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A phase I trial of AUC-directed carboplatin with infusional doxorubicin and ifosfamide plus G-CSF in patients with advanced gynecologic malignancies

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Abstract The effect of the addition of G-CSF to carboplatin, ifosfamide and doxorubicin (CIA) at the maximally tolerated dose (MTD) was studied in a phase I clinical trial. Nine patients with incurable solid tumors were treated: six endometrial and epithelial ovarian cancers, one colon cancer with pelvic masses and two unknown primary cancers. The carboplatin dose was calculated using the Calvert formula and administered in a standard 30-min intravenous infusion. The initial carboplatin dose was AUC 4.0 mg/ml per min. Fixed doses of ifosfamide (1.25 g/m^2 per day), mesna (1.0 g/m^2 per day, and doxorubicin (15 mg/m^2 per day) were combined and given as a 4-day continuous intravenous infusion in an attempt to decrease nonhematologic toxicity. The dose-limiting toxicity of CIA was myelosuppression, mainly neutropenia and thrombocytopenia. Nonhematologic toxicities were hemorrhagic cystitis, weakness, fatigue, and nausea and vomiting. The MTD for CIA was established at the first dose level of carboplatin (4.0 mg/ml per min). Following this, G-CSF was added to the regimen in an unsuccessful effort to escalate the carboplatin dose. Free and total carboplatin pharmacokinetics were determined using flameless atomic absorption spectroscopy. There was one complete response and one partial response among eight evaluable patients. Both responding patients had advanced ovarian cancer. We conclude that carboplatin dose intensification beyond an AUC of 4.0 mg/ml per min is not made feasible by the addition of G-CSF to infusional doxorubicin and ifosfamide in patients with advanced gynecologic cancer.

Key words Carboplatin · Ifosfamide · Doxorubicin · G-CSF · Combination regimen

Introduction

Carboplatin, ifosfamide and doxorubicin, are three of the most active anticancer agents in solid tumor chemotherapy. Combinations of these drugs, for example, the MAID regimen (mesna, Adriamycin, ifosfamide, and dacarbazine), have demonstrated efficacy against solid tumors, specifically sarcoma [1]. However, myelosuppression is often serious, especially in the elderly patient [2].

Ifosfamide and doxorubicin have proven active as single agents in the treatment of advanced gynecologic [3] as well as soft tissue and endometrial sarcomas [4]. However, the other alkylating component of the MAID regimen, dacarbazine, has demonstrated only limited activity in other solid tumors when used as a single agent. We therefore chose to determine the maximally tolerated doses of a drug combination of ifosfamide and doxorubicin with the addition of carboplatin. Carboplatin has proven to be a potent chemotherapeutic agent with good response rates in ovarian and lung cancer. To ameliorate the anticipated myelosuppression and allow higher drug doses, G-CSF was to be added after defining the maximum tolerated dose (MTD) of the three-drug combination.

Fixed doses of ifosfamide and doxorubicin were used in this study. Total ifosfamide doses of 5 g/m^2 and doxorubicin doses of 60 mg/m^2 were employed, as in the MAID regimen [5]. The ifosfamide and doxorubicin doses were delivered via a 4-day continuous infusion in an attempt to decrease nonhematologic toxicities of

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doxorubicin (cardiac) and ifosfamide (renal and neurologic) [6].

This phase I clinical and pharmacologic trial of carboplatin, ifosfamide, doxorubicin with and without G-CSF in patients with incurable solid tumors or soft tissue sarcomas had the following objectives: (1) to determine the MTD of carboplatin with and without G-CSF, (2) to determine the duration of hematologic toxicities associated with this regimen, (3) to evaluate nonhematologic toxicities, and (4) to evaluate the accuracy of the carboplatin AUC estimate calculated using the Calvert formula by measuring free and bound carboplatin levels in plasma by atomic absorption spectrometry.

Patients and methods

All carboplatin doses were determined based upon a targeted plasma concentration area under the curve (AUC) using the Calvert formula [7]. The Calvert formula allows for adjustment of the carboplatin dose on the basis of kidney function. Calvert et al. have used the AUC to adjust the carboplatin dose, as a single agent or in combination with other chemotherapeutic agents, while maintaining safe levels of myelosuppression. The Calvert formula assumes a fixed non-renal clearance of carboplatin of 25 ml/min. It is defined as follows: carboplatin dose (total mg) = carboplatin AUC × (GFR + 25) where the glomerular filtration rate (GFR) can be measured or estimated from serum creatinine levels.

