

Phase 1 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: A North American Brain Tumor Consortium study¹

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This study was conducted to determine the maximum tolerated dose and dose-limiting toxicity of irinotecan (CPT-11) administered every 3 weeks to adults with pro-

gressive malignant glioma who were treated with enzyme-inducing antiepileptic drug (EIAED) therapy, and to compare the pharmacokinetics with those in patients not on EIAED therapy treated at the recommended phase 2 dose for other cancers. The CPT-11 dose was 350 mg/m² i.v. every 3 weeks and remained fixed in patients not on EIAED therapy, but the dose was escalated by 50-mg/m² increments in patients on EIAED therapy. CPT-11 and its metabolites SN-38, SN-38 glucuronide (SN-38G), and APC (7-ethyl-10[4-N-(5 aminopentanoic acid)-1-piperidine]-carbonyloxycamptothecin) were characterized in both groups. Patients on EIAEDs received 350 to 800 mg/m² of CPT-11. Dose-limiting toxicity was due to grade 3 diarrhea despite maximal doses of loperamide. The systemic levels of CPT-11, APC, SN-38G, and SN-38 were all lower in the EIAED group. There was a moderate-to-fair relationship between CPT-11 dose and the area under the curve (AUC) for CPT-11 and APC over the dosage range of 350 to 800 mg/m², but no relationship between CPT-11 dose and the AUC for SN-38 or SN-38G.

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³ Abbreviations used are as follows: APC, 7-ethyl-10[4-N-(5 aminopentanoic acid)-1-piperidine]-carbonyloxycamptothecin; AUC, area under the concentration-time curve; CPT-11, irinotecan; DLT, dose-limiting toxicity; EIAED, enzyme-inducing antiepileptic drug; GBM, glioblastoma multiforme; HPLC, high-performance liquid chromatography; IS, internal standard; MRP2, multidrug resistance protein 2; MTD, maximum tolerated dose; NABTC, North American Brain Tumor Consortium; NCI, National Cancer Institute; UGT1A1, uridine-diphosphoglucuronosyl transferase.

At the 750-mg/m² dose, the AUC for CPT-11 (21.6 µg × h/ml) matched the AUC (21.6 µg × h/ml) in the non-EIAED group treated with 350 mg/m² of CPT-11. We conclude that the recommended phase 2 dose of CPT-11 for patients on EIAEDs is 750 mg/m² when given every 3 weeks. A phase 2 study of patients with recurrent malignant glioma is ongoing to assess the efficacy of CPT-11 when the dose is stratified according to the use of EIAEDs. *Neuro-Oncology* 6, 44–54, 2004 (Posted to *Neuro-Oncology [serial online]*, Doc. 03-029, December 3, 2003. URL <http://neuro-oncology.mc.duke.edu>; DOI: 10.1215/S1152 8517 03 00029 2)

The treatment of recurrent malignant gliomas using available chemotherapy drugs is ineffective for the prolongation of life in the majority of patients. The median time to tumor progression after treatment for patients with recurrent glioblastoma multiforme (GBM)³ is only 8 to 12 weeks, and fewer than 20% of patients are progression-free by 6 months (Hess et al., 1999). Patients with anaplastic gliomas other than GBM fare better, but fewer than half are progression-free at 6 months (Hess et al., 1999). The efficacy of chemotherapy for glioma has been limited because of the low activity of available antineoplastic agents, the compromised delivery of these agents to at least partially privileged intracranial sites, and the emergence or de novo presence of resistance to these agents. Irinotecan (CPT-11), a drug that is active against colon carcinoma, has been used to treat recurrent glioma. Preclinical activity of CPT-11 has been promising, with in vitro activity noted against a panel of xenografts derived from ependymoma, childhood and adult high-grade astrocytoma, and medulloblastoma (Hare et al., 1997). A phase 2 study of CPT-11 for malignant glioma was conducted at Duke University Medical Center using doses and schedules recommended for colon cancer (Friedman et al., 1999). The results suggested clinical efficacy with less toxicity, particularly diarrhea, than has been seen in other cancer patient populations. This low toxicity may be due to the treatment of many glioma patients with enzyme-inducing antiepileptic drug (EIAED) therapy, which could alter the exposure to CPT-11 in this population. However, reduced exposure to drug may also reduce efficacy.

