemistry profile (total protein, albumin, calcium, phosphate, glucose, uric acid, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, and magnesium), 24-hour creatinine clearance, and glomerular filtration rate (GFR) determination by iothalamate clearance.

After stratification for age and prior therapy, patients were randomly assigned to treatment with carboplatin alone or the combination of carboplatin and amifostine. Dosing of both carboplatin and amifostine was determined according to body surface area (BSA) based on the lesser of the actual and ideal weight. Patients receiving carboplatin alone were treated with carboplatin, 500 mg/m^2, administered intravenously

over 5–10 minutes. Patients randomized to the combination of carboplatin and amifostine also received carboplatin, 500 mg/m^2, administered intravenously over 5–10 minutes; in addition, these patients were treated with 2 doses of amifostine, 910 mg/m^2, administered intravenously over 15 minutes. The dose of amifostine was based on clinical trials demonstrating that this dose, rather than 740 mg/m^2, was the maximum tolerated dose.[11] The first dose of amifostine was administered 15–20 minutes prior to the administration of carboplatin and the second dose was given 2 hours after the completion of the infusion of carboplatin. Although the antiemetic regimen was not dictated by the protocol, all patients in both arms received ondansetron and dexamethasone. Patients were treated every 4 weeks in the absence of disease progression or unacceptable toxicity, provided that the leukocyte count had recovered to 3.5×10^9/L, the platelet count had returned to $\geq 100 \times 10^9$/L, and all acute toxicity had abated. All patients had a complete blood count with differential performed twice weekly during treatment. A physical examination, performance status evaluation, toxicity notation, and serum chemistry profile were performed every 4 weeks; special studies for disease assessment (e.g., computed tomography) were repeated every 8 weeks.

In both arms, the dose of carboplatin was reduced by 25% in subsequent cycles in the event of Grade 3–4 myelosuppression. For nonhematologic toxicity of Grade 3–4, the doses of both agents were reduced by 25% in subsequent cycles, with the exception of hypotension, for which only the dose of amifostine was modified. Blood pressure was determined prior to the administration of amifostine, at least every 3 minutes during drug infusion, and 5 minutes after the completion of each infusion. Hypotension, defined as a reduction from pretherapy systolic blood pressure, was treated by interruption of the amifostine infusion, administration of intravenous fluids, and by maintaining the patient in a supine or Trendelenburg's position. Treatment was reinstituted if the blood pressure returned to the threshold level within 5 minutes. In the event of more prolonged hypotension, subsequent doses of amifostine were reduced by 1 dose level (to 800 mg/m^2, 750 mg/m^2, 700 mg/m^2, etc.) in subsequent cycles. Hypotension during the first of the two amifostine doses during a given cycle of treatment led to modification of both doses in the subsequent cycle; however, hypotension during the second of the two doses led to dose modification only of the second dose of amifostine in the succeeding cycle.

Statistical Considerations

Patients were stratified according to age ($\leq$ 60 years vs. $>$ 60 years) and prior therapy status (previous radiation or chemotherapy vs. no previous radiation or chemotherapy) prior to randomization. Within each stratification group, patients were randomized in groups of four to treatment with or without amifostine. Randomization was performed at the Clinical Research Department of U.S. Bioscience, Inc., West Conshohocken, Pennsylvania. The study was designed to detect a 20% difference in change in platelet count at a significance of 0.05 with 80% power, using the Wilcoxon rank sum test. Based on data from the authors' Phase I trial,[17] indicating the magnitude and variability of the thrombocytopenia produced by treatment with the combination of carboplatin and amifostine, a total accrual of 50 patients was planned.

