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A phase I trial of 14-day continuous intravenous infusion mitoxantrone

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Based on clinical evidence that prolonged exposure to anti-neoplastic agents may ameliorate dose-limiting toxicity while facilitating anti-tumor activity, we conducted a phase I trial of 14-day continuous intravenous infusion mitoxantrone. Study objectives were to: (1) determine the maximally tolerated dose for phase II trials; (2) determine the incidence and severity of side effects; and (3) study the pharmacokinetics of continuous infusion mitoxantrone. Sixteen patients with drug-resistant advanced cancers were entered into the trial. Three or more patients were treated at each dose level (1.0, 1.25, and 1.5 mg/m^2/day) for a total of 33 courses (mean 2.1 courses/patient, range, 1–4). Courses were repeated every 4 weeks. The maximally tolerated dose (MTD) was found to be 1.5 mg/m^2/day. At this dose four of six patients had grade III or IV leukopenia (mean WBC nadir 1900/μl, range, 800–3600/μl). Other toxicities were grade I or II stomatitis (two patients), grade I diarrhea (one patient), and grade I nausea (one patient). Renal and hepatic toxicity were not observed. No alopecia or infectious complications occurred. Pharmacokinetic studies were performed using high-performance liquid chromatography (HPLC). Steady-state plasma levels at the 1.5 mg/m^2/day dose were reached by 48 h, with a mean steady-state plasma concentration of 3.2 ± 0.7 ng/ml, mean total body clearance of 340 ± 79 ml/min/m^2, and mean area under the plasma disappearance curve (AUC) of 955 ± 185 μg h/l. No responses were observed, although no patients with mitoxantrone-sensitive tumors were treated. We recommend proceeding with phase II trials in clinically responsive tumors using a 14-day continuous intravenous infusion with a starting dose of 1.5 mg/m^2/day.

Key words: Infusion, mitoxantrone, phase I trial.

Introduction

Mitoxantrone is a unique anti-tumor agent that was synthesized in two separate research laboratories in an attempt to find an anthracene analog with preserved tumoricidal activity but fewer side effects than the parent anthracycline compound, doxorubicin.[1–3] Mitoxantrone was found to have a broad spectrum of curative activity in a variety of murine tumor models and the ability to inhibit DNA replication through two different mechanisms: (1) DNA intercalation with inhibition of DNA and RNA synthesis;[4,5] and (2) non-intercalative electrostatic DNA interaction with resultant strand scission.[5–7]

Ensuing clinical trials using mitoxantrone found it to have useful clinical activity in acute non-lymphocytic leukemia,[8–10] metastatic breast cancer,[11,12] non-Hodgkins lymphoma,[13–15] and hepatoma,[16,17] with eventual FDA approval in 1988 for

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the treatment of acute myelogenous leukemia. Early phase I studies concentrated on the pharmacokinetics of intravenous (i.v.) bolus administration given as a single or divided dose over 3 consecutive days.[18–21] These studies established the maximally tolerated dose (MTD) to be 12–14 mg/m^2 in patients with solid tumors. At this dose mitoxantrone is well tolerated, with leukopenia the dose-limiting toxicity. Adverse effects encountered commonly with other anti-cancer agents, such as alopecia, nausea and vomiting, and mucositis, are infrequent with mitoxantrone (<20%).[18–21] Most notably, the incidence of cardiotoxicity was significantly lower than that of doxorubicin at cumulative, equimyelotoxic doses.[22,23]

In recent years a number of clinical studies using continuous infusions of anti-cancer agents have documented advantages to this method of drug delivery. Anti-tumor activity may be increased using continuous intravenous infusion schedules, as in the treatment of colon cancer with 5-fluorouracil (5-FU),[24] breast cancer with vinblastine,[25] and acute leukemia with cytosine arabinoside (Ara-C).[26] Drug toxicities also may be diminished using continuous intravenous infusion therapy. Legha *et al.* determined that the frequency of morphological changes on cardiac biopsy consistent with doxorubicin toxicity was substantially reduced in the infusion-treated patients as compared to the intravenous bolus group (9% versus 45%, respectively).[27]

Based upon these findings, we performed a phase I study using a 14-day continuous intravenous infusion of mitoxantrone to determine the maximally tolerated dose for phase II trials, as well as its toxicity profile and pharmacokinetics.

