Phase 1 Study of Weekly Polyethylene Glycol-Camptothecin in Patients with Advanced Solid Tumors and Lymphomas

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Abstract

Purpose: To determine the maximal tolerated dose and dose-limiting toxicities (DLT) of pegamotecan (polyethylene glycol-camptothecin) in patients with advanced malignancies when administered in cycles of once weekly for 3 of 4 weeks.

Experimental Design: Eligible patients had advanced solid tumors that failed to respond to standard therapy or for which no standard therapy was available, including also the following criteria: measurable disease, Eastern Cooperative Oncology Group performance status of ≤2, and acceptable organ function. Pegamotecan was administered as a 60-minute infusion, with successive patient cohorts receiving escalating doses from 800 to 4,300 mg/m^2. The primary end point was to determine the maximal tolerated dose. Other end points were toxicity, pharmacokinetics, pharmacodynamics, and efficacy. Pharmacokinetic analysis measured free camptothecin. Pharmacodynamic analysis correlated drug effects with pegamotecan dose and pharmacokinetic variables.

Results: Twenty-seven patients were enrolled. The maximal tolerated dose was 3,240 mg/m^2. Grade 4 neutropenia, the DLT, was noted in two of four patients treated at 4,300 mg/m^2. Other grade 3 and 4 toxicities were anemia, thrombocytopenia, fatigue, prolonged partial thromboplastin time, hemorrhagic cystitis, dysuria, and urinary frequency. Pharmacokinetic analysis showed the apparent terminal elimination half-life to be 46 ± 12.8 hours. Pharmacodynamic analysis showed that hematuria occurred in 8 of 15 patients with an area under the curve extrapolated to infinity ($AUC_{0-\infty}$) > 20 ng h/mL and 0 of 10 patients with an $AUC_{0-\infty} \leq 20$ ng h/mL. Unconfirmed partial responses were observed in two patients, one with metastatic small bowel adenocarcinoma and the other with metastatic esophageal cancer.

Conclusions: The maximal tolerated dose of pegamotecan when administered weekly for 3 of 4 weeks is 3,240 mg/m^2. The DLT was neutropenia. Among nonhematologic toxicities, the incidence of gastrointestinal toxicity was low, but genitourinary toxicity seems to occur in the same effective dose range as noted with native camptothecin in earlier trials (27-43 mg/m^2). The observed antitumor activity suggests that pegamotecan has single-agent activity and merits further investigation in phase 2 studies.

Camptothecin, a plant alkaloid isolated from the *Camptotheca acuminata* tree, was originally identified as an active antineoplastic in the National Cancer Institute drug screen (1, 2). Camptothecin exists in two forms, the lactone form and the 10-fold less active carboxylate form (3, 4). Native camptothecin showed antitumor activity in animal models (5) and in phase 1 clinical trials (6, 7) in the 1960s and 1970s, with myelosuppression being the dose-limiting toxicity (DLT). However, a subsequent phase 2 clinical trial failed to confirm the efficacy observed in earlier phase 1 trials (8) and was associated with severe and unpredictable gastrointestinal, genitourinary, and hematologic toxicities. Further clinical testing of native camptothecin was subsequently abandoned.

Interest in camptothecin was revived following the discovery that it blocked the activity of topoisomerase I, an enzyme required for DNA transcription and replication (9). Topoisomerase I functions by unwinding and relaxing supercoiled DNA, thereby facilitating a variety of important cellular processes. Topoisomerase I targeting agents, such as camptothecin, stabilize the DNA-topoisomerase I cleavable complex after a DNA single-strand break has occurred. In the presence of ongoing DNA synthesis, this can cause DNA double-strand breaks, which can inhibit further DNA and RNA synthesis and cause cell death (4, 10).

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Structural modifications of the A and/or B rings of camptothecin can improve water solubility and reduce plasma protein binding, two characteristics of native camptothecin that limited its clinical effectiveness (11). These advances led to the synthesis of numerous camptothecin analogues, two of which, topotecan and irinotecan, have been approved by the Food and Drug Administration for use in cancer patients.

