Phase I Dose-finding and Pharmacokinetic Trial of Irinotecan Hydrochloride (CPT-11) Using a Once-Every-Three-Week Dosing Schedule for Patients with Advanced Solid Tumor Malignancy[1]

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ABSTRACT

A Phase I study was performed to determine the maximum tolerated dose (MTD), toxicities, and pharmacokinetic profile of irinotecan (CPT-11) and its active metabolites when given on a once-every-3-week schedule. Thirty-four patients with advanced refractory solid malignancies were treated with CPT-11 (240–340 mg/m^2) administered as a 90-min i.v. infusion every 3 weeks. Patients were divided into two groups: those with and those without prior abdominal/pelvic (AP) radiotherapy. Gastrointestinal toxicity (nausea, vomiting, and diarrhea) and hematological toxicity (leukopenia and neutropenia) were dose-limiting side effects. Other common toxicities included anorexia, asthenia, and acute cholinergic symptoms (abdominal cramps, diaphoresis, and lacrimation). For patients with no prior AP radiation therapy, the MTD was determined to be 320 mg/m^2, whereas those with prior AP radiation therapy had a MTD of 290 mg/m^2. Dose-proportional increases in the mean area under the concentration-time curves for CPT-11, SN-38, and SN-38G were not observed over the narrow dose range studied. Mean values of terminal phase half-life, clearance, terminal phase volume of distribution, and steady-state volume of distribution for CPT-11 were 12.4 ± 1.8 h, 13.0 ± 3.8 liters/h/m^2, 234 ± 83 liters/m^2, and 123 ± 38 liters/m^2, respectively. The pharmacodynamic analyses indicated the strongest correlation to be between SN-38 area under the concentration-time curves and neutropenia ($\rho = 0.60$; $P = 0.001$). A total of five responses (one complete response and four partial responses) were observed in the cohort of 32 patients with previously treated metastatic colorectal carcinoma. In conclusion, gastrointestinal toxicity and hematological toxicity were the dose-limiting toxicities of CPT-11 when administered as a 90-min infusion every 3 weeks. In this trial, the recommended Phase II starting dose for patients with no prior AP radiation therapy was found to be 320 mg/m^2; for patients with prior AP radiation, the recommended Phase II starting dose was 290 mg/m^2. This once-every-3-week schedule has been incorporated into a Phase I trial of CPT-11 combined with 5-fluorouracil and leucovorin.

INTRODUCTION

Camptothecin is a plant alkaloid obtained from the Chinese tree *Camptotheca acuminata*. Camptothecin and its derivatives are potent inhibitors of topo-I[3] (1). CPT-11 (Camptosar) is a synthetic analogue of camptothecin that is rapidly converted *in vivo* to an active metabolite, SN-38. The primary target of SN-38 is topo-I (2). topo-I is a nuclear enzyme that induces single-stranded breaks in DNA, relieving torsional strain during DNA replication. SN-38 binds to the topo-I/DNA complex, preventing religation of DNA after cleavage by topo-I (3). Subsequent collision of replication forks with this complex results in double-stranded DNA breaks that lead to cell death. CPT-11 exhibits greater aqueous solubility and greater *in vitro* and *in vivo* activity and has a more predictable toxicity profile than its parent compound, camptothecin (4).

Based on initial reports from Japan of CPT-11 activity in patients with 5-FU-refractory metastatic colon cancer, clinical trials were initiated in the United States and Europe (5–7). Several Phase I trials have been performed with CPT-11 using different schedules. In the United States, the Phase I schedule that provided the background for pivotal Phase II trials was developed by Rothenberg *et al.* (6). In this schedule, weekly treatments of CPT-11 were given for 4 weeks followed by a

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[3] The abbreviations used are: topo-I, topoisomerase I; CPT-11, irinotecan; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; AP, abdominal/pelvic; 5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; IS, internal standard; AUC, area under the concentration-time curves; C_{max}, peak plasma concentrations; T_{max}, the time at which C_{max} occurred; CL, clearance; V_z, terminal phase volume of distribution; V_{ss}, steady-state volume of distribution; $t_{1/2Z}$, terminal phase half-life.

2-week rest period. The MTD was 150 mg/m^2, with DLTs of diarrhea and neutropenia. Another Phase I trial performed in the United States used an every-3-week schedule (7). The MTD was 240 mg/m^2, with DLTs consisting of a constellation of nausea and vomiting, abdominal cramping, diarrhea, and myelosuppression. The early European Phase I trials of CPT-11 evaluated several different schedules (8–10). Abigerges *et al.* (8) conducted a Phase I trial using an every-3-week schedule combined with intensive loperamide support to control diarrhea. The DLT was neutropenia at the highest dose level of 750 mg/m^2, although the current recommended dose of CPT-11 in Europe is 350 mg/m^2 given every 3 weeks. Merrouche *et al.* (11) have also performed a feasibility study using a high-dose loperamide regimen and CPT-11 doses of 500 and 600 mg/m^2 every 3 weeks.

Because of the discrepant MTDs from these initial Phase I trials, we performed another Phase I trial of CPT-11 given once every 3 weeks. We also wanted to reexamine the toxicities of the drug with this schedule and perform a pharmacokinetic analysis to assess any pharmacodynamic relationship between CPT-11, its metabolites, and DLTs.