Methods

Patients

A total of 16 patients with advanced malignancies were registered on this phase I study. Each patient satisfied the following eligibility criteria:

(1) histologic documentation of malignancy;
(2) failed conventional therapy;
(3) ECOG performance status of 0 or 1;
(4) pre-treatment WBC equal to or greater than 3500/μl and platelet count equal to or greater than 150 000/μl;
(5) a minimum of three weeks elapsed from the time of any prior therapies (chemotherapy, radiation, or surgery); and
(6) normal renal and hepatic function.

Patients with one or more of the following criteria were excluded from study enrolment:

(1) a cumulative dose of 300 mg/m^2 or greater of doxorubicin;
(2) prior chemotherapy regimens containing mitoxantrone;
(3) history of myocardial infarction or congestive heart failure; and
(4) radiotherapy to 50% or more of the pelvic bony structures and/or axial skeleton.

Informed consent was obtained from all patients. The study was approved by the Human Subjects Committee of the University Medical Center and Veterans Administration Medical Center, Tucson, Arizona.

Drug administration

Continuous intravenous drug administration was facilitated by an indwelling central venous catheter and a portable infusion pump (Provider 2000, Pancretec Inc., San Diego, CA). Mitoxantrone (Novantrone^{TM}, Lederle Laboratories, Pearl River, NY) was supplied in 10 ml vials containing 2 mg/ml. The total dose to be delivered in the 14-day infusion period was diluted with normal saline to a total volume of 500 ml. The solution was contained in a 500 ml IV solution bag (Travenol Inc., Deer Valley, IL) and administered via extension tubing with a luer lock connection to the indwelling venous catheter. The tubing passed through the portable pump, which was programmed to deliver the mitoxantrone solution as a continuous infusion over a 14-day period (336 h). The treatment was delivered on an out-patient basis, with visits to the Cancer Center or Veteran Administration clinics every 2 days.

The starting dose of mitoxantrone was 1.0 mg/m^2/day for 14 days (total dose 14 mg/m^2). A minimum of three patients were enrolled at each drug level. Successive courses of treatment were administered every four weeks if there was no evidence of disease progression or unacceptable toxicity. Treatment was delayed if leukopenia or thrombocytopenia persisted after four weeks, and the next course was administered upon hematologic recovery.

Mitoxantrone dose was escalated in 0.25 mg/m^2/day increments in sets of at least three patients. Dose escalation was allowed to proceed if no grade III toxicity occurred in the first three patients enrolled. The maximally tolerated dose (MTD) was defined as the dose at which 50% or more of the patients experienced grade III or greater toxicity. The dose could be escalated to the next level for an individual patient if one course was completed without significant toxicity and at least two additional patients were evaluable for toxicity at the next dosage level.

The World Health Organization (WHO) grading system was used for toxicity monitoring.[28] The criteria for grading leukopenia toxicity are summarized in Table 2. WBC count and differential, platelet count, serum chemistries and liver function tests were obtained on days 1, 7, 14, 21 and 28 of each 28-day cycle. Nuclear medicine multigated analysis (MUGA) of left ventricular function was required of each patient prior to the first dose of mitoxantrone and after every two treatment courses. Patients experiencing grades III or IV hematological toxicity, diarrhea or mucositis had the dose of subsequent courses reduced by 50%. Treatment for an individual patient was discontinued when there was objective evidence of disease progression or unacceptable toxicity. At least five patients were to be treated at the final dose of mitoxantrone selected for phase II trials.

