Phase I and Pharmacokinetic Study of the Cytotoxic Ether Lipid Ilmofosine Administered by Weekly Two-Hour Infusion in Patients with Advanced Solid Tumors

Bruce J. Giantonio,[1,3] Christine Derry,[2] Cecilia McAleer,[1] Joseph J. McPhillips,[2] and Peter J. O'Dwyer[1,3]

[1]Fox Chase Cancer Center, Philadelphia, Pennsylvania; [2]Boehringer Mannheim Pharmaceuticals Corporation, Rockville, Maryland; and [3]University of Pennsylvania Cancer Center, Philadelphia, Pennsylvania

ABSTRACT

Purpose: **A Phase I trial was performed to determine the dose-limiting toxicity and maximum tolerated dose, and to describe the pharmacokinetics of the alkyl-lysophospholipid, ilmofosine, when administered as a weekly 2-h infusion in patients with solid tumors.**

Experimental Design: **Thirty-nine patients were entered into a trial of ilmofosine administered weekly for 4 weeks followed by a 2-week rest period. Dose escalation occurred in 10 levels from 12 to 650 mg/m^2.**

Results: **Thirty-six patients were evaluable for toxicity. The median number of cycles per patient was 1 (range, 1–4). Dose-limiting gastrointestinal toxicity occurred at 650 mg/m^2 with grade 3 nausea in two patients and grade 3 vomiting and diarrhea in one patient. Grade 2 diarrhea was observed in four of six patients treated at 550 mg/m^2. In addition, two patients treated at 550 mg/m^2 and two patients treated at 650 mg/m^2 experienced a decline in performance status of two or more levels that was determined to be due to treatment. There were no tumor responses. Stabilization of disease for at least 8 weeks occurred in six patients. Plasma concentrations of ilmofosine and its sulfoxide metabolite were evaluated by high-pressure liquid chromatography. The elimination of both compounds was biexponential with terminal half-lives of ~40 h for ilmofosine and 48 h for the sulfoxide. The area under the concentration-time curve was dose-proportional for each compound, and there was no evidence of saturable kinetics.**

Conclusions: **The dose-limiting toxicity of ilmofosine is gastrointestinal and the recommended dose for Phase II trials is 450 mg/m^2 as a 2-h weekly infusion. The relatively long half-life of ilmofosine and its active metabolite support the use of this intermittent schedule.**

INTRODUCTION

Ilmofosine (BM 41.440, 1-hexadecylthio-2-methoxymethyl-rac-glycero-3-phosphocholine) is a thioether lysophospholipid derivative of lysophosphocholine, a component of cellular membranes. The mechanism of cytotoxicity of this class of drugs is unknown, but they appear to act primarily at the cell membrane and can affect signal transduction pathways that are involved in cell differentiation and apoptosis (1, 2). Ilmofosine has demonstrated dose-dependent *in vivo* and *in vitro* antitumor activity in various solid tumor models (3–8). *In vitro* testing of ilmofosine against human tumor explants in a colony-forming assay indicated concentration-dependent activity against non-small cell lung, breast, colorectal, gastric, renal cell, and ovarian carcinomas and melanoma (9). A dose-dependent response was observed in mice bearing xenografts of Lewis lung carcinoma and methylcholanthrene-induced fibrosarcoma (6, 10). Schedules of frequent drug administration had activity superior to a single dose (10).

Preclinical toxicological studies identified the dose lethal to 10% of the population (LD_{10}) in mice as 284 mg/m^2 and in rats as 274 mg/m^2 when ilmofosine was administered as a single dose i.p. (i.v. administration via tail veins in rodents resulted in venous irritation). Pathological findings in rats included enteritis, peritonitis, and liver and spleen enlargement.[4,5] Dogs treated i.v. experienced gastrointestinal bleeding and irritation at the infusion site. Initial Phase I testing of ilmofosine administered as a 2-h infusion every 28 days was associated with mild hematological toxicity, dose-related nausea, and vomiting in 50% of patients and with phlebitis in 20% of patients. Additionally, there was one occurrence of drug-induced hemolysis at the highest dose level (11). On the basis of the evidence for superiority of repeated doses (8), a weekly schedule was studied.

The objectives of this Phase I/pharmacokinetic study include the determination of an appropriate dose for Phase II study and the description of the major toxicities associated with ilmofosine and its pharmacokinetics when administered as a weekly 2-h i.v. infusion for 4 weeks of a 6-week cycle in patients with advanced solid tumors.