TABLE 1
Patient Characteristics

Characteristic	Carboplatin alone	Amifostine + carboplatin
No. entered	31	24
Withdrawals	1	1
No. evaluable	30	23
Age (yrs)		
Median	64	63
Range	33–84	33–79
Gender (M:F)		
Male	20	16
Female	10	7
Performance status		
0–1	25	21
2	5	2
GFR (mL/min)		
Median	108	107
Range	55–202	36–181
BSA used for dosing[a] (m^2)		
Median	1.82	1.91
Range	1.31–2.24	1.48–2.71
Calvert et al. AUC[19] (mg/mL·min)		
Median	7.0	6.7
Range	4.7–11.2	4.7–15.2

M: male; F: female; GFR: glomerular filtration rate; BSA: body surface area; AUC: area under the concentration-time curve.

[a] Lesser value of the actual and ideal body surface area.

RESULTS

Patient Characteristics

A total of 55 patients were entered on this study; 24 were randomized to treatment with the combination of carboplatin and amifostine and 31 were randomized to treatment with carboplatin alone. All were eligible. One patient in each arm withdrew from the study prior to the administration of any therapy and are not included in the outcome analyses. As shown in Table 1, patient characteristics were well matched. There were

TABLE 2
Nonhematologic Toxicity (Maximum NCI Common Toxicity Criteria Grades Observed in Any Cycle)

	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Nausea and emesis ($P = 0.002$)						
Ami + carbo	23	6	15	1	1	0
Carbo only	30	21	8	1	0	0
Hypotension						
Ami + carbo	23	9	7	7	0	0
Carbo only (not assessed)						

NCI: National Cancer Institute; Ami: amifostine; Carbo: carboplatin.

no significant differences between the two treatment groups with respect to age, gender, performance status, BSA, GFR, and estimated areas under the concentration-time curves (AUC), as determined by the method of Calvert et al.[19] (AUC = absolute dose of carboplatin/[GFR + 25]).

Toxicity

Toxicity was graded according the the National Cancer Institute Common Toxicity Criteria. Significant nonhematologic toxicities are summarized in Table 2. In general, both treatment arms were well tolerated. Nausea was more frequent among patients treated with the combination of carboplatin and amifostine, but was Grade 1 in most cases. Hypotension was assessed only in patients treated with amifostine. In most cases, hypotension was mild and reversible within 5 minutes of interrupting the amifostine infusion. In 14 of the 82 courses of therapy, hypotension did not reverse within 5 minutes of interrupting 1 of the 2 doses of amifostine, leading to dose modification in subsequent cycles. No sequelae attributable to hypotension were noted.

Thrombocytopenia was less severe in those patients treated with amifostine and carboplatin than in those treated with carboplatin alone. In particular, the median nadir platelet count was 127×10^9/L (mean, 128×10^9/L) over the 82 courses of therapy with the combination of amifostine and carboplatin as opposed to a median platelet nadir of 88×10^9/L (mean, 109×10^9/L) for the 80 courses of therapy with carboplatin alone ($P = 0.023$, Wilcoxon rank sum test). Although such an analysis might bias against finding a significant difference, owing to protocol specified dose modifications for myelosuppression, an advantage for the patients treated with amifostine was observed in every course of therapy. After the first cycle of treatment, the median platelet nadir was 144×10^9/L for patients treated with amifostine in addition to carboplatin, as opposed to a median nadir of 85×10^9/L for patients treated with carboplatin only ($P = 0.24$). The results of the six cycles of therapy are summarized in Table 3. After the first cycle of therapy, 7 of the 30 patients (23%) treated with carboplatin alone developed Grade 3–4 thrombocytopenia (platelet nadir $< 50 \times 10^9$/L), leading to a dose modification of carboplatin in subsequent cycles of therapy. After the first cycle of treatment with the combination of amifostine and carboplatin, 4 of 23 patients (17%) developed Grade 3–4 thrombocytopenia. There was a significant correlation between the carboplatin AUC calculated according to the method of Calvert et al.[19] and the percent decrease in platelet count for the first cycle (correlation coefficient [r] = 0.39, $P = 0.03$ and r = 0.53, $P = 0.01$ for carboplatin alone and in combination with amifostine, respectively). As with the analysis of the platelet nadirs, the difference between the two treatments with respect to platelet drop after the first cycle alone was not significant ($P = 0.43$). In this trial, Grade 4 neutropenia was not a problem in either treatment group, and no significant differences in the median neutrophil nadirs was observed between the two treatment arms (Table 3).