The following criteria were used to define treatment response:

(1) complete response, disappearance of all clinical evidence of disease without appearance of new sites of disease for at least 4 weeks;
(2) partial remission, greater than 50% reduction in the sum of the products of two perpendicular diameters of all measurable tumors for at least 4 weeks (no tumor could progress or new tumors appear);
(3) stable disease, less than 50% reduction or 25% increase in the sum of the products of all measurable lesions; and
(4) disease progression, appearance of new lesions or an increase of 25% or more in the product of the two perpendicular products of any measurable lesion.

Pharmacokinetics

At each dose level at least one patient had blood samples drawn for pharmacokinetics on days 1 (pretreatment), 3, 5, 7, 9, 12 and 14 during one course of treatment. Blood samples were drawn into heparinized tubes, immediately placed on ice, and processed to separate the plasma, which was then frozen at −20°C for mitoxantrone analysis.

Plasma concentrations of mitoxantrone were determined by a high-performance liquid chromatography (HPLC) method reported previously by Peng *et al.*,[29] with several modifications. A VAC-ELUT system equipped with a BOND-ELUT 1 ml C18-Bondapak reversed-phase column preceded by a guard column packed with CO:PELL octadecyl silane (Whatman Inc., Clifton, NJ) was used for all sample analyses. Mitoxantrone was eluted isocratically at ambient temperature with a solvent composition of 20% CH_3CN and 80% phosphate buffer (0.2 M, pH 2.3) at a flow rate of 2.5 ml/min. Mitoxantrone was detected at 658 nm using a Kratos model 773 fixed-wavelength detector equipped with a tungsten lamp (Kratos Analytical Instruments, Ramsey, NJ). Quantitation of mitoxantrone was done by the external standard method of analysis. Plasma standard curves were obtained by plotting the resulting peak height against the known concentration of standards added to blank plasma samples from unrelated subjects.

Plasma pharmacokinetic analysis

The steady-state plasma level of mitoxantrone was reached by 48 h (first blood draw) in every patient studied. For each patient, clearance was determined by dividing the mean steady-state plasma concentration by the 14-day infusion rate of mitoxantrone. Area under the plasma disappearance curve (AUC) was calculated using a computer program using the trapezoid method to integrate the area under the steady-state plasma concentration versus time curve from time 0 to the last sampling time point (day 14 = 336 h). Because post-infusion samples were not collected, terminal phase half-life and volume of distribution could not be determined.

Results

Patient characteristics

Sixteen patients were enrolled in this phase I study from April 1989 to January 1990. Patient characteristics and information concerning diagnosis and treatment are presented in Table 1. There were ten male and six female patients with a

Table 1. Patient characteristics and mitoxantrone dosing data

Patient no.	Age	Sex	Tumor diagnosis	No. of previous chemo regimens	Dose of infusion mitoxantrone (mg/m^2/day)	No. of courses	Total dose (mg/m^2)
1	60	M	Renal cell	7[a]	1.0	4	56.0
2	53	M	Colon	2[a]	1.0	2	45.5
					1.25	1	
3	52	M	Pancreas	1	1.0	1	14.0
4	69	M	Colon	5[a]	1.25	2	35.0
5	48	F	Colon	5[a]	1.25	2	35.0
6	66	F	Fibrosarcoma	4[a]	1.25	1	17.5
7	59	F	Colon	3[a]	1.5	1	31.5
					0.75[c]	1	
8	72	M	Renal cell	4	1.25	2	32.5
9	61	M	Colon	1	1.25	2	36.25
10	73	M	Colon	2	1.25	1	17.5
11	58	M	Squamous cell of H/N	2	1.25	4	70.0
12	70	F	Ovarian	2	1.5	1	21.0
13	65	F	Ovarian	1	1.5	2	42.0
14	41	M	Small cell lung	5[a]	1.5	3	64.5
15	34	M	Testicular	2	1.5	1	21.0
16	55	F	Undiff. carcinoma	2	1.5	1	27.0
					0.75[c]	1[b]	