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Requests for reprints: Bruce J. Giantonio, 51 N. 39th Street, MAB Suite 103, Philadelphia, PA 19104. Phone: (215) 662-8947; Fax: (215) 243-3268; E-mail: giantonio.bruce@jimmy.harvard.edu.

[4] H. Czerwek. Acute toxicity, rats, intraperitoneal. Boehringer Mannheim, F4 (Unpublished report), 1983.
[5] H. Czerwek and R. G. Hooper. Acute toxicity, mouse, intraperitoneal. Boehringer Mannheim, F3 (Unpublished report), 1984.

MATERIALS AND METHODS

Eligibility Criteria

All patients were required to be 18 years of age or older and to have a histologically confirmed diagnosis of cancer for which there was no standard therapy or that had become refractory to standard therapy. Participants in the study were also required to have: a life expectancy of at least 3 months; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; no prior chemotherapy within the previous 3 weeks (6 weeks for mitomycin C or nitrosureas); adequate marrow function (total WBC $\geq$3500 cells/mm^3, total granulocyte count $\geq$1500 cells/mm^3, platelet count $\geq$100,000 cells/mm^3, and hemoglobin $\geq$9.0 gm/dl); and adequate hepatic and renal function (total bilirubin $\leq$1.8 mg/dl, aspartate aminotransferase and alanine aminotransferase less than twice the upper limit of normal, and serum creatinine $\leq$1.8 mg/dl).

Patients with leukemia or multiple myeloma were excluded from study, as were those with a history of brain metastases or congestive heart failure. In addition, a history of pulmonary embolism or deep venous thrombosis and/or current anticoagulation therapy (excluding low-dose coumadin as prophylaxis for central line thrombosis), active infection, uncontrolled diabetes, or pregnancy precluded participation in the study. Women of child-bearing potential were eligible provided they were using adequate birth control measures.

The study was reviewed and approved by the institutional review board of the Fox Chase Cancer Center. All of the patients gave written informed consent.

Pretreatment Evaluation

Before initiating therapy, all of the patients underwent a complete history and physical examination and had baseline tumor measurements recorded. Clinical evaluation also included: chest X-ray, 12-lead electrocardiogram, complete blood count with differential, serum chemistries, and urinalysis.

Drug Supply and Administration

All of the patients were admitted to the Mary S. Schinagl Clinical Studies Unit of The Hospital of the Fox Chase Cancer Center for treatment. Ilmofosine was supplied in ampuls containing 250 mg/10 ml. Initially the drug was administered as a 2-h peripheral vein infusion in 250 ml 5% dextrose in water, however, because of frequent occurrence of peripheral phlebitis early in the study, all of the patients were subsequently required to have central venous access for drug administration.

The starting dose of ilmofosine was 12 mg/m^2 (approximately 1/25 of the i.p. LD_{10} in rodents) administered i.v. This dose was selected based on early preclinical and clinical toxicity information available at the time of the study's inception. Each treatment course consisted of a 36-day period in which drug was administered on days 1, 8, 15, and 22 of the cycle followed by 13 days of no drug treatment. The original study design used a traditional dose escalation schema; however, because information from another Phase I trial of ilmofosine demonstrated doses of 150 mg/m^2 to be well tolerated, this study was amended to allow for dose escalation by 100% increments to the 192 mg/m^2 dose. All subsequent dose increases were performed at 33% or less increments from the previous dose level. At least three patients were treated at each dose level, with an expansion of a level to six patients if dose-limiting toxicity occurred. The maximum tolerated dose was defined as that level at which grade 2 or worse toxicity occurred in four of six patients. To be evaluable for toxicity, completion of one full cycle was required. Intrapatient dose escalation was not allowed. Re-treatment was allowed in patients who did not experience progression of their disease.

All of the patients were seen weekly and were evaluated for toxicity using the toxicity criteria and grading system of the WHO (12). Clinical laboratory evaluation conducted with each visit included: complete blood count, serum chemistries, prothrombin time, partial thromboplastin time, cholesterol, and urinalysis. Blood for serum concentration determinations of ilmofosine and its metabolite were obtained in at least two patients per dose level at specified times during and after drug administration only in the first cycle. During the conduct of the study, further toxicology testing in rodents suggested a risk of drug-induced lenticular degeneration of the lens and of cellular depletion of the outer nuclear layer of the retina. Participants in the trial were subsequently required to have eye examinations (consisting of an Ishihara color test, a visual acuity test and a slit lamp examination) performed before receiving the first cycle of ilmofosine and after every other cycle. Patients were evaluated for response every other cycle.