PATIENTS AND METHODS

Eligibility

Patients entered had histologically confirmed solid tumor malignancy that was not curable by surgery, radiation therapy, or standard chemotherapy. Eligibility criteria included the following: (*a*) measurable or evaluable disease; (*b*) age ≥ 18 years; (*c*) an ECOG performance status of ≤2; (*d*) a life expectancy of at least 12 weeks; (*e*) no prior chemotherapy within the previous 4 weeks (6 weeks in patients treated with mitomycin C or nitrosoureas) and recovery from any toxic effects of prior treatment; (*f*) no more than two prior chemotherapy regimens; (*g*) no prior treatment with CPT-11 or other camptothecins; (*h*) no prior radiation therapy for at least 6 weeks and measurable lesions present outside the radiation field; (*i*) radiation therapy to ≤25% of bone marrow; (*j*) adequate hematopoiesis (neutrophil count ≥ 1,500/mm^3, platelet count ≥ 150,000/mm^3, and hemoglobin level of ≥9.0 g/dl), renal function (serum creatinine ≤ 2.0 mg/dl), and liver function (aspartate aminotransferase ≤3× institutional upper limit of normal or ≤5× institutional upper limit of normal if liver involved with metastatic disease, and serum bilirubin within institutional upper limit of normal); (*k*) no active or uncontrolled infection; (*l*) absence of pregnancy or lactation; (*m*) no known central nervous system metastases or carcinomatous meningitis; (*n*) no interstitial pneumonia or extensive/symptomatic interstitial fibrosis of the lung causing greater than or equal to grade 2 dyspnea; and (*o*) no medical (uncontrolled high blood pressure, unstable angina, active congestive heart failure, myocardial infarction within the previous 6 months, or serious uncontrolled cardiac arrhythmia) or psychiatric conditions that might place patients at risk for participation in investigational treatment. All patients gave written informed consent according to institutional and federal guidelines before treatment.

After six patients were treated on protocol, patients were divided into those with no prior AP radiation therapy and those with prior AP radiation therapy. Once the MTD was determined for those patients with no prior AP radiation, the dose level was decreased two dose levels, and additional patients with prior AP radiation were enrolled. Also, because of the significant myelosuppression seen in one patient with prior exposure to both nitrosourea and mitomycin C, additional patients treated previously with these drugs were excluded from study entry.

Treatment Plan

The starting dose of CPT-11 was 240 mg/m^2, with planned dose escalation to 290, 340, and 390 mg/m^2 every 3 weeks. An intermediate dose level of 320 mg/m^2 was subsequently added to better define the MTD after DLT was observed at the 340 mg/m^2 dose level. A minimum of three patients were enrolled at each dose level and observed for at least 3 weeks before enrolling any patients at the next dose level. If DLT was observed in one of the first three patients enrolled at a dose level, three additional patients were enrolled at the same level. DLT in two or more patients identified that level as the DLT dose level. The MTD was defined as one level below the DLT dose level. After identification of the MTD, additional patients were enrolled to more fully evaluate the toxicities at MTD. DLT was defined as (*a*) grade 4 hematological toxicity lasting for 5 or more days, (*b*) febrile neutropenia, (*c*) grade 4 diarrhea or vomiting that occurred despite adequate supportive measures, and (*d*) any other nonhematological toxicity of grade 3 intensity or higher. In addition, patients who had treatment delayed for 2 weeks as a result of toxicity related to CPT-11 were considered to have DLT. Intrapatient dose escalation was not permitted on this study.

CPT-11 was supplied by Pharmacia & Upjohn (Peapack, NJ) in two forms, 2-ml vials containing 40 mg of drug and 5-ml vials containing 100 mg of drug. The appropriate dose, based on actual calculated body surface area, was mixed in 500 ml of 5% dextrose and infused through a free-flowing i.v. catheter over a 90-min period.

Pretreatment and Follow-Up Evaluations

Prestudy evaluations comprised a complete history and physical examination including height and weight, ECOG performance score, complete blood count, serum electrolytes and chemistries, tumor markers (where appropriate), serum pregnancy test in women with childbearing potential, chest X-ray, baseline tumor measurements, and an electrocardiogram. Patients were seen by an oncologist before each CPT-11 infusion. During off-treatment weeks, an experienced oncology nurse made phone inquiries about toxicity. Complete blood counts were performed weekly. Patients were evaluated before each treatment. Serum electrolytes and serum chemistries, tumor markers, and indicator lesions were measured every other cycle. Patients were continued on therapy if they tolerated treatment and their disease did not progress. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria.

Concurrent Therapy

Loperamide (Imodium or Kaopectate 1-D) was given to patients at the earliest signs of diarrhea that occurred more than

12 h after the CPT-11 infusion. Loperamide was prescribed at a dose of 4 mg after the first loose bowel movement and then at 2 mg every 2 h until diarrhea resolved for at least 12 h. Patients were allowed to take loperamide, 4 mg every 4 h, during the night. Atropine was also given at doses of up to 1 mg i.v. for diarrhea or abdominal cramping that occurred during or immediately after the CPT-11 infusion. Dexamethasone and other antiemetics (ondansetron or granisetron) were used as clinically indicated. Patients who were taking warfarin had prothrombin time monitoring weekly during the trial due to previous report of a possible interaction between CPT-11 and warfarin.

Pharmacokinetics

Sample Collection. Blood samples (7 ml) were drawn via venipuncture or indwelling i.v. cannula into heparin-containing tubes at the following times: (*a*) before beginning the CPT-11 infusion; (*b*) 45 and 90 min after beginning the infusion; (*c*) 5, 10, 15, and 30 min after the end of the infusion; and (*d*) 1, 2, 4, 6, 8, 10, 12, 24, 32, and 48 h after the end of the infusion. Blood samples were collected from the arm contralateral to the infusion line. If a heparin lock was used, 1 ml of whole blood was withdrawn and discarded before sample collection.