[a] Previous doxorubicin.
[b] Infusion stopped day 8, course 2.
[c] 50% dose reduction.

median age of 59 years (range 34–73). Diagnoses included nine different tumor types in advanced state: six colon carcinoma, two renal cell carcinoma, two ovarian carcinoma, and one each of pancreatic carcinoma, testicular carcinoma, squamous cell carcinoma of the head and neck, undifferentiated carcinoma of unknown primary, small cell carcinoma of the lung, and fibrosarcoma. All patients had received an average of three previous chemotherapy regimens, with seven patients having been treated with doxorubicin-containing therapies. Three patients had also received radiation. All patients had a performance status of 0 or 1 on the ECOG performance scale.

Infusion mitoxantrone doses and courses

An average of 2.1 courses of treatment were delivered per patient for a total of 33 courses. Two courses were not evaluable because of failure to obtain appropriate blood draws (patient 1, course 4; patient 11, course 4), one due to termination of therapy on day 12 for deterioration of performance status (patient 8, course 2), and one because of pump malfunction on day 11 resulting in an inadvertent bolus of the remaining dose (patient 5, course 2). The second course for patient 16 was stopped on day 8 for neutropenia with fever. Therefore, a total of 28 courses were evaluable. One patient had dose escalation to the next level for his second course as allowed by the protocol (patient 2), while one patient required a 50% dose reduction after experiencing grade IV leukopenia with the first course at 1.5 g/m^2/day (patient 7). Fourteen out of 16 patients received all courses at the dosage level at which they were entered on study.

Toxicity data associated with infusion mitoxantrone

The criteria used for the grading of myelotoxicity, diarrhea, and mucositis are presented in Table 2. The toxicity data separated by mitoxantrone dose level are shown in Table 3. Patient 7 received the only course administered at 0.75 mg/m^2/day in the study after suffering grade IV leukopenia with the first course of 1.5 mg/m^2/day. Grade II leukopenia and grade I stomatitis were still observed following the 50% dose reduction. Three patients received a

Table 2. Hematologic and gastrointestinal toxicity grading criteria

System	Grade 0	Grade I	Grade II	Grade III	Grade IV
Hematologic					
A. WBC/μl	>4 000	3 000–3 999	2 000–2 999	1 000–1 999	<1 000
B. Platelets/μl	>100 000	75 000–99 999	50 000–74 000	25 000–49 999	<25 000
C. Hemoglobin, gμ%	>10.0	9.0–9.9	7.0–8.9	5.0–6.9	<5.0
Gastrointestinal					
A. Diarrhea	<3 BM daily	3–4 liquid stools	>4 liquid stools Dehydration Requires i.v. fluids	Bloody diarrhea Requires i.v. fluids ± blood transfusions	
B. Stomatitis	Normal	Erythema	Ulcers; able to eat	Unable to eat because of ulcerations	
C. Nausea and vomiting	Normal	Nausea; no vomiting	Vomiting (<6 × day); controlled with antiemetics	Vomiting >6 × day; uncontrolled with antiemetics	

total of six courses of treatment at the 1.0 mg/m^2/day dose. Grade II leukopenia occurred in two patients, grade I leukopenia, anemia, diarrhea, and nausea and stomatitis in one patient each.

Eight patients were enrolled on the 1.25 mg/m^2/day level for a total of 12 evaluable courses. At this dose level, two out of the first three patients experienced grade III or IV leukopenia; therefore it was decided to enroll an additional five patients. The toxicities observed included grade III leukopenia in three patients, grade II in one patient, and grade I in four patients. One patient developed a grade II anemia following the third cycle.