Although toxicity determination was the primary objective of this trial, patients were also evaluated for response. A complete remission was defined as the disappearance of all measurable and clinically evaluable evidence of disease for at least 4 weeks. A partial response was defined as a 50% or greater reduction in the size of the indicator lesions as measured by the sum of the products of the greatest length and the maximum perpendicular width of all measurable lesions for at least 4 weeks. Progressive disease was defined as an increase of 25% or more in the size of the indicator lesions (as measured by the same criteria) or the appearance of new lesions. Those who did not meet criteria for complete or partial remission or progression were categorized as stable disease, provided that this state lasted for a minimum of 8 weeks.

Pharmacokinetics

Sample Acquisition. At scheduled times (immediately before the start of, 1 h into, and immediately at the completion of the infusion; then at 5, 10, 20, 40, 60, 90, and 120 min and 2, 6, 10, 16, and 24 h after completion of infusion; and at 24-h intervals for the subsequent 7 days), 10-ml blood samples were collected from at least two patients at each dose level only in the first cycle of treatment. Serum was separated, labeled, frozen, and stored at -20°C or lower in screw-top polyethylene tubes.

Analytical Methods. Determinations of the serum concentrations of ilmofosine and the sulfoxide metabolite were made using a validated high-pressure liquid chromatography method.[6] The analyses of ilmofosine and the sulfoxide metab-

[6] P. Frank, E. Nusser, and Z. B. Salama. Determination of ilmofosine in human plasma by HPLC and electrochemical detection, L.A.B. No. 91235, September 1991, on file at L. A. B. GmbH & Co, Analytic Research Center Wgenerstrasse 13, D-89231 Neu-Ulm, Germany.

olite were conducted by the HPLC Department/Analytical Research Center, LAB GmbH & Co., New-Ulm, Germany.

Kinetic Analysis. The maximum serum concentration (C_{MAX}) and time to reach C_{MAX} (T_{MAX}) for ilmofosine and the sulfoxide metabolite were obtained directly from the data. The elimination rate constant, $\lambda_{Z,}$ was calculated from the negative of the slope of the terminal log-linear portion of the serum concentration-time curve, using linear regression of the natural logarithm of the serum concentration *versus* time. The specific data points used for the calculation were determined by visual inspection of the semilogarithmic plot of concentration *versus* time.

The area under the concentration-time curve from zero to the final measurable sample (*AUC*_TF) was calculated using the linear trapezoidal method, and extrapolated to infinity using:

$$AUC = AUC\_TF + C_{tf}/\lambda_Z$$

where C_{tf} is the observed serum concentration at the final sampling time.

The elimination half-life ($t_{1/2}$) was calculated according to:

$$t_{1/2} = 0.693/\lambda_Z$$

Apparent volume of distribution (V_Z) was calculated according to:

$$V_Z = \text{dose}_{iv}/(AUC_{iv} * \lambda_Z)$$

and total plasma clearance was calculated using

$$CL = DOSE_{iv}/AUC$$

All of the calculations were done with SAS version 6.08.

RESULTS

Clinical Findings. Thirty-nine patients were entered and received 60 courses of ilmofosine. Thirty-six were included in the toxicity evaluation: thirty five patients received at least one complete cycle of therapy, and one patient experienced dose-limiting toxicity at the highest dose level and did not complete a full cycle of therapy (described below). The median number of cycles per patient was 1 (range, 1–4). These patients were of excellent PS and more than one-half had colorectal cancer. Patient characteristics are listed in Table 1.

Table 1 Patient characteristics

Total enrolled	39
Evaluable	35
Nonevaluable[a]	4
Median age (range)	62 (41–74)
Sex	
Male	26
Female	13
Performance status	
0	4
1	35
Primary site[b]	
Colon/rectum	21
Renal	4
Lung	3
Gynecologic	4
Melanoma	2
Other	6
Prior therapy	
Chemotherapy (chemo)	20
Chemo/radiation (rad)	8
Chemo/rad/biologic (biol)	4
Chemo/biol	3
Biol/rad	1
Radiation alone	1
Biologics alone	1
None	1

[a] Did not receive full course.
[b] Two patients had two primary malignancies.