The initial dose of AUC 4 mg/ml per min was selected because it is well tolerated in patients who have had heavy, prior chemotherapy exposure and who will be receiving combination chemotherapy [6]. Additionally, at the maximally tolerated dose of carboplatin, we evaluated the accuracy of the Calvert formula in predicting the actual assayed amount of carboplatin ultrafiltrate in plasma.

Patient selection

All subjects were required to have histologic proof of advanced-stage malignant solid tumor or soft tissue sarcoma not curable with surgery, radiation therapy or standard chemotherapy. In addition, all participants had to have a performance status of 2 or less (ECOG), to be greater than 18 years of age, and to have an anticipated life expectancy of at least 12 weeks. Measurable disease, while desired, was not required. Patients were required to have adequate bone marrow function (total white cell count greater than 4000/μl and platelets greater than 100,000/μl), liver function (total serum bilirubin less than 2.0 mg/dl), and renal function (serum creatinine less than 2.0 mg/dl). Patients who had received prior doxorubicin therapy were excluded, as were those with previous myocardial infarction. All participants were informed of the experimental nature of the study and provided consent in accordance with institutional and federal guidelines.

Pretreatment evaluation and follow-up studies

Before each course of treatment, a complete history and physical examination were performed. Weekly laboratory studies included complete blood count (CBC), differential white blood count (WBC), platelet count, chemistries (including renal and liver function studies), appropriate serum tumor marker, and urinalysis. Twice-weekly CBC, differential WBC, and platelet counts were evaluated in patients receiving G-CSF. Radiologic studies to evaluate tumor response were performed prior to every third course of treatment.

Study design

A minimum of three patients were to be studied at each carboplatin dose level. Carboplatin doses were combined with fixed doses of ifosfamide/mesna and doxorubicin. Toxic side effects were graded based on the Common Toxicity Criteria (SWOG) [8]. If significant toxicity (grade 2 or greater) was observed, an additional three patients were to be treated at that same dose level. The MTD was defined as the dose level at which the majority of patients experienced a dose-limiting toxicity of at least moderate severity (grade 3 or more). Once the MTD was established, G-CSF was to be added to the regimen in an effort to escalate the carboplatin dose further and allow additional courses of chemotherapy. Dose reductions for myelotoxicity were performed on subsequent courses as shown in Table 1.

Patients were able to continue study treatment as long as their disease did not progress and a cumulative doxorubicin dose of 750 mg/m^2 (given by continuous infusion) was not exceeded. Criteria for removal of patients from the study included disease progression after two courses of therapy, development of unacceptable toxicity, or patient decision to withdraw from the study. All patients treated were evaluated for toxicity. All treatment courses were administered in the outpatient setting.

Drug administration

Carboplatin was administered by a 30-min intravenous (i.v.) infusion on day 1 of each course. The target AUC of 4.0 mg/ml per min was derived from the Calvert formula using the Cockcroft-Gault method of estimating GFR using serum creatinine levels.

Ifosfamide 1.25 g/m^2 per day, mesna 1.0 g/m^2 per day, and doxorubicin 15 mg/m^2 per day were combined in 1 l normal saline and administered over 24 h by continuous i.v. infusion. The infu-

Table 1 Dose adjustments

Parameter	Value	Dose adjustment		
		Carboplatin	Doxorubicin	Ifosfamide
Platelet nadir (cells/mm^3)	≥25,000	100%	100%	100%
	<25,000, uncomplicated	75%	75%	75%
	<25,000, with bleeding	50%	50%	50%
Total WBC nadir (cells/mm^3)	Does not drop to <1000 for 5 consecutive days	100%	100%	100%
	<1000 for 5 consecutive days or more	G-CSF dose increased to 10 μg/kg/day		
	<1000 for 5 consecutive days or more after G-CSF	75%	75%	75%

sion began immediately after the carboplatin administration. Drug administration took place over four consecutive days. An ifosfamide dose of 1.25 g/m^2 per day for 4 days was used, since in combination, doses of 1–5 g/m^2 over 3–5 days have demonstrated efficacy [9].