Collection tubes were immediately placed into a slurry of ice water. The plasma was separated by centrifugation of the samples at 1000–1200 × *g* for 20 min and then transferred into plastic tubes. The plasma specimens were stored at −30°C until assay, and the time of the storage was within the year supported by stability data for CPT-11 and SN-38.

Assay Methods. Plasma specimens were assayed for concentrations of total CPT-11 and SN-38 using validated, sensitive, and specific isocratic high-performance liquid chromatography methods with fluorescence detection (12). Briefly, each plasma specimen was mixed with an IS (camptothecin) in acidified acetonitrile to precipitate plasma proteins and incubated for 15 min at 40°C to convert the analytes to their respective lactone forms. After the addition of triethylamine buffer (pH 4.2), the sample was centrifuged, and the supernatant was transferred to an amber vial for injection (40 μl) onto the high-performance liquid chromatography system. Chromatographic separation was achieved using a Zorbax-C8 column (MacMod) and a mobile phase consisting of 28:72 (v/v) acetonitrile:0.025 M triethylamine buffer (pH 4.2). The fluorescence detector was operated at an excitation wavelength of 372 nm; CPT-11 and IS were monitored at an emission wavelength of 425 nm, whereas SN-38 was monitored at 535 nm. To determine the concentrations of SN-38G, a separate portion of each plasma sample was hydrolyzed via the addition of a β-glucuronidase solution. The conversion reaction was terminated by precipitating the proteins using an acidified acetonitrile solution of the IS, and the remainder of the procedure was repeated. Plasma concentrations of SN-38G were estimated as the increase in SN-38 concentration after incubation of plasma with β-glucuronidase.

Calibration standard responses were linear over the range of 1.28–3840 ng/ml for CPT-11 ($r^2 \geq 0.998$) and over the range of 0.48–640 ng/ml for SN-38 ($r^2 \geq 0.999$). The lower limit of quantitation of CPT-11 (expressed as the free base) and SN-38 (expressed as the monohydrate) was 1.28 and 0.48 ng/ml, respectively. The mean assay precision, which was expressed as the coefficient of variation of the estimated concentrations of quality control standards, averaged 4.5%, 4.3%, and 6.9%, respectively, for low (12.8 ng/ml), medium (160 ng/ml), and high (3200 ng/ml) concentrations of CPT-11 and averaged 4.9%, 4.5%, and 3.2%, respectively, for low (1.20 ng/ml), medium (12.0 ng/ml), and high (320 ng/ml) concentrations of SN-38. Assay accuracy, expressed as the ratio (%) of the estimated: theoretical QC standard concentrations, averaged 96–99.1% for CPT-11 and 90–99% for SN-38.

Calculation of Pharmacokinetic Parameters. Doses of CPT-11 administered in this trial were expressed as the hydrated hydrochloride salt (CPT-11 hydrochloride trihydrate). For pharmacokinetic analyses, CPT-11 concentrations were expressed in free base units (M_r of the hydrochloride trihydrate = 677.19; M_r of the anhydrous free base = 586.69), and SN-38 concentrations were expressed as monohydrate equivalents (M_r of the monohydrate = 410.44; M_r of anhydrous SN-38 = 392.42).

CPT-11, SN-38, and SN-38G plasma concentration data were analyzed by noncompartmental methods (13). The actual times of the initiation of drug infusion and blood sampling were recorded, and the time interval relative to the start of drug infusion was used to calculate the AUCs. The apparent terminal elimination rate constants (λz) were determined by linear least-squares regression of plasma-concentration time points that were determined to lie in the terminal log-linear region of the plasma concentration-time profiles. The apparent elimination half-life ($t_{1/2}$) was calculated as 0.693/λz.

C_{max} and T_{max} values were determined from individual patient CPT-11, SN-38, and SN-38G concentration-time curves. $AUC_{0\text{-}T}$ values were determined using the linear trapezoidal rule from time 0 to the last sampling time at which quantifiable drug concentrations were detected (C_T). Area under the CPT-11 plasma concentration-time curves through infinite time ($AUC_{0\text{-}\infty}$) was calculated by adding $C_T/\lambda z$ to AUC_{0-48}. The CL and apparent V_z of CPT-11 were calculated as dose/$AUC_{0\text{-}\infty}$ and CL/λz, respectively, where dose is the administered dose of CPT-11 expressed in free base equivalents. A metabolite ratio, estimated as the ratio of metabolite SN-38 $AUC_{0\text{-}\infty}$:CPT-11 $AUC_{0\text{-}\infty}$, was used as a measure of the relative extent of the conversion of CPT-11 to SN-38.

Statistical Considerations

The main focus of this Phase I protocol was to determine the MTD of CPT-11 when CPT-11 was given once every 3 weeks. The MTD was defined as the dose level below which two or more DLTs were observed. Toxicity data were summarized via basic descriptive statistics (frequency and severity) using the National Cancer Institute Common Toxicity Criteria grading taxonomy. Hematological toxicity was also summarized by distributional statistics (mean, median, and so forth).

