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A Phase I Study of Continuous Infusion Cilengitide in Patients with Solid Tumors

Peter H. O'Donnell[1,2], **Samir D. Undevia**[1], **Walter M. Stadler**[1,3], **Theodore M. Karrison**[3,4], **M. Kelly Nicholas**[5], **Linda Janisch**[1], and **Mark J. Ratain**[1,2,3]

[1]Section of Hematology/Oncology, Department of Medicine, The University of Chicago, 5841 S. Maryland Ave., MC 2115, Chicago, IL 60637

[2]Committee on Clinical Pharmacology and Pharmacogenomics, The University of Chicago, 5841 S. Maryland Ave., MC 2115, Chicago, IL 60637

[3]Comprehensive Cancer Center, The University of Chicago, 5841 S. Maryland Ave., MC 2115, Chicago, IL 60637

[4]Department of Health Studies, The University of Chicago, 5841 S. Maryland Ave., MC 2115, Chicago, IL 60637

[5]Department of Neurology, The University of Chicago, 5841 S. Maryland Ave., MC 2115, Chicago, IL 60637

Abstract

Background—Cilengitide (EMD121974) is a cyclized pentapeptide that is a potent and selective integrin antagonist which has shown activity in malignant gliomas. In all previous studies, cilengitide has been administered in an intermittent fashion. However, cilengitide has a short half-life of 3-5 hours with no evidence of drug accumulation. These data prompted the initiation of this phase I study of continuous infusion cilengitide.

Methods—Cilengitide was administered as a continuous infusion without break in 4-week cycles. Plasma samples for pharmacokinetic studies were obtained weekly in cycle 1 immediately prior to and 2 hours after infusion bag change.

Results—Thirty-five patients were treated (median age 56; 23 males) at dose levels of 1, 2, 4, 8, 12, 18, 27, and 40 mg/hr. Toxicities were limited to grade ≤ 2 and showed no relation to dose. Fatigue was most common (17%), while all other toxicities were reported in <10% of patients. No dose-limiting toxicities were observed, and therefore the maximum tolerated dose was not reached. Pharmacokinetic analysis showed that values for clearance and volume of distribution were comparable across dose levels, and the steady-state concentration increased proportionally with dose.

Conclusions—Cilengitide can be safely administered as a continuous infusion at doses up to at least 40 mg/hr, which represents the maximum feasible dose due to drug solubility and delivery limitations. The pharmacokinetics of continuous infusion cilengitide are linear and consistent with the results obtained using a twice weekly infusion.

INTRODUCTION

Cilengitide (EMD121974) is a cyclized pentapeptide that is a potent and selective integrin antagonist [1]. Integrins are cell surface transmembrane proteins which perform cross-talk signaling between the extracellular matrix and the intracellular growth machinery of a cell [2] and mediate a variety of cell activities, including angiogenesis [3]. In receptor binding experiments, half-maximal inhibition (IC_{50}) of the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ was achieved

with 2 nM and 120 nM of cilengitide, respectively, and cilengitide was also shown to inhibit $\alpha_v\beta_3$ and $\alpha_v\beta_5$-mediated cell adhesion at an IC_{50} of ~1 μM [4]. Cilengitide inhibits tumor growth in various *in vivo* systems, including the chorioallantoic membrane model, nude mice, and severe combined immunodeficient mice inoculated with human tumor cells [4,5]. In the latter model, tumor growth was prevented even when α_v-integrin-negative tumor cells were used as the inoculum, demonstrating that the inhibitor did not directly affect the tumor cells but likely affects the tumor microenvironment [5]. As such, cilengitide has been previously investigated in several clinical trials as a potential anticancer agent [6-9] and has shown promise in the treatment of malignant gliomas [10].

Importantly, in the human studies performed to date, it has had few significant toxicities, and a maximally tolerated dose was not reached in phase I testing of doses up to 2400 mg/m^2 twice weekly [7]. All of the reported dosing strategies of cilengitide in humans have been twice weekly or other intermittent schedules. In preclinical models, tumor growth inhibition was found in mice treated twice daily, every day, and every other day [4], but tumors continued to grow after therapy with cilengitide was stopped [11,12], suggesting that therapy with this compound, as with other antiangiogenic compounds, may require continuous, long-term administration. Additionally, cilengitide has a short plasma half-life of 3-5 hours and has a clearance of 34-66 mL/min/m^2, with no evidence of metabolism, drug accumulation, or enterohepatic circulation. The majority of the drug is cleared via renal elimination [7]. Despite the reported efficacy of an intermittent dosing schedule in some preclinical tumor models and in some patients with gliomas [11,12], broader activity of cilengitide as a single agent has not been documented, also supporting the idea that continuous exposure to cilengitide may be necessary for efficacy and warrants investigation.