Pegamotecan is a water-soluble macromolecule consisting of two camptothecin molecules conjugated to a 40-kDa polyethylene glycol using an alaninate ester linkage. Free camptothecin must be cleaved from the polyethylene glycol to be pharmacologically active. The hydroxyl group (-OH) at the 20-position of camptothecin is the active portion of the molecule responsible for the conformational changes between the active lactone and relatively inactive carboxylate forms. In pegamotecan, the 20-OH of camptothecin is blocked by the alaninate linker, which stabilizes the camptothecin molecule into its active lactone conformation (12). Entry of high molecular weight conjugates into the tumor tissue extracellular matrix may be facilitated by the "leaky" nature of tumor vasculature. Pegamotecan can facilitate the delivery of camptothecin to tumor tissues via a process known as the enhanced permeability and retention effect (13, 14). This can lead to retention of these conjugates followed by a slow release of biologically active camptothecin within the tumor.

The purpose of this phase 1 study was to assess the safety, toxicity, pharmacokinetics, and pharmacodynamics of pegamotecan in patients with advanced malignancies using a schedule of a 1-hour infusion weekly for 3 weeks followed by 1 week off treatment. The starting dose was 800 mg/m^2 (13.3 mg/m^2 of active camptothecin). This was based on prior experience in an every 3-week dosing phase 1 study in which toxicity was first noted at 4,800 mg/m^2. This dose was divided by three to account for the weekly versus the every 3-week schedule and then further divided by two to account for the potential cumulative toxicity from a weekly schedule.

Patients and Methods

Patient selection. Patients with histologically confirmed advanced solid tumors or lymphomas that had failed to respond to standard therapy or for which no standard therapy was available were eligible to participate. Other inclusion criteria included measurable or assessable disease, age at least 18 years, Eastern Cooperative Oncology Group performance status of ≤2, life expectancy of ≥3 months, and adequate organ function defined as absolute neutrophil count of ≥1,500/μL, platelet count of ≥100,000/μL, hemoglobin of ≥8.5 g/d, serum creatinine level of ≤1.5 mg/d, total bilirubin of ≤1.5 mg/d, and aspartate aminotransferase and alanine aminotransferase levels ≤2.5 times the upper limit of normal (or ≤5 times the upper limit of normal if liver metastases were present). Patients must have been off previous anticancer therapy, including radiation therapy, for at least 30 days (42 days if the previous therapy included a nitrosurea or mitomycin) and must have recovered from the toxic effects of any previous therapy. Patients were excluded from the study if they had any unstable, preexisting medical condition, history of hemorrhagic cystitis or evidence of microscopic hematuria (unless a nonbladder primary origin was documented), or evidence of central nervous system metastases. Pregnant and lactating women were also excluded, and all patients with reproductive potential were required to use an effective contraceptive method if they were sexually active. All patients gave written informed consent according to federal and institutional guidelines.

Study design. This was an open-label, dose-ascending, phase 1 study of pegamotecan. Pegamotecan was administered as a 60-minute infusion once weekly for 3 of 4 weeks, with 4 weeks considered a single course. Courses were repeated every 29 days until a DLT occurred, disease progression was detected, or the patient was removed from the study. Accrual to the next dose level occurred after all patients at the preceding level were observed for 4 weeks without DLT. Intrapatient dose escalation was not permitted.

Dose escalation and definition of study end points. The dose of pegamotecan was increased in increments according to the degree of toxicity observed in the preceding dose level cohort following careful review by the study investigators and pharmaceutical sponsor. The dose escalation scheme was 50% above the previous dose if the toxicity was grades 0 to 2, 33% for grade 3 toxicity, 25% for grade 4 toxicity that was not a DLT, and 20% for a single DLT. Based on these criteria, the dose levels of pegamotecan studied were 800, 1,200, 1,800, 2,700, 3,240, and 4,300 mg/m^2.