CPT-11 (*M_r* anhydrous freebase, 587) is oxidized in the liver by the highly inducible CYP3A4, yielding 2 less active metabolites, APC (7-ethyl-10[4-N-(5 aminopentanoic acid)-1-piperidine]-carbonyloxycamptothecin [*M_r* 619]) and NPC (7-ethyl-10[4-(piperidine)-1-amino]carbonyloxycamptothecin [*M_r* 519]) (Haaz et al., 1998; Santos et al., 2000). Additionally, CPT-11 is bioactivated by hepatic and tissue carboxylesterases (predominately hCE2) to the potent topoisomerase-I inhibitor SN-38 [*M_r* anhydrous base, 393] (Humerickhouse et al., 2000; Khanna et al., 2000; Slatter et al., 1997). SN-38 is excreted unchanged or conjugated by the highly polymorphic and inducible uridine-diphosphoglucuronosyl transferase (UGT1A1)-generating SN-38 glucuronide [*M_r* 569] (Iyer et al., 1998). Subsequently, CPT-11 and its metabolites are exported from the hepatocytes by specific apical, membrane-bound transporters. The canalicular, multi-

specific organic anion transporter multidrug resistance protein 2 (MRP2) reportedly is responsible for the biliary transport of the inactive carboxylate forms of CPT-11 and SN-38 as well as the lactone and carboxylate forms of SN-38 glucuronide (Chu et al., 1998). SN-38 has recently been identified as a substrate for the canalicular, ATP-binding cassette (ABC) transporter (ABCP, ABCG2), the breast cancer resistant protein (BCRP), and mitoxantrone-resistance half-transporter (MXR) (Brangi et al., 1999; Maliepaard et al., 2001).

Recent preclinical and clinical studies have demonstrated that EIAEDs can alter the metabolism and elimination of CPT-11 and its metabolites. Pretreatment of rats with the antiepileptic drug phenobarbital, an inducer of UGT1A1 and CYP3A4, has been shown to enhance the formation of SN-38G and decrease the area under the concentration-time curve (AUC) for both CPT-11 and SN-38. However, the non-EIAED valproic acid increased the AUC of SN-38, presumably by inhibiting the glucuronidation of SN-38 (Gupta et al., 1997). In contrast to the induction of UGT1A1 and CYP3A4, phenobarbital has recently been shown not to increase the expression of MRP2 in rat hepatocytes (Hagenbuch et al., 2001). A recent study of CPT-11 in patients with malignant gliomas receiving EIAEDs indicated significantly lower systemic exposure (decreased AUC) to CPT-11, SN-38, and SN-38G compared to historical controls (Friedman et al., 1999).

Based upon the background above, the North American Brain Tumor Consortium (NABTC) began a phase 1 study of CPT-11 in patients on EIAEDs to determine the optimal phase 2 dose when given every 3 weeks and to compare the pharmacokinetics with those in patients not on EIAEDs treated at the recommended phase 2 dose for other cancers. A phase 2 study has begun based upon the results of this trial.

Patients and Methods

Study Population and Patient Eligibility

Patients 18 years or older with histologically confirmed diagnosis of a progressive or recurrent malignant glioma were eligible to participate, provided they had measurable disease, a Karnofsky performance status of 60 or greater, and acceptable hematologic, liver, and renal function. The latter required an absolute neutrophil count $\geq 1500/\text{mm}^3$, a platelet count of $\geq 100,000/\text{mm}^3$, serum creatinine < 1.5 mg/dl, serum bilirubin < 1.5 mg/dl, and AST < 3 times the institutional upper normal limits. Patients in the phase 1 portion (group B) of this study had undergone no more than 2 prior chemotherapy regimens, including 1 prior adjuvant therapy and 1 prior regimen for recurrent tumor, or 2 prior regimens for recurrent disease. Patients not on EIAED (group A) received a fixed dose of 350 mg/m² and were considered part of an expanded phase 2 trial that will be reported separately. These patients had undergone no more than one prior chemotherapy regimen, either as adjuvant chemotherapy or for recurrent disease. In both groups, the interval from prior irradiation or chemotherapy had to be at least 4

weeks, and 6 weeks if prior nitrosourea therapy had been used.