Relationships between treatment-related toxicities and pharmacokinetic parameters (C_{max} and AUC values) for CPT-11, SN-38, and SN-38G were assessed. Initial assessment included an examination of scatterplots and simple correlational statistics in an attempt to demonstrate potential relationships between toxicity parameters and either C_{max} or AUC values for CPT-11, SN-38, and SN-38G. If relationships were observed, further modeling was performed to characterize these relationships. These efforts included ordinary least-squares linear and

Table 1 Patient characteristics

No. of assessable patients	34
Median age (range) (yrs)	61 (31–80)
Sex (M/F)	21/13
ECOG performance status	
0	20
1	11
2	3
Tumor type	
Colorectal	32
Esophageal	1
Gallbladder	1
Prior surgery	33
Prior systemic therapy	
Chemotherapy (1 regimen/2 regimens)	34 (12/22)
Mitomycin C/nitrosourea	2
Immunotherapy	5
Prior radiation therapy	17
AP	14
Other	3
No. of sites of metastases	
1	8
2	9
3 or more	17

Table 2 Dose levels

Dose level (mg/m^2)	No. of patients with no prior AP radiation	No. of patients with prior AP radiation
240	1	2
290	5	7
320	8	5
340	6	0

logistic regression models. Limited sampling models were explored relating serum concentration levels with AUC using a series of regression models. The results of these analyses are reported elsewhere (14).

RESULTS

A total of 35 patients consented to study participation. One patient did not receive treatment due to small bowel obstruction. Patient characteristics for the 34 patients receiving CPT-11 are shown in Table 1. The number of patients enrolled at each dose level and their prior AP radiation status is shown in Table 2. A total of 174 assessable courses of CPT-11 were administered (median, 4 courses; range, 1–18 courses).

Hematological Toxicity. Hematological toxicity observed in cycle 1 is outlined in Table 3. For patients without prior AP therapy, dose-limiting hematological toxicity (grade 4 neutropenia for $\geq$5 days or febrile neutropenia) occurred in two patients treated with 340 mg/m^2. Another patient at this dose level experienced grade 4 neutropenia lasting $<$5 days. Thrombocytopenia was mild and infrequent, except in one patient treated at a dose of 290 mg/m^2 who had undergone extensive prior treatment with mitomycin C and a nitrosourea. This patient experienced grade 4 myelosuppression (leukocytes, neutrophils, and platelets).

For patients with prior AP radiotherapy, three of five patients at the 320 mg/m^2 level experienced grade 4 neutropenia. The neutropenia persisted for more than 7 days in only one patient. One episode of transient grade 4 leukopenia was encountered at the 290 mg/m^2 dose level. Significant thrombocytopenia was not encountered in this patient cohort. Two patients experiencing dose-limiting neutropenia received granulocyte colony-stimulating factor support after the occurrence of grade 4 neutropenia.

Gastrointestinal Toxicity. Several gastrointestinal toxicities encountered during the first cycle are summarized in Table 4. Dose-limiting gastrointestinal toxicities were encountered in both groups of patients. For those patients without prior AP radiotherapy, two episodes of grade 4 diarrhea (including hemorrhagic colitis in one patient) were reported at the 340 mg/m^2 dose level. Another patient without prior AP radiation therapy had grade 4 diarrhea at the 320 mg/m^2 dose level, but this patient did not use the intensive loperamide regimen to limit the severity of symptoms. Significant grade 4 diarrhea was seen in two patients with prior AP radiotherapy at both the 290 and 320 mg/m^2 dose levels. The patient treated with 290 mg/m^2 received diphenoxylate/atropine (Lomotil) for supportive care because of loperamide intolerance.

Nausea, vomiting, and anorexia were also observed during this trial, despite supportive measures (Table 4). Vomiting was considered dose limiting in two patients without prior AP radiotherapy; one had started therapy at a CPT-11 dose of 290 mg/m^2, and one was treated with 320 mg/m^2 CPT-11. One patient treated with 320 mg/m^2 CPT-11 experienced grade 4 vomiting, which was felt to be due to small bowel obstruction from progressive disease. For patients with prior AP radiation therapy, two episodes of grade 4 vomiting were encountered at doses of both 290 and 320 mg/m^2. The patient treated with 320 mg/m^2 also experienced DLT neutropenia and grade 3 fatigue. Antiemetic measures included 5-hydroxytryptamine 3 receptor inhibitors and dexamethasone in three of the four patients with DLT episodes.

Cholinergic Symptoms. CPT-11 administration has been associated with transient cholinergic symptoms that occur during or immediately after the drug infusion (15). These symptoms include abdominal pain, diaphoresis, early diarrhea, lacrimation, salivation, bradycardia, hypotension, and visual changes. Patients reported several of these symptoms, with abdominal pain being the most frequently described symptom (see Table 5). Most events were mild ($\leq$grade 2), although one patient at the 320 mg/m^2 dose level had grade 4 early diarrhea that resolved spontaneously without the use of atropine. Cholinergic symptoms appeared to occur more frequently at higher dose levels. The incidence of cholinergic symptoms ranged from 33% of patients at the 240 mg/m^2 dose level to 83% of patients treated at a starting dose of 340 mg/m^2. Use of atropine was effective in ameliorating these symptoms. No clinically significant bradycardia or hypotension was noted during first cycle CPT-11 administration.