The objectives of this study were to (a) characterize the safety and tolerance of cilengitide when administered by continuous intravenous infusion; (b) determine the dose-limiting toxicity, maximum tolerated dose (MTD), and recommended phase II dose of cilengitide; and (c) describe the pharmacokinetics of cilengitide when administered by continuous intravenous infusion.

METHODS

Study Participants

The study was conducted at The University of Chicago from December 2003 - March 2008 after Institutional Review Board approval in accordance with the Declaration of Helsinki. All patients provided written informed consent. Follow-up was continued through December 2008.

Subjects were adults with a histologically confirmed, solid tumor or lymphoma that was refractory to standard therapy or for which no standard therapy existed, an ECOG performance status between 0 - 2, normal organ and marrow function (as defined by leukocytes ≥3,000/μL, absolute neutrophil count ≥1,500/μL, platelets ≥100,000/μL, serum creatinine at or below the upper limit of institutional normal [1.4 mg/dL], and total bilirubin within normal institutional limits [unless due to documented Gilbert's syndrome]). Patients who had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who had not recovered from adverse events due to agents administered more than 4 weeks earlier were ineligible.

Treatment Plan

Cilengitide was supplied by the Division of Cancer Treatment and Diagnosis of the National Cancer Institute as an isotonic solution containing 450 mg of lyophilized cilengitide dissolved in 30 mL of sodium chloride and water, or 500 mg of lyophilized cilengitide

dissolved in 33.3 mL of sodium chloride and water (both = 15 mg/mL). Cilengitide was then diluted with 0.9% sodium chloride or 5% dextrose in water in a 250 mL or 500 mL sterile saline viaflex bag to the desired concentration and administered as a continuous infusion (via a subcutaneous venous access device, such as a Port-a-Cath). Each infusion bag lasted seven days and was prepared at the time of use with a 7-day dose. A total of 4 infusion bags was used for each 4-week cycle. The starting dose was 1 mg/hr, without a break. This dose was equivalent to more than an order of magnitude lower than the highest administered dose of 1600 mg/m^2 in the phase I study which was administered twice weekly and was well tolerated. A fixed dose was used in the absence of data justifying dosing based on body surface area.

Due to minimal toxicity in intermittent infusion schedules, the dose escalation scheme followed an accelerated titration design (Steps A and B below), followed by more gradual dose escalation (Step C below). The maximum dose was 40 mg/hr and was based on a 500 mL intravenous bag, which was carried by the subject with the infusion pump, and the current drug formulation, which limited the maximum concentration to 15 mg/mL. Although treatment was continuous, a cycle was defined as 4 weeks of therapy. The portable infusion bag containing study drug was replaced weekly.

Step A—The initial dose escalations of 100% were performed in cohorts of at least one assessable patient after one cycle of treatment (4 weeks). If any grade ≥ 2 toxicity probably/definitely related to treatment or any grade ≥ 3 toxicity possibly/probably/definitely related to treatment occurred, dose escalation switched to Step B. If any DLT was observed, dose escalation switched to Step C. Dose escalation was permitted to proceed after one patient had been treated for 4 weeks and was fully assessable. To maximize pharmacokinetic sampling and safety parameters, we proceeded to step B when 6 mg/hr or higher doses were reached.

Step B—Dose escalations of 50% were performed in at least three evaluable patients per cohort. At least three patients must have been treated for at least 4 weeks and fully assessable prior to dose escalation. Subjects that were not fully assessable were replaced. If any DLT, grade 3 neutropenia, or grade 3 thrombocytopenia was observed, dose escalation switched to Step C. During dose escalation in Step B, additional patients were enrolled at any dose level if deemed necessary to better establish safety and pharmacokinetics.

Step C—If a DLT was observed, subsequent dose levels were to enroll at least 6 patients. If only 1 of 6 patients had a DLT, dose escalations of 25% were to continue in subsequent cohorts of 6. If 2 or more patients had a DLT, dose escalation was to normally terminate. However, if DLTs were inconsistent with other data (e.g., different toxicities observed to date), additional enrollment up to a maximum of 12 patients was permissible. Dose escalation was to proceed if less than one-third of patients had a DLT.