For the purpose of escalation to the next dose level, only DLTs occurring during the first cycle of therapy were considered. Toxicities were scored using the National Cancer Institute Common Toxicity Criteria, version 2. DLTs were defined as any of the following: grade 4 neutropenia lasting at least 5 days or associated with fever >38.0°C or infection; platelets <25,000/μL; other grade 4 hematologic toxicity, including a decrease in hemoglobin, at the discretion of the principal investigator; grade 3 or 4 nausea, vomiting, or diarrhea in patients receiving prophylaxis or treatment with an optimal antiemetic or antidiarrhea regimen; grade 3 nonhematologic toxicity; or a delay of >2 weeks in initiating the second cycle of therapy due to unresolved toxicity. If one patient at a dose level experienced DLT during the first two courses of therapy (8 weeks), three additional patients were treated at that dose level to a maximum of six patients. The maximal tolerated dose was defined as the dose level at which no more than one of six patients experienced a DLT. Patients who experienced DLT could continue treatment at a modified dose at the discretion of the treating physician if they seemed to be benefiting from the therapy.

Pretreatment and follow-up studies. Before initiation of therapy, all patients had a history and physical examination, assessment of Eastern Cooperative Oncology Group performance status, radiographic tumor measurements, 12-lead ECG, urinalysis, serum tumor markers, and routine laboratory studies. All laboratory tests to assess study eligibility were completed within 14 days before the start of cycle 1. History, physical examination (including Eastern Cooperative Oncology Group status, vital signs, and body surface area), and both hematologic and nonhematologic laboratory tests were repeated within 24 hours of day 1 of each cycle of therapy. Assessment of toxicity and hematology laboratory evaluations were done weekly during each cycle of therapy. Tumor assessments by computed tomography scans were done after every two cycles, with response assessed according to the WHO criteria (the sum of the products of bidimensional measurements from index lesions). A complete response was defined as complete disappearance of all measurable and evaluable disease lasting for at least 4 weeks and no new lesions. A partial response was defined as >50% decrease in all evaluable and measured lesions lasting at least 4 weeks and no new lesions. Progressive disease was defined as an increase of ≥25% of one or more measurable lesions, the reappearance of any lesion that had disappeared, worsening of any evaluable disease, the appearance of new sites of disease, or significant clinical deterioration. Stable disease was defined as disease that did not fit any of the previous three categories.

Pharmacokinetics. Serial blood samples were collected in 26 patients for analysis of free camptothecin concentration. Blood samples were drawn over 29 days starting on day 1 of cycle 1 at the following times: predose, 15 minutes after the start of the infusion, 59 minutes (1 minute before the end of the infusion), and at the following times after infusion: 15 and 30 minutes, 1, 4, 8, 10, 24, 48, and 72 hours, day 5, days 8 and 15 just before the start of and just after the end of

the infusion, and days 22 and 29. Approximately 3 mL of blood were collected in a heparinized tube and centrifuged at 3,000 rpm for 15 minutes. The plasma was transferred to a sample tube, labeled, frozen at −20°C, and transferred to the laboratory of Dr. Jinee Rizzo at the Institute for Drug Development in San Antonio. Free camptothecin was measured using a validated high-performance liquid chromatography–based assay with a lower limit of quantification of 5.0 ng/mL.

Pharmacokinetic analysis. Free camptothecin plasma concentrations-versus-time data were analyzed using noncompartmental methods (15). The apparent terminal elimination half-life ($t_{1/2}$) was estimated by linear regression of the terminal concentration-time data plotted on a log-linear scale. Actual sampling times and the linear trapezoidal method were used to calculate the area under the curve extrapolated to infinity ($AUC_{0-\infty}$; ref. 15) as implemented in WinNonLin Standard, version 3.1 (Pharsight Corp., Mountain View, CA). Maximal plasma concentrations (C_{max}) and the time of maximal plasma concentration (T_{max}) were determined by direct inspection of the data. Because free camptothecin is a metabolite of pegamotecan, standard noncompartmental variables, such as volume of distribution at steady state and clearance, could not be calculated. Instead, only the following pharmacokinetic variables for free camptothecin in plasma are presented: AUC, C_{max}, T_{max}, and apparent $t_{1/2}$. Mean values and SDs were determined for all variables except $t_{1/2}$'s for which harmonic means and pseudo-SDs are presented (16).