Pharmacokinetic Results. Pharmacokinetics were characterized for all 34 patients who received CPT-11. Doses ranged from 240–340 mg/m^2. A representative plasma concentration-time curve is shown in Fig. 1. Maximum CPT-11 concentrations were generally observed at the termination of the infusion, with subsequent peak metabolite levels occurring approximately 1 h

Table 3 Hematological toxicity

Dose level (mg/m^2)	No. of patients	Leukopenia				Neutropenia				Thrombocytopenia			
		1	2	3	4	1	2	3	4	1	2	3	4
240	3	1	1	0	0	0	1	1	0	2	0	0	0
290													
No prior AP RT[a]	5	1	1	0	1	1	1	0	1	0	0	0	1
Prior AP RT	7	0	1	2	1	0	2	2	1	0	0	0	0
320													
No prior AP RT	8	4	1	2	0	2	2	0	2	2	0	0	0
Prior AP RT	5	0	1	3	1	1	1	0	3	1	0	0	0
340	6	0	2	0	1	1	0	0	3	2	1	0	0

[a] RT, radiotherapy.

Table 4 Gastrointestinal toxicity

Dose level (mg/m^2)	No. of patients	Nausea			Vomiting				Diarrhea				Anorexia			
		1	2	3	1	2	3	4	1	2	3	4	1	2	3	4
240	3	2	1	0	1	0	0	0	2	0	0	0	1	0	0	0
290																
No prior AP RT[a]	5	1	3	1	1	1	0	1	1	1	0	0	1	2	0	0
Prior AP RT	7	4	0	1	0	0	0	1	2	3	0	1	3	2	0	0
320																
No prior AP RT	8	3	3	2	2	2	1	1	3	2	1	1	3	2	0	0
Prior AP RT	5	2	1	1	2	0	0	1	4	0	0	1	2	0	1	0
340	6	2	2	0	2	2	0	0	3	1	0	1	2	2	0	0

[a] RT, radiotherapy.

Table 5 Cholinergic symptoms

Symptom	NCI[a] grade				% of 34 patients
	1	2	3	4	
Abdominal pain	6	4	4	0	41.2
Diaphoresis	7	1	0	0	23.5
Diarrhea (early)	3	2	0	1	17.6
Lacrimation	2	0	0	0	5.9
Salivation	1	0	0	0	2.9

[a] NCI, National Cancer Institute.

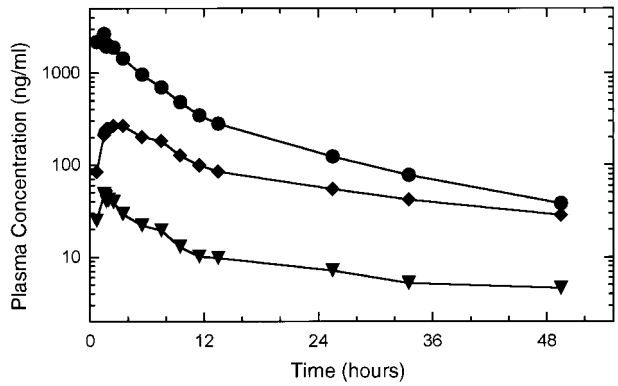

Fig. 1 Representative patient plasma profile of CPT-11 (●), SN-38 (▼), and SN-38G (♦) after a 90-min i.v. infusion of 320 mg/m^2 CPT-11.

after the 90-min infusion. SN-38 peak concentrations were approximately 60-fold lower than CPT-11 peak concentrations, and SN-38G peak concentrations were approximately 20-fold lower than CPT-11 peak concentrations. CPT-11, SN-38, and SN-38G pharmacokinetics were determined by noncompartmental analysis (Table 6). Due to the substantial interpatient variability in AUC values at each dose level and the narrow dose range studied, a dose-proportional increase in mean CPT-11 AUC values was not observed in this study (Fig. 2*A*). Similarly, there was extensive interpatient variability in the plasma CL of CPT-11, but these values were comparable to those reported previously and were independent of dose (Fig. 3). Mean values of $t_{1/2Z}$, CL, V_Z, and V_{ss} for CPT-11 were 12.4 ± 1.8 h, 13.0 ± 3.8 liters/h/m^2, 234 ± 83 liters/m^2, and 123 ± 38 liters/m^2, respectively.

Substantial interpatient variability was also observed for the CPT-11 metabolites SN-38 and SN-38G (Fig. 2, *B* and *C*, respectively). Peak plasma concentrations of SN-38 were found 2 h after the beginning of the CPT-11 infusion, and the disappearance of SN-38 was somewhat longer than that of CPT-11, with a $t_{1/2Z}$ of 21.1 ± 7.3 h. Plasma exposure to SN-38 was approximately 5% of that found for the parent drug. A relationship between dose and SN-38 AUC was not observed. A moderately strong relationship was seen between CPT-11 AUC and SN-38 AUC (Pearson correlation coefficient = 0.43; $P = 0.01$).

Peak plasma concentrations of SN-38G were found 2 h after the beginning of the CPT-11 infusion, and the disappearance of SN-38G paralleled that of CPT-11, with a $t_{1/2Z}$ of 18.3 ± 5.3 h. The plasma exposure to the inactive metabolite SN-38G was approximately 15% of that found for the parent drug. A relationship between dose and SN-38G AUC was not

Table 6 Summary of mean ± SD CPT-11, SN-38, and SN-38G pharmacokinetic parameters