Rounding of the dose to two significant digits was utilized. Only one patient per week was treated in Steps A and B. If a decision was made to enroll more than 6 patients per dose level, up to 2 patients per week were treated. Patients who experienced DLT were treated in subsequent cycles at the next lower dose level as long as there was no evidence of progressive disease and all of toxicities had resolved to baseline or grade 1. Patients must have resumed treatment within six weeks. Withdrawal from study treatment occurred for any of the following: disease progression, intercurrent illness that prevented further administration of treatment, an unacceptable adverse event, DLTs that did not resolve to baseline or grade 1 within 6 weeks of discontinuing study drug, or specific changes in the patient's condition that rendered the patient unacceptable for further treatment in the

judgment of the investigator. Tumor assessments were performed every 8 weeks (i.e., every two cycles).

Toxicity Monitoring

Dose-limiting toxicity (DLT) was defined as the occurrence of any of the following during the initial four weeks of therapy: 1) grade 3 or higher nonhematologic toxicity except transient fatigue, nausea, vomiting (persistent grade 3 or higher fatigue, nausea, or vomiting was unacceptable); 2) grade 4 hematologic toxicity; 3) any fever accompanied by granulocyte count $<1000/mm^3$; 4) grade 3 or 4 hemorrhage/bleeding. The MTD was defined as the highest dose studied for which the incidence of DLT is less than 33%.

Supportive Care

Patients received full supportive care including transfusions, antibiotics, antiemetics, antidiarrheal agents, etc., when appropriate. Palliative radiation therapy was not permitted while a patient was on study.

Pharmacokinetic Measurements

Blood sampling—On day 1 pharmacokinetic sampling was performed before the start of cilengitide (pre-dose sample), and 2 hrs after starting infusion. On day 8 and weekly thereafter for the first four weeks, a blood sample was taken just prior to the change to a new infusion bag and at 2 hrs following the start of therapy from the new infusion bag. Ten milliliters of blood were collected in heparinized tubes. Plasma was separated by centrifugation (2,500 rpm, 10 min, 4°C) and frozen at −80°C until analysis, which was performed by Merck KGaA, Darmstadt, Germany, using high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Samples were analyzed in duplicate as previously described (see supplemental appendix of Nabors et al. [9], available with the online electronic version of that publication). Levels were extrapolated from a standard curve analyzed each run day.

Pharmacokinetic parameters—A pharmacokinetic profile of cilengitide was constructed for each patient. Data were analyzed by noncompartmental method using the WinNonlin software (Pharsight, Mountain View, CA). The pharmacokinetic parameters routinely estimated included the steady state concentration, volume of distribution at steady state, and clearance. Mean and standard deviation were calculated for each parameter. Volume of distribution calculations were based on an assumed population drug half-life of 4 hours.

RESULTS

Patient Characteristics

The characteristics of the 35 enrolled patients are shown in Table 1.

Summary of Dose Escalation

Three patients were enrolled at dose level 1 (1 mg/hr), two at dose level 2 (2 mg/hr), four at dose level 3 (4 mg/hr), three at each of dose levels 4 and 5 (8 mg/hr and 12 mg/hr, respectively), four at dose level 6 (18 mg/hr), nine at dose level 7 (27 mg/hr), and seven at dose level 8 (40 mg/hr). Further dose escalation beyond was not possible because the current drug formulation limited the maximum concentration to 15 mg/mL and higher doses could not be administered using the 500 mL IV bag compatible with the continuous infusion pumps. Therefore, 40 mg/hr was considered the maximum feasible dose. The average

number of drug cycles administered per patient (1.8 cycles for the overall cohort, or just over seven weeks) did not significantly differ by dose level.

Toxicity

By convention, we restricted formal attribution of toxicities to those observed during cycle 1. The cycle 1 toxicities that were considered at least possibly related to study drug are summarized in Table 2. Treatment-related hypertension did not occur in any patients. For all observed toxicities, there was no identifiable relationship to dose. No DLT was observed, and therefore, the MTD was not reached.

Although no serious drug-related toxicities were observed during cycle 1, we extended our examination to subsequent cycles to specifically review all cases in which bleeding, cardiac events, and/or vascular/thromboembolic complications occurred, since cilengitide has known antiangiogenic properties. Pulmonary emboli (grade 4) were observed in two patients: a patient with metastatic renal cancer to the lungs at the 12 mg/hr dose level during week 2 of cycle 3; and a patient with metastatic chondrosarcoma to the lungs at the 18 mg/hr dose level during week 3 of cycle 2. Relationships to study drug were impossible to determine and therefore the toxicities were considered possibly related to drug. Grade 3 transient ischemic attack occurred in a patient with esophageal carcinoma at the 27 mg/hr dose level during week 3 of cycle 1. The patient subsequently had a cerebrovascular accident after being removed from the study. Both events were considered unlikely drug related. One patient at the 4 mg/hr dose level was found to have a non-ST-elevation myocardial infarction after being admitted with sepsis during cycle 2. The events were considered unlikely related to drug. With regard to bleeding complications, epistaxis (grade 2) was observed in a patient with follicular thyroid carcinoma at 27 mg/hr during week 2 of cycle 3. Spontaneous resolution occurred without intervention and the event was considered possibly drug-related.