The dose proportionality of the AUC and C_{max} variables was examined by two separate methods, the intercept test (17) and the power model (18). For the intercept test of dose proportionality, weighed linear regression of the untransformed AUC and C_{max} versus dose level plot was done and the intercept estimated for each (17). If the intercept was not significantly different from zero, then the condition of dose proportionality held. The power model test for dose proportionality is somewhat more sensitive and involves unweighed linear regression of the log-transformed AUC or C_{max} plotted as a function of log-transformed dose level. Under conditions of dose proportionality, the slope of this log-log plot should equal 1. The 95% confidence interval (95% CI) for the slope of this regression line was determined using the software program ADAPT II (19), and if the 95% CI included a value of 1, then the dose proportionality criteria as predicted by the power model were satisfied.

Pharmacodynamics. Pharmacodynamic analysis attempted to correlate the effects of pegamotecan with administered dose and pharmacokinetic variables.

Results

Patient characteristics. Between February 2000 and December 2001, 27 patients were enrolled. Their characteristics are summarized in Table 1. The median age was 60 years (range, 19-76) and the median Eastern Cooperative Oncology Group performance status was 0 (range, 0-2). Seventeen patients had previously received only chemotherapy, and 10 had been treated with both chemotherapy and radiation therapy. These 27 patients received a total of 60 cycles of pegamotecan. Two patients did not complete the first cycle of therapy. One of these two patients (2,700 mg/m^2) did not receive study drug on day 15 of cycle 1 and was discontinued 1 week later due to grade 4 pain associated with progressive disease. The other patient (4,300 mg/m^2) did not receive study drug on day 15 of cycle 1 due to grade 4 neutropenia (DLT) and grade 2 thrombocytopenia. This patient with a history of recurrent adenocarcinoma of the gastroesophageal junction was hospitalized with grade 4 gastrointestinal hemorrhage, grade 4 thrombocytopenia, and grade 3 hematuria and died secondary to the hemorrhage within 4 days of presenting to the hospital.

Toxicity. The most common toxicity observed during the first cycle of chemotherapy was myelosuppression (Table 2). Grade 4 neutropenia was the DLT in two of four patients treated at 4,300 mg/m^2, and grade 3 thrombocytopenia was also noted in two of the four patients treated at this level. Only one other patient experienced clinically relevant grade 3 myelosuppression, a patient who developed grade 3 thrombocytopenia at 3,240 mg/m^2.

In 22 of 27 patients there was a prolongation of partial thromboplastin time. There seemed a trend towards an increase in its frequency with increasing administered dose (Table 2). At 800 and 1,200 mg/m^2, four of seven (57%) patients experienced grade 2 or 3 prolonged partial thromboplastin time versus 9 of 13 (69%) patients at 2,700 and 3,240 mg/m^2. Elevations in prothrombin time were sporadic and mostly grade 1. No trend of increased frequency of prothrombin time prolongation was noted with increasing administered pegamotecan dose. There were no clinical findings such as unexpected bleeding episodes in the patients with prolonged partial thromboplastin time to suggest a dysfunction of the intrinsic clotting system.

Bladder irritation, a known side effect of camptothecin, was a common nonhematologic toxicity (Table 3). Its severity ranged

Table 1. Patient characteristics

Characteristics	No. patients (%)
Total patients enrolled	27
Men	16 (59)
Women	11 (41)
Age (y), median (range)	60 (19-76)
ECOG performance status (baseline)	
0	15 (56)
1	9 (33)
2	3 (11)
Race	
Caucasian	21 (78)
African descent	5 (19)
Other	1 (3)
Prior therapy	
Chemotherapy only	17 (63)
Chemotherapy and radiation	10 (37)
Primary tumor diagnosis	
Colon/rectum	9 (33)
Liver (hepatocellular)	3 (11)
Esophagus	2 (7)
Lung	2 (7)
Unknown primary	2 (7)
Sarcoma	2 (7)
Anus	1 (4)
Gastroesophageal junction	1 (4)
Head and neck	1 (4)
Mesothelioma	1 (4)
Ovary	1 (4)
Pancreas	1 (4)
Small bowel	1 (4)
Time from initial diagnosis (mo), mean (range)	18.3 (5.9-37.3)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Hematologic toxicity