	Dose (mg/m^2)			
	240 (n = 3)	290 (n = 12)	320 (n = 13)	340 (n = 6)
CPT-11				
$t_{1/2}$ (h)	12.9 ± 3.6	12.8 ± 1.8	11.9 ± 1.7	12.2 ± 1.6
C_{max} (ng/ml)	2810 ± 314	3418 ± 975	3432 ± 587	3392 ± 874
AUC (ng/ml·h)	18091 ± 1657	22270 ± 5882	22695 ± 8546	22998 ± 7336
CL (liters/h/m^2)	11.6 ± 1.0	12.1 ± 3.8	13.6 ± 4.3	12.1 ± 3.8
V_z (liters/m^2)	215 ± 60	229 ± 91	240 ± 95	229 ± 91
V_{ss} (liters/m^2)	120 ± 13	122 ± 52	122 ± 35	122 ± 52
SN-38				
T_{max} (h)[a]	1.55 ± 0.05	1.84 ± 0.72	2.15 ± 0.83	2.02 ± 0.40
C_{max} (ng/ml)	41 ± 2	68 ± 40	68 ± 27	56 ± 28
AUC (ng/ml·h)	638 ± 124	797 ± 405	712 ± 276	714 ± 415
$t_{1/2}$ (h)	27.1 ± 12.5	21.5 ± 5.7	19.3 ± 7.0	21.0 ± 8.2
SN-38G				
T_{max} (h)[a]	1.83 ± 0.14	2.07 ± 0.40	2.37 ± 0.61	1.84 ± 0.35
C_{max} (ng/ml)	109 ± 30	160 ± 61	198 ± 81	168 ± 69
AUC (ng/ml·h)	1710 ± 465	2421 ± 1347	2663 ± 1413	2329 ± 1199
$t_{1/2z}$ (h)	20.3 ± 3.8	19.7 ± 7.0	17.0 ± 4.5	17.2 ± 3.6
AUC ratios[b]				
SN-38/CPT-11	5.0 ± 0.5	5.2 ± 2.2	4.8 ± 2.1	4.3 ± 1.8
SN-38G/CPT-11	13.7 ± 4.6	15.4 ± 7.2	16.8 ± 8.4	14.1 ± 4.9

[a] Time relative to the start of the infusion.
[b] Ratio of SN-38 or SN-38G to CPT-11 AUC, expressed as a percentage.

Table 7 Spearman correlation between AUC of CPT-11, SN-38, and SN-38G and worst grade toxicity for cycle 1

	CPT-11		SN-38		SN-38G	
Toxicity	ρ	P	ρ	P	ρ	P
Nausea	0.19	0.27	0.42	0.01	0.42	0.01
Vomiting	0.37	0.03	0.41	0.02	0.23	0.19
Diarrhea	0.23	0.19	0.33	0.05	0.13	0.45
Neutropenia	0.31	0.07	0.60	0.001	0.13	0.45
Leukopenia	0.27	0.12	0.30	0.09	0.13	0.47
Thrombocytopenia	0.12	0.51	0.31	0.07	0.35	0.04

observed (Fig. 2*C*). A relationship was seen between CPT-11 AUC and SN-38G AUC (Pearson correlation coefficient = 0.58; P = 0.001).

Further exploratory analysis was undertaken to evaluate the relationships between several pharmacokinetic parameters and toxicity. Results indicate significant correlations between CPT-11 AUC and vomiting; between SN-38 AUC and nausea, vomiting, and neutropenia; and between SN-38G and nausea and thrombocytopenia (Table 7). The relationship between SN-38 AUC and neutropenia expressed as the percentage change from baseline (Fig. 4) was also significant (Spearman ρ = 0.72; P = 0.001).

Efficacy Results. Five patients with previously treated metastatic colorectal carcinoma demonstrated a >50% reduction in tumor size. The four partial responses and one complete response were confirmed with follow-up radiographs. Response duration ranged from 3.7–11.8 months. One patient achieved a complete response of liver and lung metastases after nine cycles of CPT-11 chemotherapy. Treatment was discontinued, and the patient was observed for approximately 5 months. After progression of his disease, CPT-11 chemotherapy was reinstituted, and further regression of the metastases was noted.

DISCUSSION

This Phase I study reports a single-center dose-escalation study of CPT-11 administered i.v. over a 90-min period every 3 weeks. Previous Phase II studies of CPT-11 in refractory colorectal cancer in the United States have used a 6-week course of weekly therapy for 4 weeks followed by a 2-week rest (16, 17). An earlier United States Phase I trial evaluating CPT-11 administered every 3 weeks indicated a MTD of only 240 mg/m^2 (7). Previous European Phase II studies of CPT-11 in advanced colorectal cancer patients used a dose of 350 mg/m^2 (18). Given the extensive European experience indicating the safety and efficacy of CPT-11 administered at 350 mg/m^2 every 3 weeks, reevaluation of this schedule in the United States was felt to be warranted.

Our patient population consisted mainly of patients with previously treated metastatic colorectal carcinoma (Table 1). Most patients had received two prior chemotherapy regimens. This Phase I study initially treated patients at the previously reported MTD of 240 mg/m^2. Two patients experienced grade 4 vomiting at 290 mg/m^2, but in one of these patients, this toxicity was related to small bowel obstruction and was not treatment