Mesna 500 mg/m^2 was administered i.v. over 15 min at the beginning and at the end of the continuous 4-day doxorubicin/ifosfamide infusion. Normal saline (2 l) was given prior to the start of drug administration and 1 l normal saline was infused at the end of the continuous infusion on day 4. Fluid needs were assessed for each individual on a daily basis. An additional liter of intravenous normal saline was provided as necessary. In addition, patients were directed to drink at least 2 l of fluid each day of treatment.

Once the MTD of the three-drug combination was established, self-injected, subcutaneous G-CSF was added to the regimen in an effort to escalate the carboplatin dose. The initial dose of G-CSF was 5.0 μg/kg per day beginning on day 2 of a treatment course. Dosing continued until the post-nadir absolute neutrophil count (ANC) recovered to ≥10,000/μl on two successive determinations. If after discontinuation of G-CSF, the ANC dropped below 1500/μl, G-CSF was restarted at half dose (2.5 μg/kg per day) until the ANC recovered to a range of 5,000/μl to 10,000/μl. If the ANC remained ≤1000/μl for five consecutive days during a course of therapy, the G-CSF dose was increased to 10 μg/kg per day for all subsequent courses.

Carboplatin pharmacokinetics

Plasma samples were collected from each patient during the initial course of therapy for pharmacokinetic studies of carboplatin. Peripheral venous blood samples (7–10 ml) were drawn at 5, 15, and 45 min and 2.75, 3.75, 4.75, 6.75, 8.75 and 24 h after the carboplatin infusion. The blood was centrifuged immediately at 2000 rpm in Centriflo ultrafiltration cones (CF-50; Amicon, Danvers, Mass.) at 4 °C for 20 min. Both the ultrafiltered sample and the remaining plasma sample were stored at −20 °C until the time of assay at which time an aliquot of the supernatant plasma was processed immediately for determination of the non-protein-bound free platinum.

Carboplatin plasma assays

Platinum measurements were performed using the method of Priesner et al. [10] as modified by Xu et al. [11]. A Perkin-Elmer model Zeeman/3030 atomic absorption spectrophotometer (Norwalk, Conn.) was used for this assay. The relative standard deviation of the method was 4% and the detection limit was 5 ppb. The AUCs achieved using the Calvert formula were statistically compared with the desired AUC of 4.0 mg/ml per min using a one-sample *t*-test performed on untransformed AUC values, and on natural log transformations to reduce skewness. An alpha value of 0.05 was used to assume statistical significance.

Results

Patient characteristics

A total of nine female patients were entered onto this trial. Patient characteristics are outlined in Table 2. The median age was 52 years with a range of 37 to 67 years. Eight patients had measurable disease and had received at least two prior chemotherapy regimens. Six patients had epithelial type ovarian cancer. One patient had colon cancer with pelvic metastases. The remaining two patients had a metastatic primary tumor of unknown origin. All patients had an ECOG performance status of 0 or 1.

Table 2 Patient characteristics

	Number of patients
Patients entered	9
Assessability	
Toxicity	9
Response	8
Age	
Median	52 years
Range	37–67 years
Sex	
Male	0
Female	9
Performance status (ECOG)	
0	2
1	7
2	0
Primary site	
Ovarian	6
Colon with pelvic metastases	1
Unknown primary	2
Previous therapy	
Surgery	6
Chemotherapy	9
Radiation	0

Toxicity

The dose-limiting toxicity of the three-drug chemotherapy combination was myelosuppression, characterized by grade 4 neutropenia and grade 3 thrombocytopenia. Nadir neutrophil and platelet counts occurred between day 8 and day 15. The nadir period lasted for 2 to 13 days with an average of 6 days after the first course of treatment. In three patients, recovery occurred by day 28 allowing administration of the second course of therapy, as scheduled. For the remainder of the patients, course 2 was delayed by 2–3 weeks to allow the recovery of leukocytes to ≥4000/μl.

The MTD of carboplatin when combined with fixed doses of ifosfamide and doxorubicin was defined after the first three patients were entered at dose level 1 (carboplatin AUC 4 mg/ml per min). The addition of G-CSF in six other patients allowed more rapid resolution of neutropenia to leukocytes >10,000/μl after approximately 8–11 days of G-CSF therapy. The addition of G-CSF did not significantly reduce the severity of myelosuppression; therefore, further escalation of the carboplatin dose was not possible. Although, the six patients who received G-CSF prophylactically had a more rapid resolution of neutropenia, they still required a 25% dose reduction in subsequent courses due to severe or life-threatening thrombocytopenia and neutropenia. One patient completed three courses of CIA with G-CSF support at full doses. Grade 3 myelosuppression occurred after the third course. This patient was removed from the study because of progressive disease.