Antitumor Effects

Because multiple tumor types were treated and because bidimensionally measurable disease was not a requirement for study entry, no conclusions regarding the efficacy of therapy for either arm can be made. All of the responses occurred in patients with nonsmall cell lung carcinoma, which was the most common tumor type entered. Among the 12 patients with nonsmall cell lung carcinoma treated with carboplatin alone were 7 patients with measurable disease and 5 with evaluable disease; 3 partial responses were produced. Among the nine patients with nonsmall cell lung carcinoma who were treated with the combination of amifostine and carboplatin, five had measurable disease whereas four had evaluable disease; one objective response was recorded. The survival times

TABLE 3
Hematologic Toxicity

Cycle no.	No. of patient cycles: CBDCA\CBDCA + amifostine	CBDCA alone: median platelet nadir	CBDCA + amifostine: median platelet nadir	*P* Value	CBDCA alone: median neutrophil nadir	CBDCA + amifostine: median neutrophil nadir	*P* Value
Pre-Rx	30/23	320	331	0.779	3.23	3.07	0.247
1	30/23	85	144	0.240	1.69	1.96	0.570
2	21/20	105	128	0.217	2.26	2.22	0.607
3	11/15	116	131	0.363	1.84	1.85	0.663
4	8/13	105	124	0.361	1.59	2.33	0.202
5	5/6	64	115	0.082	1.22	1.90	0.274
6	5/5	61	143	0.100	1.65	2.07	0.728
Total	80/82	88	127	0.023	1.84	1.85	0.966

Pre-Rx: before treatment; CBDCA: carboplatin.

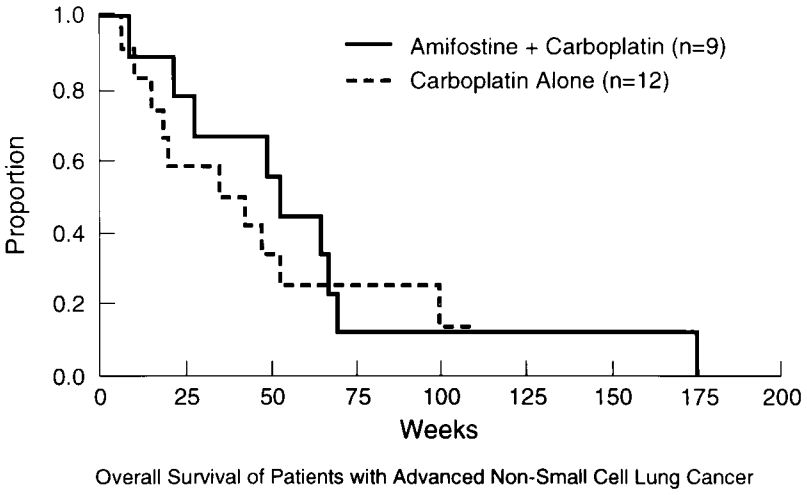

FIGURE 1. The survival of patients with nonsmall cell lung carcinoma did not differ significantly according to treatment ($P = 0.116$, log rank test).

of these 21 patients with advanced nonsmall cell lung carcinoma are displayed for each treatment arm in Figure 1. The median survival of the 12 patients treated with carboplatin alone was 39 weeks, whereas the median survival of the 9 patients treated with the combination of carboplatin and amifostine was 52 weeks ($P = 0.116$, log rank test).