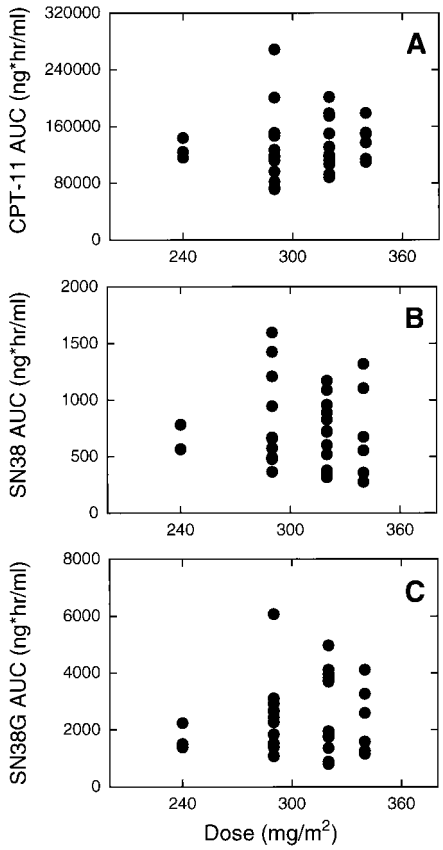

Fig. 2 Scatterplots of patient CPT-11 (A, $n = 34$), SN-38 (B, $n = 34$), and SN-38G (C, $n = 34$) AUC values *versus* dose.

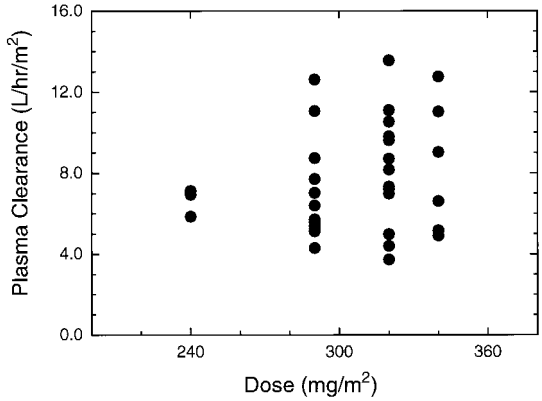

Fig. 3 Scatterplot of CPT-11 plasma CL *versus* dose ($n = 34$).

related. One patient experienced grade 4 myelosuppression at 290 mg/m^2; however, this patient received extensive prior mitomycin C and nitrosourea. Given alternative explanations for these toxicities, further dose escalation was pursued, and eligibility for previous chemotherapy and radiotherapy was amended. At the next dose level of 340 mg/m^2, three of six patients experienced DLT. This includes one patient who experienced simultaneous neutropenic sepsis and grade 4 diarrhea. An intermediate dose of 320 mg/m^2 was evaluated in eight patients. One patient experienced grade 4 vomiting and diarrhea. Thus, the MTD for patients without prior AP radiation was determined to be 320 mg/m^2 administered every 3 weeks.

Patients with prior AP radiation were enrolled at 290 mg/m^2. One episode of grade 4 diarrhea and vomiting was noted in the seven patients treated at this dose level. With subsequent dose escalation to 320 mg/m^2, two of five patients experienced DLT. This included one patient with grade 4 diarrhea and another patient with grade 4 vomiting and neutropenia lasting for >5 days. The MTD of CPT-11 administered every 3 weeks was 290 mg/m^2 for patients with prior AP radiation therapy. This slightly lower MTD for patients with prior pelvic radiation therapy is not unexpected, given the finding of an increased incidence of grade 4 leukopenia in patients with prior pelvic radiotherapy reported in a Phase II trial using the weekly schedule (17). Despite intensive loperamide support, diarrhea remained a DLT, along with other gastrointestinal toxicities including nausea and vomiting. A constellation of gastrointestinal symptoms including abdominal cramping limited dose escalation in the previous United States Phase I trial (7). This CPT-11-induced side effect of abdominal cramping was common in our patient population (Table 5) but was easily ameliorated by atropine as described in previous trials (15, 19).

Discrepancies between MTDs reported in Phase I trials may be due to several factors. Patient populations can differ, as can the definitions of MTD. In the current trial, one patient experienced DLT at 340 mg/m^2 that consisted of hemorrhagic colitis. This toxicity has been reported previously in prior Phase I and II trials; however, it is not the typical dose-limiting diarrheal toxicity reported with CPT-11 treatment. Older age has also been associated with a greater risk of diarrhea (20, 21). In the current trial, all patients experiencing DLT at 340 mg/m^2 were >65 years of age, suggesting a potential contribution of age in this small subset of our patients. CPT-11-induced toxicity may also be influenced by baseline bilirubin levels (22). One patient with prior pelvic radiation therapy and an abnormal baseline bilirubin had DLT in the current trial. Different definitions of MTD may lead to discrepant results. Abigerges *et al.* (8) used a MTD defined as the dose level below that which causes greater than 50% grade 3 or 4 toxicity in the same category of toxicity. Our definition of MTD was based on the occurrence of grade 3 or 4 toxicity in only two of six patients (33%) at a given dose level, with no requirement for identical DLTs to be observed in these patients. Finally, differences in the MTD may be the result of pharmacogenetic differences between the patient populations enrolled in various Phase I studies for enzymes involved in CPT-11 metabolism. Two forms of carboxylesterase catalyze the conversion of CPT-11 to SN-38 (23), but a polymorphism has not been identified for the high-affinity form that most likely catalyzes the conversion at concentrations found *in vivo* after a dose of CPT-11. A mutant allele of UDP-glucuronosyltransferase (*UGT1A1*28*), the enzyme that catalyzes the conversion of SN-38 to SN-38G, has reduced capacity for SN-38 glucuronidation (24). The relationship between the mutant genotype and SN-38 AUC has not been defined in a large group of patients.