Three patients who did not complete the first cycle for reasons described below were not included in the overall toxicity evaluation. One patient demonstrated rapidly progressive disease at the first dose level and was removed from study. One patient had a marked decline in PS (from PS 1 to PS 4) after 2 weeks of therapy at 48 mg/m^2 that was associated with rapidly progressive disease. One patient developed a small bowel obstruction on the day he was to receive the third dose at 255 mg/m^2 and died 3 days later.

The side effects associated with ilmofosine administration were mild and well-tolerated until the 550 and 650 mg/m^2/week dose levels. At these dose levels, gastrointestinal toxicity became dose limiting (Table 2). Nausea and vomiting were observed at doses $\geq$339/mg/m^2 and were easily controlled. However, at 650 mg/m^2 two of the three patients had grade 3 nausea and one had grade 3 vomiting. In addition, two patients at each of the highest dose levels experienced a decline in PS of two or more levels that was determined to be due to treatment. The three patients treated at the 650 mg/m^2 dose level are described below.

A 59-year-old man with colon cancer metastatic to the liver developed, within hours of treatment, a syndrome of severe focal abdominal pain associated with grade 3 nausea, grade 2 vomiting, and grade 3 elevations of transaminases and bilirubin (baseline values were grade 1). Diagnostic evaluation including radiographic studies did not reveal a specific cause for the pain, which resolved about 24 h after the drug was discontinued. By the 2nd week, his liver function tests had returned to their baseline values, but therapy was withheld because of persistent abdominal symptoms and decreased PS. He could not be re-treated because of a continued poor PS, and an evaluation 1 month later demonstrated rapidly progressive disease. Also at this dose level, a 62-year-old woman with colon cancer involving the liver experienced grade 3 nausea, vomiting, and diarrhea on the 1st day of therapy without associated hepatic function alterations. By the 2nd week of treatment, the nausea and vomiting had resolved, and she went on to complete the cycle. A third patient treated at this dose level did not experience toxicity greater than grade 2. After two cycles of therapy at full dose, a third cycle was dose-reduced because of a 2-point decline in PS related to fatigue. She also experienced a grade 2 increase in transaminase levels. Malaise, fatigue, and a progressive decline in PS occurred in all of the patients at this dose level.

Similar but less severe gastrointestinal toxicity was observed in the seven patients treated at the 550-mg/m^2 dose level.

Table 2 Gastrointestinal and constitutional toxicity greater or equal to grade 2 at dose levels ≥255 mg/m^2[a]

	Dose level[b]				
Grade	255 mg/m^2 $n = 4$	339 mg/m^2 $n = 3$	450 mg/m^2 $n = 6$	550 mg/m^2 $n = 7$	650 mg/m^2 $n = 3$
Nausea					
2		1	2	2	1
3				1	2
4					
Vomiting					
2		1		2	1
3				1	1
4					
Diarrhea					
2				4	1
3					1
4					
Constipation					
2				1	1
3					
4					
AST[c]					
2			1 (g1)		2 (1g1)
3			1 (g1)		1 (g1)
4					
ALT					
2			1		
3					1
4					
Bilirubin					
2					
3	2 (1g2)				1
4			1		
Abdominal cramps					
2		1			
3					1
4					
Anorexia					
2			2	3	
3					2
4					
Decreasing weight					
2				1	
3					
4					
Fatigue/weak					
2		1		1	2
3					1
4					
Decline in PS					
−1		1	3	1	
−2		2		2	1
−3					1

[a] Based on first course.
[b] Pretreatment grade (g) is in parentheses.
[c] AST, aspartate aminotransferase; ALT, alanine aminotransferase; PS, performance status.

One patient experienced grade 3, and two patients, grade 2, nausea and vomiting. Four patients experienced grade 2 diarrhea; abdominal cramping, however, did not occur. A decline in Eastern Cooperative Oncology Group PS by two levels occurred in two patients and by one in a single patient. In three patients treated with repeated cycles, one did not complete the second cycle, one had a dose reduction for the second cycle, and one received four cycles at full dose with worsening of gastrointestinal toxicity from G1 to G2. These findings established gastrointestinal toxicity as dose limiting for this schedule of administration.