Grade	Dose (mg/m^2)																	
	800 (n = 4)			1,200 (n = 3)			1,800 (n = 3)			2,700 (n = 7)			3,240 (n = 6)			4,300 (n = 4)		
	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Neutrophils													1	1			1	2
Hg	1	1		2			2			2			3	1		2	1	
Platelets														1			2	
PTT	1	1		1	1		2			4				5		1	1	
PT													1			1		

Abbreviations: Hg, hemoglobin; PTT, partial thromboplastin time; PT, prothrombin time.

from microscopic hematuria to hemorrhagic cystitis. Hemorrhagic cystitis was observed in three patients who received doses ranging from 2,700 to 4,300 mg/m^2. Cystitis required dose reductions in two patients and a dose delay in one patient. Symptoms of bladder irritation typically occurred after the third weekly treatment. The relationship between the $AUC_{0\text{-}\infty}$ and hematuria is shown in Fig. 1. Hematuria, both microscopic and gross, was observed in 8 of 15 patients with an $AUC_{0\text{-}\infty} \geq 20$ μg h/mL versus 0 of 10 patients with an $AUC_{0\text{-}\infty} < 20$ μg h/mL.

Pharmacokinetics. Pharmacokinetic data were collected from 26 patients at each of the six dose levels listed in Table 4. T_{max}, C_{max}, apparent terminal elimination half-life, $AUC_{0\text{-}72}$, $AUC_{0\text{-last measured time point}}$, and $AUC_{0\text{-}\infty}$ for free camptothecin were calculated for each patient. The majority of patients had pharmacokinetic blood sampling out to 7 days. The harmonic mean and the pseudo-SDs (16) of the apparent terminal elimination half-life of free camptothecin in this study was 46 ± 12.8 hours. Interpatient variability at a given dose level was moderate; for example, the coefficient of variation of $AUC_{0\text{-}\infty}$ at 3,240 mg/m^2 was 57%. Using the intercept test, both the C_{max} and $AUC_{0\text{-}\infty}$ for free camptothecin increased proportionally with increasing dose level (Figs. 1 and 2). Using the more sensitive power model, the 95% CI for the log(C_{max}) versus log(dose level) was 0.266 to 1.242, which includes a value of 1.0 and is consistent with a proportional increase in C_{max} over the dose range studied. In contrast, the 95% CI for the slope of the log($AUC_{0\text{-}\infty}$) versus log(dose level) plot was <1 (95% CI, 0.315-0.992), consistent with a modest deviation from dose proportionality in which the $AUC_{0\text{-}\infty}$ over this dose range did not increase proportionally with increasing dose level. Exclusion of two outlier patients with high C_{max} values (Fig. 2) did not substantially alter these conclusions; therefore, these data points were retained in the current analysis.

Efficacy. Although this study was not designed to evaluate efficacy, two patients were noted to have had evidence of objective response. One patient with metastatic small bowel adenocarcinoma treated at 2,700 mg/m^2 had a 66% decrease in lung metastases but then developed a symptomatic brain metastasis before the time of planned confirmatory scans. Another patient with metastatic esophageal carcinoma treated at 3,240 mg/m^2 had a 59% reduction in index lesions but was then lost to follow-up before the time that confirmatory scans would have occurred. Each of these patients developed symptomatic bladder irritation, with the patient treated at 2,700 mg/m^2 requiring a dose reduction.