Table 3. Hematological and gastrointestinal toxicities

	Dose (mg/m^2/day)			
	0.75	1.0	1.25	1.5
No. of evaluable patients	1	3	8	6
No. of evaluable cycles	1	6	12	9
Leukopenia				
Grade I		4	4	1
II	1	2	1	
III			3	3
IV				1
WBC nadir for grades I–IV				
Median (/μl)		3016	2663	1900
Range		2100–3800	1200–2900	800–3600
Anemia				
Grade I		1	1	2
II				
Diarrhea				
Grade I		1		1
II				
Stomatitis				
Grade I		1		1
II				1

In addition to grade III leukopenia, patient 2 experienced an elevation of total bilirubin (0.6 mg/dl to 7.1 mg/dl), SGOT (50 mg/dl to 157 mg/dl) and alkaline phosphatase (775 mg/dl to 1036 mg/dl) during his third course at the 1.25 mg/m^2/day dose level. The liver function abnormalities were attributed to progression of disease since they failed to correct after stopping mitoxantrone treatment. Computerized tomography (CT) of the liver documented marked progression of liver metastasis compared to pre-treatment CT.

Three courses at 1.25 mg/m^2/day were not evaluable. Patient 5 had a pump malfunction with course 2 resulting in a drug bolus on day 11 which may have contributed to the development of a grade IV leukopenia (WBC 0.9/μl) on day 14. Patient 11 failed to have mid-course blood draws performed with course 4, and patient 8 had the second course terminated on day 12 for deterioration in clinical condition.

Six patients received a total of nine evaluable courses at the 1.50 mg/m^2/day dose level. Three of six patients had grade III leukopenia, one grade IV, and one grade I. All patients with grade III or IV leukopenia experienced nadirs at mid-cycle (day 14) with recovery by day 28. The mean WBC nadir

in patients with grade I–IV leukopenia was 1900/μl (range 800–3600/μl). Patient 14 received three mitoxantrone courses at 1.5 mg/m^2/day with no evidence of myelosuppression (lowest WBC nadir 5900/μl). Patients 7, 13, and 16 had mild declines in platelet counts from baseline on day 21 following the first or second courses; however, platelet nadirs never dropped below 100 000/μl (124 000/μl, 133 000/μl, and 146 000/μl, respectively). Other toxicities observed at 1.5 mg/m^2/day were minimal: grade I nausea in two patients, grade I or II stomatitis in two patients, and grade I diarrhea in one patient. There were no instances of hepatic or renal toxicity on the basis of weekly blood chemistry and liver function test results. Patient 16 had the second course stopped on day 8 because of progressive leukopenia (WBC 3.4 and 2.3/μl on days 1 and 8, respectively) and fever. All bacterial cultures were negative and the patient's fever resolved on antibiotics by day 14 with recovery of WBC count to baseline.

Left ventricular dysfunction, as assessed by MUGA scan after course 2, was not observed, though the maximal total dose received by any one patient was only 70 mg/m^2. Two patients experienced complications with their central venous catheters. Patient 4 had to have a second catheter placed after the first clotted off. Patient 14 developed a left subclavian thrombosis requiring heparin and coumarin therapy. No treatment-related alopecia or infections were observed.

At the 1.5 mg/m^2/day dose level, four out of six patients experienced grade III or greater leukopenia; therefore 1.5 mg/m^2/day was considered to be the maximally tolerated dose of mitoxantrone that could be administered as a 14-day continuous intravenous infusion.

Treatment response

No objective responses were observed in the 16 treated patients. Fourteen patients were taken off study because of disease progression. The remaining two patients had stable disease when they chose to discontinue treatment.