Low-grade fever occurred with drug administration at all dose levels except the first (Table 3). Of the 27 patients noted to have temperature elevations, only three had temperatures above 38°C, and there were no temperature elevations above 40°C. Phlebitis was reported in nine patients with none worse than grade 2. This appeared to be dose related, occurring at the 550 mg/m^2 dose level in three of seven patients. Because of this finding, all subsequently treated patients were required to have central lines for drug administration. Hematological toxicity was negligible. Eight patients had grade 2 anemia (two with grade 2 and one with grade 1 pretreatment) and one had grade 3 anemia (grade 2 pretreatment). A grade 2 leucopenia occurred in one patient. No drug-related ocular toxicities were identified by slit lamp examination, visual acuity testing, and Ishihara color testing.

There were no tumor responses noted. Stabilization of disease occurred in 6 of 35 evaluable patients for a median of 16 weeks (range, 16–20.5 weeks). Stable disease was seen in the following tumor types: colorectal, 3; non-small cell lung cancer, melanoma, and cervical, 1 each.

Pharmacokinetics. The total dose of ilmofosine administered per infusion ranged from 18 mg to 1440 mg. For all pharmacokinetic analyses, only those serum concentrations that were above the validated limit of quantitation were reported. The limits were 0.05 μg/ml for ilmofosine and 0.50 μg/ml for the sulfoxide metabolite. The duration of infusion was ~2 h with the exception of two patients (3.88 h and 5.17 h). Patient samples below the 255 mg/m^2 dose level were not routinely assayed for the metabolite.

The pharmacokinetic parameter estimates for ilmofosine and its sulfoxide metabolite in this study were highly variable within and between dose levels (Tables 4 and 5). The T_{MAX} corresponded to the end of infusion in the majority of patients (data not shown). The C_{MAX} seemed to increase in relation to increasing total doses of ilmofosine, and a similar relationship was seen for *AUC* (Fig. 1, *A* and *B*).

The distribution and elimination of ilmofosine was polyphasic at doses ≥255 mg/m^2, the doses at which concen-

Table 3 Fever and phlebitis at dose levels ≥255 mg/m^2

	Dose levels				
Grade	255 mg/m^2 $n = 4$	339 mg/m^2 $n = 3$	450 mg/m^2 $n = 6$	550 mg/m^2 $n = 7$	650 mg/m^2 $n = 3$
Fever					
1	2	2	5	5	3
2		1	1	1	
3					
4					
Phlebitis					
1	1	1		2	
2			2	1	
3					
4					

Table 4 Mean ilmofosine pharmacokinetic parameter estimates, mean ±SD

Dose level (mg/m^2)	n^a	$C_{MAX}{}^b$ (μg/ml)	$t_{1/2}$ (h)	*CL* (ml/min)	*AUC* (h*μg/ml)	V_Z (liter)
255	4	11.33 (5.90)	39.99 (33.95)	225 (114)	49.09 (34.01)	708 (813)
450	5	30.20 (1.78)	37.15 (18.81)	129 (26)	109.20 (9.90)	404 (179)
550	7	31.23 (9.73)	15.39 (22.33)	843 (1270)	76.82 (70.42)	241 (131)
650	3	33.91 (8.81)	41.65 (11.39)	156 (97)	148.26 (60.16)	625 (556)

[a] Number of patients with samples.
[b] C_{MAX}, maximum serum concentration; $t_{1/2}$, half-life; *CL*, clearance; *AUC*, area under the concentration time curve; V_Z, apparent volume of distribution.

Table 5 Mean ilmofosine sulfoxide (metabolite) pharmacokinetic parameter estimates, mean ±SD

Dose level (mg/m^2)	n^a	$C_{MAX}{}^b$ (μg/ml)	$t_{1/2}$ (h)	*AUC* (h*μg/ml)
255	4	6.56 (3.31)	38.78 (4.91)	238.30 (39.33)
450	5	15.50 (4.33)	48.33 (10.82)	504.59 (287.37)
550	7	15.13 (10.72)	48.62 (15.01)	473.80 (250.71)
650	3	21.40 (7.64)	49.72 (35.86)	656.0 (416.67)

[a] Number of patients with samples.
[b] C_{MAX}, maximum serum concentration; $t_{1/2}$, half-life; AUC, area under the concentration-time curve.

trations of ilmofosine were detectable beyond 48 h from the start of the 2-h infusion. At dose levels below 255 mg/m^2, plasma concentrations of ilmofosine were below the validated limit of the assay (0.05 μg/ml) in samples collected at 24 h after the end of infusion, the time after which the prolonged terminal phases appear. In nine patients who were treated at dose levels ≥255 mg/m^2 and who had samples obtained at more than 48 h after the start of the 2-h infusion, the mean $t_{[1/2]}$ (±SD) was 45.15 h (±15.92 h). These half-life data are consistent with information previously reported for ilmofosine (manufacturer's brochure).