Discussion

There are several rationales for an improved therapeutic profile for pegamotecan versus native camptothecin. First, polyethylene glycol modification improves the water solubility of camptothecin. Second, pegamotecan is passively targeted to tumors via the enhanced permeability and retention effect as

Table 3. Nonhematologic toxicity

Grade	Dose (mg/m^2)																	
	800 (n = 4)			1,200 (n = 3)			1,800 (n = 3)			2,700 (n = 7)			3,240 (n = 6)			4,300 (n = 4)		
	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Nausea													1			1		
Vomiting													1					
Fatigue	2				2					2	1		3			2		
Hepatic						1												
Cystitis/UTI				1			1						1	1				
Hemorrhagic cystitis											1					1	1	

Abbreviation: UTI, urinary tract infection.

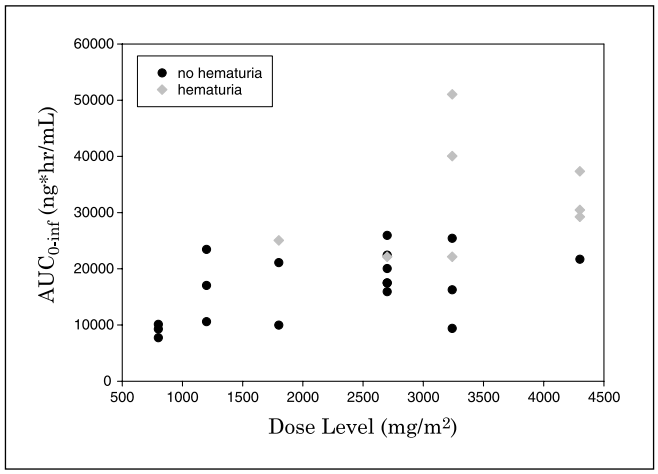

Fig. 1. Patients who developed microscopic hematuria (*light gray diamonds*). The majority of cases occurred at the higher dose levels and with an AUC ≥ 20 ng h/mL.

described by Maeda (13, 20). In preclinical studies, the enhanced permeability and retention effect was shown to result in a higher accumulation of pegamotecan in tumors compared with native camptothecin (21). Third, the low-pH milieu of the tumor shifts the equilibrium of camptothecin towards the active lactone. Finally, pegamotecan significantly prolongs the $t_{1/2}$ of free camptothecin versus the administration of native camptothecin.

In this study, pegamotecan was administered using a weekly regimen consisting of three weekly doses followed by 1 week of no treatment in patients with advanced solid tumors and lymphomas. As anticipated, the DLT was myelosuppression, specifically neutropenia. Other relevant toxicities included thrombocytopenia, bladder irritation, and fatigue. Bladder toxicity seemed related to drug exposure. As seen in Fig. 1, genitourinary toxicity occurred when the $AUC_{0\text{-}\infty}$ was > 20 ng h/mL. Observed in conjunction with the prolonged terminal $t_{1/2}$ of pegamotecan, this may explain the similar overall incidence of genitourinary toxicity observed when pegamotecan was dosed weekly at lower administered doses when compared with as opposed to another phase 1 study in which pegamotecan was administered every 3 weeks but generally at higher doses (22). Patients currently receiving pegamotecan are encouraged to increase their fluid intake up to 3 L/d, an intervention that has been noted to decrease genitourinary toxicity with another camptothecin analogue (23). Prolongation of partial thromboplastin time is of questionable significance, and studies are ongoing to further evaluate its cause.

In general, pegamotecan was well tolerated at doses up to and including the maximum tolerated dose of 3,240 mg/m^2 using this schedule. Few patients experienced clinically significant fatigue (grade ≥2) and gastrointestinal toxicity that was commonly observed with native camptothecin (7). The use of this weekly schedule, however, must be contrasted with the prior experience dosing pegamotecan every 3 weeks. Preliminary antitumor efficacy was also observed, as was dose-limiting myelosuppression and non–dose-limiting hemorrhagic cystitis. Thus, given the long apparent terminal elimination $t_{1/2}$ of camptothecin in plasma after a short infusion of pegamotecan, there is no apparent advantage with weekly administration.