Eight patients died while on study. One patient at the 27 mg/hr dose level experienced an unobserved death. He had had a myocardial infarction 10 months earlier and noted similar symptoms for two days prior to being found. The other seven patients died due to progressive disease.

Tumor Response

Only 17 of the 35 patients remained on study to undergo the first formal radiographic tumor assessment at the end of cycle 2. Of the 18 who did not, essentially all were removed from the study prior to the end of cycle 2 due to subjective evidence of disease progression (new symptomatology and/or clinical deterioration). No objective responses were observed. Stable disease was demonstrated in two patients (one patient at the 4 mg/hr dose level and one patient at the 12 mg/hr dose level) for a median of 3.5 cycles. We found no significant relationship between dose level or steady state concentration (C_{ss}) of cilengitide with change in tumor size after two cycles (data not shown).

Pharmacokinetics

The calculated pharmacokinetic parameters for cilengitide are shown in Table 3. Pharmacokinetic samples were not available for three patients (subjects 31, 32, and 34). The pharmacokinetics of continuous infusion cilengitide appear linear, as clearance and volume of distribution were not significantly different across dose levels, and C_{ss} increased proportionally to dose (Table 3).

DISCUSSION

This study shows that cilengitide can be administered safely as a continuous intravenous infusion. No dose-limiting toxicities were observed, and therefore a maximum tolerated dose was not established. Instead, a maximum feasible dose was the endpoint of the study as the current formulation required patients to carry a 500 mL infusion bag in order to receive the highest dose of 40 mg/hr. With a different drug formulation, studies of higher doses could take place. However, over the dose range studied here, there was no evidence that the observed toxicities, nor response, were related to escalating dose.

As has been seen in previous studies of cilengitide given on an intermittent schedule [7,9], the drug was generally well tolerated as a continuous infusion, although accrual to the study was slow because we found that patients were not as willing to accept continuous intravenous dosing as we had anticipated. There were few, mild drug-related toxicities. Given the putative antiangiogenic properties of cilengitide, it is particularly noteworthy that bleeding events, cardiac events, and vascular/thromboembolic complications were rare, were not more common at higher doses, and were not clearly related to drug in any case, consistent with previous experiences [7,9]. Treatment-induced hypertension did not occur in any patients. Proteinuria was not assessed. These toxicities, likely due to inhibition of vascular endothelial growth factor rather than inhibition of integrin-mediated angiogenesis, have not been reported in any of the prior phase I studies of cilengitide.

Pharmacokinetics of the continuous infusion were similar to intermittent studies of cilengitide. As a comparison, human pharmacokinetic measurements were performed in a European phase I study with groups of three to six patients administered 30 to 1,600 mg/m^2 cilengitide twice weekly by 1-hour infusion [7]. Pharmacokinetic parameters were approximately linear with respect to dose, a finding that was similarly demonstrated in our continuous infusion study. In the European study, cilengitide clearance (mean 34 – 66 mL/min/m^2) was similar to the range calculated in our study (55 – 88 mL/min/m^2). However, mean volume of distribution in the prior study was 9 – 12 L/m^2, which is slightly lower than the range observed in our study (18 – 31 L/m^2). We believe this may be due to the fact that the volume of distribution calculations in our study required us to assume the drug half-life, which we estimated at 4 hours [7]. However, others have reported shorter half-lives for cilengitide [9], and if we had indeed used a shorter estimated half-life this would have resulted in accordingly lower calculated volumes of distribution in our study. There was no evidence of accumulation of cilengitide in the plasma over time in our study, consistent with prior evidence that drug accumulation was also not observed with intermittent dosing schedules [7]. Finally, from prior work, an intermittent cilengitide dose of 120 mg/m^2 or higher achieves drug exposure levels that are within the range used in preclinical models of cell adhesion and angiogenesis inhibition [10,13]. Our continuous infusion approach, at the 2 mg/hr dose level, results in drug exposure equal to that observed with 120 mg/m^2 cilengitide on an intermittent schedule [9]. Therefore, one might consider the 2 mg/hr continuous infusion dose as a minimum biologic dose, but this does not mean it represents the optimal biological dose, and clearly higher doses are tolerable. In the absence of dose-limiting toxicity with this drug to date, and in the absence of a validated predictive biomarker, the recommended dose (and schedule) remain speculative, in our opinion, and future studies should continue to explore a wide range of doses.