The study was designed to include women and minorities but was not designed to measure differences of intervention effects. No exclusion was allowed based upon race. Patients were excluded if they were pregnant or breast feeding, if they had severe nonmalignant systemic disease or active infection, or if they had any uncontrolled medical conditions that, in the judgment of the investigator, would make the patient inappropriate for entry. Patients previously treated with CPT-11, topotecan, or other topoisomerase 1 inhibitors were also excluded. All patients were provided with and had to sign a written informed consent approved by the local institutional review board at each institution before treatment, informing them of the investigational nature of this study.

Treatment

Patients who met eligibility requirements and signed an informed consent received an intravenous infusion of CPT-11 over a 90-min period every 3 weeks. The initial dose was 350 mg/m² in both groups. Patients in group A (not on EIAEDs) continued to receive this dose throughout treatment until tumor progression, unacceptable toxicity, or completion of 12 treatment cycles. Patients in group B (on EIAEDs) were treated in groups of 3, beginning at the initial dose. If the first group of 3 patients did not experience dose-limiting toxicity (DLT), a subsequent group of 3 additional patients was enrolled, and the dose was increased by 50-mg/m² increments. Cohorts of 3 patients were thus enrolled until the DLT was determined. Up to 3 patients were enrolled simultaneously. These patients were observed for DLT for at least 3 weeks from the first day of treatment before new patients were enrolled at the next higher dose. The following dose-escalation rules were used. Three patients were studied at the first dose level. If none of these 3 experienced DLT, then the dose was escalated to the next dose in 3 subsequent patients, but if 1 of 3 patients experienced DLT, then 3 more patients were enrolled at the same dose. If none of these 3 patients experienced DLT, then the dose was escalated to the next dose in 3 subsequent patients. If 1 or more of the additional 3 patients experienced DLT, the maximum tolerated dose (MTD) was considered to have been exceeded, and 3 more patients were treated at the next lower dose (if only 3 were treated at that dose). If 2 or more patients experienced a DLT, the MTD was considered to have been exceeded.

A treatment cycle was considered to be 1 infusion and a 3-week evaluation period. Doses assigned were not allowed to be escalated, and patients remained on that dose until tumor progression, unacceptable toxicity, or completion of 12 treatment cycles.

The definition of DLT for group B patients was based upon the National Cancer Institute (NCI) Common Toxicity Criteria scale (NCI, 1999) and included the following:

- Hematologic toxicity: Grade 4 neutropenia lasting >5 days; neutropenic fever (defined as grade 4 neu-

tropenia with >grade 2 fever); neutropenic infection; or grade 4 thrombocytopenia.

- Diarrhea: Grade ≥ 3 diarrhea despite maximal intensive supportive treatment with loperamide. Guidelines for loperamide use were to initiate drug at the earliest sign of a poorly formed stool or at the occurrence of 1 to 2 more bowel movements than usual in 1 day. Loperamide was provided to patients at the initial treatment visit.
- Nausea or vomiting: Grade >3 despite maximal antiemetic therapy. All patients were treated with dexamethasone 10 mg i.v. and either ondansetron or granisetron before infusion of CPT-11. Ativan (Wyeth-Ayerst Pharmaceuticals, Collegeville, Penn.) or Compazine (GlaxoSmithKline, Research Triangle Park, N.C.) was also allowed at the discretion of the treating physician.
- Other nonhematologic toxicity: Grade >3 toxicity attributable to CPT-11 therapy.
- Failure to recover: Failure to recover sufficiently from toxicity to be eligible for retreatment with CPT-11 within 28 days of the start of the first cycle of CPT-11 treatment.

The definition of the MTD was the dose level at which 0/3 or 1/6 patients experienced DLT, with at least 2/3 or 2/6 patients experiencing DLT at the next higher dose.