The first three patients, at dose level 1 did not receive prophylactic G-CSF. They experienced grade 3 and 4 leukopenia and thrombocytopenia. The third patient

developed grade 4 neutropenia and consequently underwent G-CSF rescue on day 9. All subsequent patients received prophylactic G-CSF at dose level 1 (AUC 4 mg/ml per min) with grade 3 and 4 leukopenia and thrombocytopenia continuing during the first course. When doses of carboplatin, doxorubicin, and ifosfamide were decreased by 25%, grade 3 and 4 hematologic toxicity persisted in three patients (33%).

Cumulative myelosuppression was observed in this study. Of the four patients who received more than two courses of therapy with prophylaxis, three eventually developed grade 4 neutropenia and grade 3 thrombocytopenia. Four patients (44%) were hospitalized with neutropenic fever. Two patients developed grade 4 thrombocytopenia and required platelet transfusions. Bleeding from thrombocytopenia was not observed. Decreased hemoglobin level was seen in only patient, secondary to severe hemorrhagic cystitis. This patient required red blood cell transfusions.

Nonhematologic adverse effects related to carboplatin, ifosfamide and doxorubicin combination are summarized in Table 3. Tolerance to the combination of drugs was generally good, with most nonhematologic toxicities being mild to moderate (grade 1 or 2). The most common nonhematologic toxicities were nausea and vomiting (60%), fever (60%), weakness and fatigue (40%), constipation (33%), and cystitis (20%). Cystitis occurred in two patients, one of whom developed severe hemorrhagic cystitis necessitating withdrawal from the study. Further problems with cystitis may have been avoided by instituting more aggressive hydration: oral intake of 2 l per day and 1 l normal saline i.v. per day. Other side effects were edema (20%), stomatitis (10%), and anxiety (10%).

Response

Eight patients were evaluable for response. The ninth patient was removed from the study during the second course of therapy due to grade 3 hemorrhagic cystitis. Two (25%) objective responses were seen. One patient with stage III ovarian cancer experienced a complete response with no clinical evidence of disease after four courses of treatment. She received an additional three courses of combination chemotherapy and had no clinical evidence of disease after 9 months of follow-up. One patient with ovarian cancer experienced a partial response after two courses. She was removed from the study after the third course secondary to life-threatening myelosuppression. Two patients had stable disease after two courses of treatment; however, disease progression was identified during the third and fourth treatment cycle, respectively. Four patients developed progressive disease after two courses of treatment.

Table 3 Summary of nonhematologic toxicities (grade 3 or greater)

Toxicity	Grade	Number of patients
Fever	1	3
	2	2
	3	1
Diarrhea	1	1
	3	1
Cystitis	3	1
Hematuria	3	1

Carboplatin pharmacokinetics

Free (ultrafilterable) and total plasma carboplatin pharmacokinetics in the eight patients for whom adequate blood samples were available for carboplatin assay are summarized in Table 4. Platinum pharmacokinetics could be modeled in six patients. For free carboplatin, the mean ($\pm$SD) terminal phase half-life, AUC, volume of distribution and clearance rate were 7.85 $\pm$ 7.73 h, 3.35 $\pm$ 0.71 mg/ml per min, 80.39 $\pm$ 79.58 l and 7.09 $\pm$ 0.82 1/h, respectively. For total plasma carboplatin, the mean terminal phase half-life, AUC, volume of distribution and clearance rates were 46.45 $\pm$ 57.11 h, 11.24 $\pm$ 8.82 mg/ml per min, 107.74 $\pm$ 75.56 l and 2.86 $\pm$ 1.62 1/h, respectively. Free carboplatin AUCs ranged from 2.53 to 4.35 mg/ml per min or 63% to 109% of the target AUC. Thus the mean AUC value of 3.35 mg/ml per min underestimated the desired target AUC of 4.0 mg/ml per min by an average of 16%, but the mean difference was not statistically significant. The *t*-test value for the untransformed AUCs was 0.0778 and for the natural log-transformed AUCs, 0.0748.