We observed no relationship between dose (or concentration) and change in tumor size, which could be due to a complete lack of antitumor activity, or alternatively evidence that the lowest dose is as effective as the highest dose. This lack of dose-response was similarly observed in the phase I study of cilengitide in patients with malignant glioma [9]. In contrast, the phase II study in malignant glioma patients suggested that higher drug exposure

may be important, since patients randomized to a dose of 2000 mg twice weekly exhibited improved survival compared to those randomized to 500 mg twice weekly, although the differences were not statistically significant [10]. If further studies can clearly show that drug exposure correlates with antitumor activity (or some toxicity), then this might also justify raising the question of whether a fixed dose approach is appropriate or whether dosing based upon something like glomerular filtration rate would provide more uniform drug exposure. Precise dosing is only justifiable if such a relationship is established. Indeed, in the absence of such data, the current phase III study with cilengitide has chosen to use a fixed dose approach (clinicaltrials.gov study identifier NCT00689221).

Continued studies of cilengitide by continuous infusion should be considered in light of the positive data with other angiogenesis inhibitors that use continuous schedules, however a new formulation would be required to continue dose-escalation of the continuous infusion beyond 40 mg/hr. It is interesting to note that the 40 mg/hr continuous infusion dose intensity (representing 6720 mg/week) is actually higher than that which has been chosen for the current phase III cilengitide study (2000 mg flat dose twice per week, which represents a dose intensity of only 4000 mg/week). Yet the possible true advantage to the continuous administration strategy lies in the idea of sustained exposure—from a mechanistic standpoint—for this drug, since for other antiangiogenic compounds, evidence of loss of the antiangiogenic effects between doses during intermittent administration is well demonstrated [14,15]. This hypothesis, for cilengitide, would perhaps best be tested by comparing equivalent dose intensities or drug exposure levels of a continuous infusion schedule with an intermittent schedule in a select group of patients like those with malignant glioma.

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Table 1

Patient Characteristics

	No. of Patients
Patients enrolled	35
Gender (M:F)	23:12
Median age, years (range)	56 (30-76)
ECOG performance status	
0	17
1	13
2	5
Primary tumor type	
Colorectal	8
Sarcoma	4
Melanoma	3
Pancreas	4
Non-small cell lung	2
Kidney	2
Primary CNS	5
Other*	7
Prior therapy	
Chemotherapy	35
Radiotherapy	16
Immunotherapy	3

CNS = central nervous system.

*Other tumor types included thyroid, gastrointestinal stromal tumor, esophageal, prostate, ovarian, giant cell tumor of the foot, and cancer of unknown primary.

Table 2

Incidence and Severity of Cycle 1 Toxicities Considered At Least Possibly Related to Study Drug, for All Patients (Pts)

Toxicity		Number of Patients Exhibiting Toxicity Per Dose Level								Total Pts. (%)
Type	Grade	1 mg/hr	2 mg/hr	4 mg/hr	8 mg/hr	12 mg/hr	18 mg/hr	27 mg/hr	40 mg/hr	
Anorexia	1							1		2 (6)
	2			1						
Constipation	1								1	1 (3)
Diarrhea	1		1						1	2 (6)
Fatigue	1					1			2	6 (17)
	2			2				1		
Fingernail changes	1						1			1 (3)
Mucositis	1			1						1 (3)
Insomnia	1					1				1 (3)
Nausea	1		1					1	1	3 (9)
Pain	1							1		1 (3)

Table 3

Cilengitide pharmacokinetic parameters as calculated in the cohort

Rate (mg/h)	Subject	Css (ng/mL)	CL (L/h)	V (L)
1	N	3	3	3
	Mean	150.0	8.31	48.0
	Stdev	95.5	3.89	22.4
2	N	2	2	2
	Mean	365.3	5.72	33.0
	Stdev	105.9	1.66	9.6
4	N	4	4	4
	Mean	600.8	6.69	38.6
	Stdev	48.9	0.57	3.3
8	N	3	3	3
	Mean	1316.1	6.69	38.6
	Stdev	470.0	2.62	15.1
12	N	3	3	3
	Mean	1766.4	6.85	39.5
	Stdev	195.0	0.77	4.4
18	N	4	4	4
	Mean	2960.0	6.11	35.3
	Stdev	257.2	0.51	3.0
27	N	9	9	9
	Mean	3922.4	7.80	45.0
	Stdev	1378.2	3.25	18.8
40	N	4	4	4
	Mean	4670.0	9.62	55.5
	Stdev	1807.3	3.76	21.7