The apparent volume of distribution (V_Z) varied from 33 liters to 281 liters with a mean of 114 liters (±82 liters). Clearance (*CL*) values were between 108 ml/min and 357 ml/min, with a mean of 202 ml/min (±98 ml/min).

At dose levels below 255 mg/m^2, serum concentrations of ilmofosine sulfoxide were below the limit of quantitation of the assay beyond 18 h from the start of infusion. The mean pharmacokinetic parameter estimates for the sulfoxide metabolite of ilmofosine are shown in Table 5.

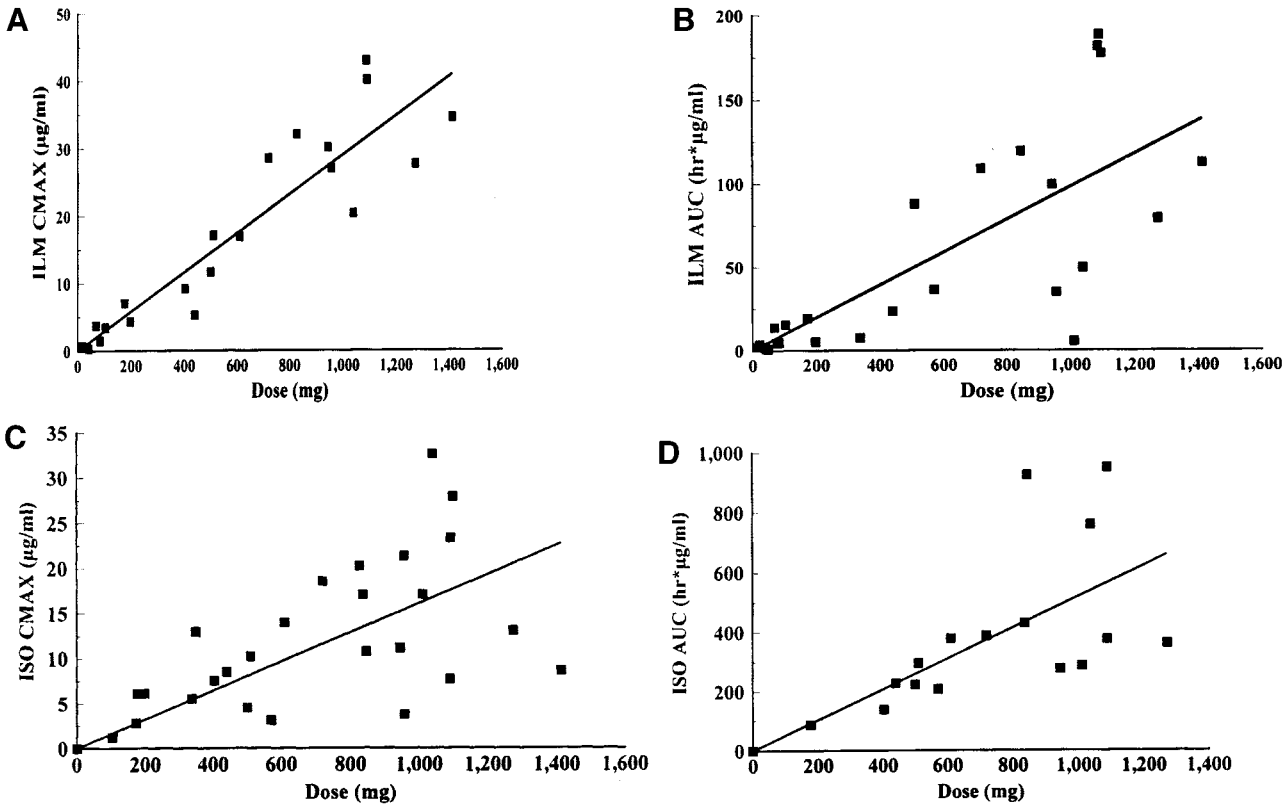

Fig. 1 The maximum serum concentration (C_{MAX}) and the area under the concentration-time curve (*AUC*) for ilmofosine (*ILM*; *A* and *B*, respectively) and the ilmofosine sulfoxide metabolite (*ISO*; *C* and *D*, respectively) demonstrate a dose-response relationship after a 2-h injection.