The pharmacokinetics of total CPT-11, its active metabolite

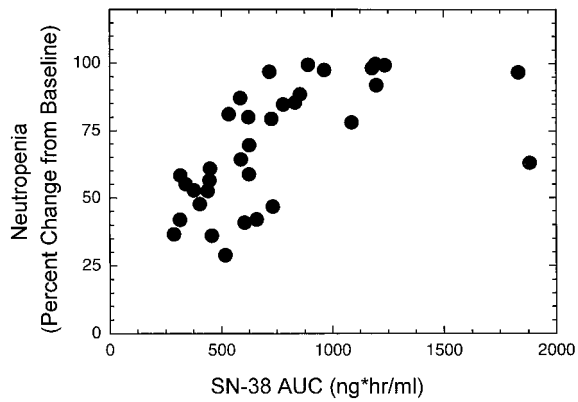

Fig. 4 Scatterplot of SN-38 AUC and neutropenia (percentage change from baseline) for cycle 1 ($n = 34$).

SN-38, and the inactive glucuronide conjugate SN-38G were determined in all 34 patients treated on this study. The pharmacokinetics of CPT-11 and SN-38 lactones were not performed based on the correlation between lactone and total concentrations (25). The half-life values for SN-38 and SN-38G were longer than the previously reported values; however, this likely reflects differences in the number of points used to calculate the terminal elimination half-life and a longer specimen collection period for the current study (6–8). We did not detect a correlation between AUC and CPT-11 dose level as was reported in previous Phase I studies (7, 8). This is likely explained by the narrow dose range over which the AUC values were determined, as well as the substantial variability in CPT-11 pharmacokinetics among the patients enrolled in this study. Correlations were found between CPT-11 AUC values and metabolite (SN-38 and SN-38G) AUC values.

Systemic exposure to SN-38 has been associated with hematological toxicity, and SN-38 biliary excretion has been associated with gastrointestinal toxicity (26–28). We examined baseline total bilirubin with regard to toxicity incidence, but we did not find a strong correlation (data not shown). This could be related to the small number of patients and the different starting dose levels in the trial. Evaluation of the relationship between AUCs and toxicities in this study did suggest several potential correlations (Table 7). The strongest relationship was between SN-38 AUC and neutropenia, a finding that is generally consistent with the critical role of SN-38 as the active CPT-11 cytotoxic metabolite. Both CPT-11 and SN-38 AUCs were significantly correlated with vomiting. However, because these variables are correlated with each other, it is difficult to know whether CPT-11, SN-38, or both CPT-11 and SN-38 were most responsible for emesis. Correlations between CPT-11 or SN-38 exposure and vomiting or diarrhea were less than those for neutropenia, which may be due in part to the less precise quantitative nature of assessment of these toxicities. Thrombocytopenia is not a prominent finding with CPT-11 treatment and was only weakly associated with the AUCs of its metabolites. Although correlations between CPT-11, SN-38, and SN-38G AUC values and several toxicities were observed, there was considerable overlap in AUCs for patients experiencing grade 0–4 toxicities. The variability in SN-38 exposure may be due to pharmacogenetic variability in the carboxylesterase and UDP-glucuronosyltransferase. Variation of as much as 33-fold has been observed for human carboxylesterase (23). Similarly, a 50-fold variation in the SN-38G formation rate has been observed in normal human liver microsomal preparations (29). This variability is reflected in ρ coefficients, which ranged from 0.33–0.60 (Table 7). Collectively, these results suggest that identification of patients at risk of experiencing severe neutropenia, vomiting, or diarrhea may not be predictable based solely on the magnitude of pharmacokinetic parameter estimates with a high degree of precision. Further evaluations in larger patient populations would be required to confirm these findings.

Although antitumor activity was not the primary end point in this Phase I trial, several objective responses were recorded. We observed four partial responses and one complete response in the 32 patients with refractory colorectal carcinoma. The overall response rate in this subset of patients was 15% (95% confidence interval, 5.3–32.8%), which is very similar to previous Phase II results using a different schedule and different doses (16–18).

Recent multicenter Phase III studies have demonstrated survival benefit as the result of CPT-11 therapy in patients with advanced colorectal carcinoma (30, 31). These Phase III trials used a starting dose of CPT-11 at 350 mg/m^2 given every 3 weeks. For patients with poor performance status or age greater than 70 years, 300 mg/m^2 was the recommended starting dose. Whereas our data support the use of this schedule, a starting dose of 350 mg/m^2 could not be reached in this patient population with good performance status. The current study adds to the prior dosing recommendations by documenting that patients with prior AP radiation therapy appear to be at increased risk of toxicity. Based on the findings of this study, a lower starting dose (290–300 mg/m^2) should be used in these patients. Because of the frequency of gastrointestinal side effects, routine use of supportive measures including atropine, dexamethasone, a 5-hydroxytryptamine 3 antagonist, and intensive loperamide are recommended in this palliative setting.

The every-3-week schedule has been the basis for a Phase I trial in which CPT-11 is combined with 5-FU and leucovorin (32). This regimen involves the administration of CPT-11 on day 1 of each cycle; 5-FU and leucovorin are given on days 2–5 of each 3-week cycle. This sequence was derived from *in vitro* studies suggesting synergistic cytotoxicity with this sequence (33). Further evaluation of this combination regimen in a Phase III trial for previously untreated advanced colorectal cancer is planned.

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Clinical Cancer Research

Phase I Dose-finding and Pharmacokinetic Trial of Irinotecan Hydrochloride (CPT-11) Using a Once-Every-Three-Week Dosing Schedule for Patients with Advanced Solid Tumor Malignancy

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