Table 4 Plasma pharmacokinetics of carboplatin dosed according to the Calvert equation[a] using an AUC of 4 mg/ml per min

Patient no.	k (h_1)	$t_{1/2}$ (h)	AUC (mg/ml per min)	v_d (1)	Cl (1/h)
Free carboplatin					
1	0.21	3.31	3.51	31.66	6.63
2	0.44	1.57	3.02	16.91	7.49
3	0.25	2.82	2.71	30.40	7.46
4	0.10	6.73	4.35	56.43	5.81
5	0.07	10.50	2.53	124.21	8.20
6	0.03	22.18	3.97	222.74	6.95
Mean	0.18	7.85	3.35	80.39	7.09
SD	0.15	7.73	0.71	79.58	0.82
Total carboplatin					
1	0.02	35.53	9.78	122.05	2.38
2	0.00	169.43	32.06	172.49	0.71
3	0.02	37.51	9.74	112.23	2.08
4	0.11	6.31	9.96	23.02	2.53
5	0.01	91.03	10.88	252.18	1.92
6	0.05	13.50	8.53	63.10	3.24
7	0.15	4.56	2.69	40.34	6.13
8	0.05	13.72	6.27	76.54	3.87
Mean	0.05	46.45	11.24	107.742	2.855
SD	0.05	57.11	8.82	75.562	1.617

[a] Calvert equation: carboplatin dose (total mg) = carboplatin AUC $\times$ (25 + glomerular filtration rate) [7]

Discussion

This study determined the MTD of carboplatin in combination with fixed doses of ifosfamide/mesna and doxorubicin with and without G-CSF to be AUC 4 mg/ml per min. Mean ultrafilterable carboplatin plasma AUCs measured by atomic absorption were an average of 16% below the desired carboplatin plasma AUC calculated by the Calvert equation. This discrepancy may be related to the known underestimation of creatinine clearance by both the Jelliffe and Cockroft-Gault equations for patients with relatively normal renal function [12, 13, 14].

This differs from slight overestimation of carboplatin AUC values when GFR is estimated using the Cr-EDTA radioisotope method of Calvert et al. [7]. Chatelut et al. [15] found that other methods of estimating GFR, such as renal scintigraphy using 99mTc-DTPA, and serum creatinine by the Cockcroft-Gault method, consistently underestimate carboplatin clearance and therefore slightly underestimate carboplatin doses when used in AUC-directed dosing schemes. This is compatible with the current findings. The fact that the MTD of carboplatin was achieved at the first dose level in the current trial, and the observed AUC was only 3.35 mg/ml per-min, the tolerability of this regimen may be reduced if more precise AUC estimation methods are employed.

The CIA regimen plan was best tolerated in individuals who had not received multiple prior chemotherapy exposures. The dose-limiting toxicity was myelosuppression, characterized by neutropenia and thrombocytopenia. Seven of nine patients (77%) who had heavy prior chemotherapy exposure experienced grade 3/4 myelosuppression with the first course of the present therapy. At this dose level, seven patients required a 25% dose reduction for subsequent cycles of therapy. Seven patients experienced grade 3 neutropenia (ANC $<500/\mu l$). While five patients had grade 4 thrombocytopenia (platelet counts $<50{,}000/\mu l$). This is similar to the degree of myelosuppression observed with the MAID regimen.

The most common nonhematologic toxicities were nausea, vomiting and fever (60%), weakness and fatigue (49%), and constipation (33%). Five patients (55%) experienced treatment-related grade 1–2 infections toxicity. Despite hydration and mesna, hemorrhagic cystitis was identified in 22% of patients. One patient experienced grade 3 cystitis resulting in withdrawal from the study. The inclusion of mesna in the infusion solution might provide greater efficacy than the pre-/postinfusion dosing schedule used in the current study. In addition, grade 1–2 edema (22%), diarrhea (22%), anxiety (11%), anorexia (11%), and stomatitis (11%) were noted (Table 3).

The MTD of carboplatin with near-optimal doses of ifosfamide and doxorubicin with and without G-CSF is AUC 4 mg/ml per min in gynecologic cancer patients who have received prior chemotherapy. Since this regimen was active and no major organ toxicities other than hemorrhagic cystitis were seen, continued clinical evaluation of this regimen is justified.

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