The observed C_{MAX} and estimated *AUC* of the sulfoxide metabolite seem to increase with increasing doses of ilmofosine (Fig. 1, *C* and *D*). Serum concentrations of the metabolite were higher than serum concentrations of ilmofosine in most patients; the ratio of metabolite *AUC* to ilmofosine *AUC* ranged from 2.07 to 15.26.

The profile of the elimination of the sulfoxide metabolite is multiexponential. There are at least two distinct postabsorption phases, a faster initial rate followed by a much slower terminal rate (data not shown).

DISCUSSION

Ilmofosine is a thioether-phospholipid analogue of lysophosphatidylcholine, a relatively new class of antitumor agents that appear to be membrane interactive and effect cytotoxicity independent of direct DNA damage. Several mechanisms of action for this class of agents have been proposed including the inhibition of protein kinase C membrane signal transduction (13–16) and membrane disruption (17, 18), and may also include induction of apoptosis (2, 19) and immunomodulation (20, 21).

Consistent with trials of other schedules of ilmofosine (22–25), gastrointestinal toxicity was found to be dose limiting. One individual treated at 650 mg/m^2 experienced severe abdominal cramping and grade 3 hepatotoxicity in addition to nausea and vomiting; this syndrome has been reported by us at higher doses using a 24-h infusion (25).

Preclinical animal studies demonstrated enteritis and peritonitis in rodents at high doses. The prompt resolution of the abdominal cramps in our patients, however, argues against a cytotoxic etiology but may support a cytokine-mediated event. The low-grade constitutional symptoms, such as fever, malaise, anorexia, and functional status decline, seen at almost all dose levels are similar to toxicities reported for cytokines such as interleukin 1, interleukin 6, and tumor necrosis factor. In addition, hepatotoxicity has been associated with the clinical application of IFN-α, interleukin 6, and tumor necrosis factor. Several alkyl-phospholipids have demonstrated immunomodulatory effects that include production of interleukin 6 and tumor necrosis factor (21). Inflammatory cytokines have been implicated in the pathogenesis of necrotizing enterocolitis by their ability to induce the local production of nitrous oxide and the induction of apoptosis of enterocytes (26). Moreover, tumor necrosis factor has been implicated as a mediator of Crohn's disease; recently, a chimeric antibody to this cytokine has shown therapeutic efficacy in this illness (27). Cytokine elaboration in response to ilmofosine therapy was not included in the pharmacological evaluation of this study but should be considered in future clinical trials of ether lipids. As with our previously reported findings, hematological toxicity was negligible.

Even though ilmofosine kinetics demonstrates a prolonged half-life, the delayed terminal phase accounts for less than 20% of total *AUC* in most patients and supports an intermittent weekly dosing schedule. At highest dose levels, the maximum plasma concentrations were 33.91 μg/ml (64.4 μM), which exceeded the concentrations at which cytotoxicity assays were performed *in vitro* (1.9 μM, and 1.9 μM for the metabolite). Plasma concentrations, however, were not sustained and immediately before the next weekly dose were generally below the limit of quantitation (0.095 μM). It would be of interest to know whether lower doses result in prolonged phosphokinase C inhibition because, even if ilmofosine has limited activity as a single agent, it may have a role in combination therapy.

We have found gastrointestinal toxicity and a decline in performance status to be dose limiting when ilmofosine is administered as a weekly 2-h infusion and recommend 450 mg/m^2 as the dose for Phase II study. On the basis of our findings and those of others (23–25), the role of ilmofosine as an anticancer agent is uncertain. It has been suggested that these agents may have additive or synergistic effects when combined with conventional chemotherapeutics (28, 29) and radiation (2, 30, 31). More promising results have been reported for other alkylphospholipids such as miltefosine (HePC) when applied topically to treating cutaneous lymphoma (32) and breast cancer metastases (33, 34). In addition, perifosine (D-21266) a more potent structural analogue of miltefosine (35) is currently in clinical development (36).

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