The pharmacokinetics of free camptothecin showed moderate interpatient variability with substantial overlap in drug exposures at different dose levels (Figs. 1 and 2). The mean C_{max} and AUC values are comparable to those reported when pegamotecan was administered every 3 weeks and similar dose levels are compared (22). In the current study, the apparent terminal elimination $t_{1/2}$ of free camptothecin was 46 ± 12.8 hours, and the C_{max} of free camptothecin increased proportionally with dose over the dose range studied (800-4,300 mg/m^2). In contrast, using the power model analysis, the increase in AUC was somewhat less than dose proportional over this same dose range, although the magnitude of this deviation was modest (Fig. 2). In the every 3-week dosing study, dose proportional kinetics were observed for both AUC and C_{max} (22). However, this earlier study used much higher doses of pegamotecan (600-8,750 mg/m^2); >85% of patients received administered doses of >4,800 mg/m^2. Thus, the pharmacokinetic variables in these two studies may not be directly comparable. The every 3-week dosing study also reported a longer apparent terminal elimination $t_{1/2}$ for free camptothecin in plasma (77 ± 36.8 hours) than did the current clinical trial. However, the longer $t_{1/2}$ may reflect the extended time period for blood sampling and the higher plasma camptothecin concentrations in the prior study rather than a true difference in drug kinetics.

Conclusions

The maximal tolerated dose of pegamotecan when administered weekly for 3 weeks followed by 1 week off is

Table 4. Plasma pharmacokinetics of free camptothecin after pegamotecan administration (mean ± SD)

Dose level (mg/m^2)	*n*	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	$t_{1/2}$ (h)*
800	3	101 ± 22	20.4 ± 8.1	9,032 ± 1,215	48 ± 9
1,200	3	158 ± 34	48.2 ± 0.2	17,022 ± 6,436	51 ± 17
1,800	3	666 ± 861	17.1 ± 13.7	18,710 ± 7,826	42 ± 13
2,700	7	258 ± 70	11.3 ± 10.2	20,199 ± 3,530	53 ± 18
3,240	6	496 ± 516	9.86 ± 9.05	27,383 ± 15,487	44 ± 8
4,300	4	404 ± 99	9.6 ± 11.2	29,689 ± 6,413	38 ± 11

*Harmonic means and pseudo-SDs.

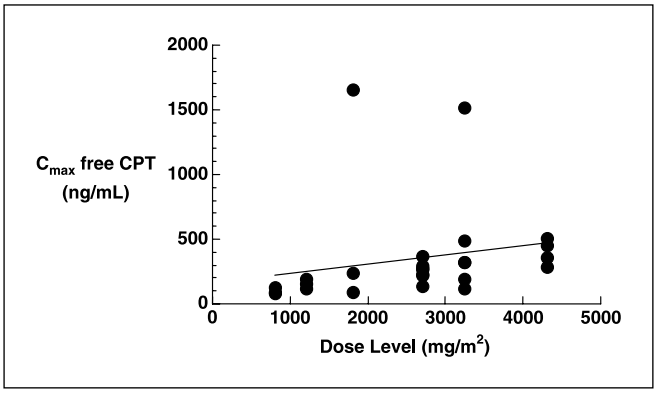

Fig. 2. There is a limited increase in the maximum serum concentration of free camptothecin (*CPT*) as the administered dose of pegamotecan is increased.

3,240 mg/m^2. The DLT was grade 4 neutropenia, observed in two of four patients administered 4,300 mg/m^2. Prolongation of partial thromboplastin time was noted, but no clinically relevant bleeding abnormalities occurred; further evaluation of this phenomenon is under way. Among nonhematologic toxicities, the incidence of gastrointestinal toxicity was low, but genitourinary toxicity seems to occur in the same effective dose range as noted with native camptothecin in earlier trials (27-43 mg/m^2; ref. 7). Hemorrhagic cystitis, a known toxicity of native camptothecin, was observed in three patients (11%), and seemed to correlate with AUC. Increased fluid intake of up to 3 L/d is recommended for patients receiving pegamotecan. The observed antitumor activity suggests that pegamotecan has single activity and merits further investigation in phase 2 studies.

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