DISCUSSION

This trial again demonstrates that two doses of amifostine can be given safely on the same day with carboplatin. A trend toward a reduction of the thrombocytopenia after the first cycle of therapy was observed in patients receiving amifostine, but this difference was not statistically significant, even when analyzed in terms of calculated AUC of carboplatin. The number of patients developing severe thrombocytopenia was lower than anticipated, and a statistically significant reduction in Grade 3–4 thrombocytopenia could not be demonstrated. However, the cumulative thrombocytopenia produced by carboplatin was significantly less in the patients treated with the combination of amifostine and carboplatin than in those patients treated with carboplatin alone, consistent with the hypothesis that amifostine partially protects the hematopoietic system from the cytotoxicity of carboplatin. In another small study comparing carboplatin alone with the combination of carboplatin and amifostine, severe thrombocytopenia was produced in both the carboplatin alone and carboplatin plus amifostine arms, but a more rapid recovery to a platelet count of $\geq 100 \times 10^9$/L was observed in the patients receiving amifostine.[20] In that study, a trend toward a reduction in hospitalization for chemotherapy-related complications was noted among patients receiving the combination of carboplatin and amifostine, but no difference in transfusion requirements could be demonstrated. In the current study, neutropenia was mild in

both arms, and no meaningful analysis of recovery from thrombocytopenia could be performed because only 16 patients treated with carboplatin alone and 8 patients treated with the combination of amifostine and carboplatin had a platelet nadir of $< 100 \times 10^3$/L after the first cycle of therapy. The current study was designed to detect a biologically significant effect of amifostine on the myelosuppression produced by carboplatin, but was not sufficiently large, nor was the dose of carboplatin sufficiently toxic, to address the question of whether the observed biologic effect on thrombocytopenia was associated with significant clinical benefits, such as a reduction in the need for platelet support or a reduction in bleeding episodes. Such effects can only be inferred from the results of the current trial, and further studies of amifostine in conjunction with carboplatin-containing regimens are warranted.

At the time this trial was conceived, carboplatin dosages were generally determined on the basis of BSA. However, the relationship between renal function and carboplatin elimination was well known so the authors chose to carefully assess the GFR of all patients by measuring iothalamate clearance prior to study entry. The two treatment groups were comparable in terms of renal function, so that the observed difference in myelosuppression did not appear to be attributable to differences in carboplatin exposure consequent to determining carboplatin dosage on the basis of BSA rather than estimated GFR.

Another possible explanation for the reduced thrombocytopenia observed in the combination therapy arm would be a pharmacokinetic interaction between amifostine and carboplatin which resulted in a reduction in carboplatin AUC. Detailed pharmacokinetic studies of carboplatin given alone and with amifostine have failed to show a statistically significant effect of amifostine on the AUC of carboplatin.[21] In these studies, a trend toward an increased AUC for carboplatin when given with amifostine was reported, along with a significant increase in the terminal half-life of carboplatin in patients treated with three doses of amifostine in conjunction with carboplatin. Thus, the results of the current study cannot be ascribed to a pharmacokinetic interaction of amifostine and carboplatin.

Because this trial was open to patients with all tumor types and did not require bidimensionally measurable disease, the effect of amifostine on the efficacy of therapy with carboplatin cannot be assessed rigorously. However, no evidence of impaired survival was observed in patients with nonsmall cell lung carcinoma who were treated with the combination of amifostine and carboplatin compared with the patients treated with carboplatin alone. The current study results are similar to those reported in a small randomized trial comparing carboplatin with the combination of carboplatin and amifostine in patients with advanced nonsmall cell lung carcinoma, in which a median survival of 14 months was reported for the 11 patients treated with the combination of amifostine and carboplatin and a median survival of 9 months was reported for 10 patients treated with carboplatin alone.[20]

The current study was designed to determine whether amifostine exerts a biologic effect on the myelosuppression produced by carboplatin, which would justify additional studies of this combination. This study indicates that such an effect is present, in that amifostine appears to reduce the cumulative thrombocytopenia produced by carboplatin. A Phase III randomized trial of the combination of carboplatin and paclitaxel with and without amifostine in patients with advanced nonsmall cell lung carcinoma has been initiated to confirm the clinical benefit of amifostine in patients treated with carboplatin-based chemotherapy.

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