Plasma pharmacokinetic results

The plasma concentrations of mitoxantrone of the three patients studied at the 1.0 mg/m^2/day dose level were inconsistent as a result of improper collection and processing (i.e. blood draws through the central drug administration line). With the proper method of collection, the plasma concentrations at the 1.25 and 1.5 mg/m^2/day dose levels were consistent and evaluable (Table 4). Five patients at the 1.25 mg/m^2/day dose and three at 1.5 mg/m^2/day were studied. Steady-state plasma levels were reached by 48 h of the 14-day infusion (sample 1) in all patients. There was no evidence of drug accumulation from one treatment course to the next. At 1.25 mg/m^2/day, the mean steady-state plasma level was 1.8 $\pm$ 0.2 ng/ml (range 1.5–2.0 ng/ml), mean plasma clearance 498 $\pm$ 50 ml/min/m^2 (range 441–578 ml/min/m^2), and the mean plasma AUC 462 $\pm$ 146 μg h/l (range 251–627 μg/h/l). At 1.5 mg/m^2/day, the mean steady-state plasma level was 3.2 $\pm$ 0.7 ng/ml (range 2.5–3.9 ng/ml), mean plasma clearance 340 $\pm$ 79 ml/min/m^2 (range 265–423 ml/min/m^2) and mean plasma AUC 955 $\pm$ 185 μg h/l (range 775–1144 μg h/l).

Table 4. Pharmacokinetics of mitroxantrone administration by continuous 14 day intravenous infusion

	Dose (mg/m^2/day)	
	1.25	1.50
Number of patients	5	3
Mean steady-state plasma concentration (ng/ml)	1.8 $\pm$ 0.2	3.2 $\pm$ 0.7
Mean plasma clearance (ml/min/m^2)	498 $\pm$ 50	340 $\pm$ 79
Mean plasma AUC (μg h/l)	462 $\pm$ 146	955 $\pm$ 185

Discussion

Prior to 1989 only one phase I trial reported the pharmacokinetics and toxicity of mitoxantrone given as a continuous infusion.[30] Anderson *et al.* treated leukemia patients with a 24-h continuous intravenous infusion of mitoxantrone. The maximally tolerated dose (12 mg/m^2) and attendant toxicities were similar to that experienced with i.v. bolus administration. Rowland and Sewell first studied the efficacy of continuous mitoxantrone infusion in solid tumor patients.[31] They performed a phase II trial treating patients with metastatic breast cancer using a 14-day infusion at 2 mg/m^2/day. An impressive response rate of 70% was reported; however, follow-up results, including pharmacokinetics, have not been published in manuscript form.

More recently two groups have examined continuous infusion mitoxantrone in clinical trials. Kaminer *et al.* conducted a phase II trial of a 5-day continuous infusion in patients with relapsed or refractory acute myeloid leukemia.[32] Using a myeloablative dose of 12 mg/m^2/day, a mean steady-state plasma level of 16.8 ng/ml was maintained with a clearance rate that was not significantly different from that known to be associated with i.v. bolus administration. The study suggested an enhanced antileukemic effect with a 95% or greater reduction in leukemic cell mass observed in 82% of the patients by day 6. The second study, performed by Greidanus *et al.*, was a phase I trial of a 21-day continuous mitoxantrone infusion.[33] The concentrations of mitoxantrone in plasma and leukocytes were measured during the infusion period, with the objective of determining the correlation between plasma steady state and leukocyte intracellular drug levels. At the maximally tolerated dose of 1.1 mg/m^2/day, mitoxantrone was highly concentrated within leukocytes, with the most significant finding being that an intraleukocyte steady-state concentration was not reached during the 21-day infusion. This confirmed earlier reports of extensive accumulation of mitoxantrone in WBCs and autopsy tissues of patients that were treated with the drug weeks before their death.[34–36]

In the present study using a 14-day continuous intravenous infusion of mitoxantrone we determined that dose-limiting leukopenia occurs at 1.5 mg/m^2/day (total dose of 21 mg/m^2). At this dose, four of six patients experienced grade III or IV leukopenia with a mean WBC nadir of 1900/μl. As might be expected, maximal myelosuppression occurred later in the course of therapy (approximately day 14) than with i.v. bolus; however, leukocyte counts returned to baseline by day 28 in 31 of 33 courses. This permitted treatments to be administered on a 4-week schedule. Other toxicities were minimal. Twenty-five percent of patients experienced mild nausea without vomiting, 12% grade I diarrhea, and 18% grade I or II stomatitis. No alopecia was observed. The 14-day continuous infusion permits significantly more drug to be delivered safely than by i.v. bolus (21 mg/m^2 versus 14 mg/m^2, respectively) with equal or less toxicity.

Compared to the 21-day infusion schedule,[33] the latter provides only the delivery of an additional 2 mg/m^2 of mitoxantrone, while there is a trend to a higher mean steady-state plasma level using the 14-day infusion (i.e. 3.2 versus 2.8 ng/ml, respectively). The present study also documents a significantly higher plasma AUC achieved with continuous infusion than with i.v. bolus (i.e. 955 versus 300 μg h/l, respectively), a difference that can be explained by the ability of the infusion method to deliver a larger dose over a prolonged period of time.

There is strong scientific rationale for administering certain anti-cancer agents by continuous intravenous infusion based on *in vitro* evidence that length of time exposure of cultured tumor cells to anti-neoplastic agents may be as important as peak drug concentrations in determining tumoricidal activity.[37] This has been proven clinically with continuous, long-term intravenous 5-FU infusions in patients with colon cancer, where the single agent i.v. bolus response rate of 10–20% has been significantly improved to 30–40% with continuous infusion.[24] However, the data of Link *et al.* suggest that mitoxantrone may prove as cytotoxic after short-term (i.e. 1 h) versus long-term (i.e. 24 h) exposure to tumor cells *in vitro*.[37]

One discrepancy between our pharmacokinetic data and that of others involves the calculated plasma clearance rate. At 1.25 mg/m^2/day, the mean clearance was 498 $\pm$ 50 ml/min/m^2, dropping to 340 $\pm$ 79 ml/min/m^2 with the dose escalation to 1.5 mg/m^2/day. This is significantly lower than reported with 5-day continuous infusion or i.v. bolus schedules (i.e. 519 ml/min/m^2 and 570 ml/min/m^2, respectively).[32,34] Though large variability can be observed in the clearance of drugs which undergo primary hepatic metabolism, these data raise the possibility of saturation pharmacokinetics occurring between the 1.25 and 1.5 mg/m^2/day mitoxantrone dose levels. More patients would need to be studied at higher dose levels to determine if this trend continues with dose escalation. Drug saturation at a specific dose level is important to recognize, particularly in the setting of high-dose mitoxantrone regimens prior to bone marrow transplantation.

We observed no response in this phase I clinical trial; however, no patients were treated with tumors known to exhibit consistent sensitivity to mitoxantrone. The next step in the development of continuous infusion mitoxantrone as a clinically useful schedule would involve phase II trials in the treatment of tumors with proven mitoxantrone sensitivity, such as breast carcinoma or non-Hodgkins lymphoma. Also, tumors with marginal sensitivity (e.g. non-small cell lung cancer, myeloma, and ovarian cancer) may prove to be much more responsive to continuous infusion delivery than to i.v. bolus.

Conclusions

We conducted a phase I trial of 14-day continuous intravenous infusion mitoxantrone. The maximally tolerated drug dose was determined to be 1.5 mg/m^2/day on a 14-day schedule with severe to life-threatening leukopenia the dose-limiting toxicity. WBC nadir occurred mid-cycle (day 14) with recovery by day 28. Toxicity was equal to or less than intravenous bolus injection, and a larger total dose (21 mg/m^2) could be delivered with a mean steady-state plasma concentration of 3.2 ng/ml. We recommend proceeding with phase II trials to study the response rates of tumors with proven sensitivity to mitoxantrone and neoplasms with marginal response rates that may improve using the continuous infusion approach.

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