Patient Monitoring and Toxicity Assessment

Complete physical and neurological examinations, including Karnofsky performance status, were performed every other cycle. Weekly complete blood counts with differential and platelets were obtained throughout the course of treatment. Creatinine, BUN, total bilirubin, AST, and serum electrolyte counts were obtained before each cycle. Magnetic resonance imaging of the brain was done every other cycle to assess response. Patients with stable or responding disease received the same dose at the next cycle or a reduced dose if adverse events were observed in the current cycle. If a patient experienced a DLT, the dose of the subsequent cycle was reduced by one dose level (50 mg/m²). If a toxicity was thought to be directly related to CPT-11, subsequent doses were not re-escalated, even if there was minimal or no toxicity at the reduced dose. A new course of treatment could begin if the absolute neutrophil count was $\geq 1500/\text{mm}^3$ and the platelet count was $\geq 100,000/\text{mm}^3$ and any other treatment-related toxicity was \leq grade 1. If, after a 1-week delay, toxicity was \leq grade 1, treatment resumed. If the toxicity did not resolve in 1 week, a second week's delay was allowed, but retreatment required a reduction of 1 dose level. If retreatment had to be held off for more than 2 weeks, or if the administered dose would be ≤ 200 mg/m², the patient was removed from the study. Routine prophylactic use of hematologic growth factors was not allowed in the first cycle of therapy. Therapeutic use in cycles complicated by neutropenic infection was allowed at the discretion of the treating physician. Because of the possibility of lacrimation, diaphoresis, flushing, abdominal cramping, diarrhea, or other symptoms of early cholin-

ergic syndrome in patients receiving CPT-11, we allowed subcutaneous or intravenous administration of atropine, both therapeutically and prophylactically as needed.

Patients were removed from study if tumor progression was determined by MRI. In this phase 1 trial, the definition of progression was a 25% increase in the sum of the products of all measurable disease over the smallest sum observed, or clear worsening of any evaluable disease, or the appearance of any new lesion. Failure to return for evaluation due to death or deteriorating condition was considered to represent progression.

Pharmacokinetic Evaluation

Sample Collection. Heparinized blood samples (7 ml) were drawn via venipuncture or through an indwelling i.v. heparin lock. One milliliter of blood was withdrawn from the heparin lock and discarded before sample collection at the following times: before drug administration (baseline), 45 min into the infusion, and at the end of the infusions, then 15, 30, 60, and 90 min and 2, 3, 4, 6, 8, 10, and 24 h after the end of infusion on day 1 of a patient's first cycle, for a total of 14 samples per patient.

Blood samples were immediately centrifuged. Plasma was removed and frozen at $\leq 20^{\circ}\text{C}$ for subsequent analysis by high-performance liquid chromatography (HPLC) for total concentrations of CPT-11 and SN-38 as well as for concentrations of SN-38 glucuronide (SN-38G) and APC. The total time of frozen storage was less than 1 year. The long-term stability of total CPT-11 and SN-38 in plasma has been documented to be at least 2 years when samples were stored at $\leq 20^{\circ}\text{C}$.

Analytical Methods. Plasma samples were analyzed for total concentrations of CPT-11, APC, and SN-38 by using a validated and sensitive HPLC method (Saltz et al., 1996). In brief, the plasma specimen was mixed with the internal standard (IS, camptothecin) in acidified acetonitrile to precipitate plasma proteins, and the mixture was incubated for 15 min at 40°C to convert the analytes to their respective lactones. After addition of triethylamine buffer (pH 4.2), the sample was centrifuged. The supernatant was transferred to an amber vial for injection (60 μl) onto the HPLC system. Chromatographic separation was achieved with a Zorbax-SB-C8 column (MacMod Analytical, Inc., Chadds Ford, Penn.) and a mobile phase consisting of 25:75 (v/v) acetonitrile/0.025 triethylamine buffer (pH 4.2). The fluorescence detector was operated at an excitation wavelength of 372 nm; the CPT-11 and APC were monitored at an emission wavelength of 425 nm; SN-38 and the IS were monitored at 535 nm. To determine the concentrations of SN-38 glucuronide, 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. The conversion of SN-38G to total SN-38 was 100%. The remainder of the procedure was repeated as described above.

The lower limits of quantitation of CPT-11 (expressed as the freebase, M_r 587), SN-38 (expressed as monohydrate, M_r 410), and APC (M_r 618) were 1.28 ng/ml, 0.480

ng/ml, and 0.960 ng/ml, respectively. The assay precision for CPT-11 [APC values in brackets], expressed as the coefficient of variation (% CV) of the estimated concentrations of quality control samples, was 4.9% [8.3%], 4.1% [9.3%], and 5.4% [7.0%], respectively, for the low (12.8 [1.20] ng/ml), medium (160 [12.0] ng/ml), and high (3200 [320] ng/ml) concentrations of CPT-11 [APC] and 10.8%, 3.5%, and 5.1%, respectively, for the low (1.2 ng/ml), medium (12.0 ng/ml), and high (320 ng/ml) concentrations of SN-38. Assay accuracy, expressed as the ratio (or percent) of the estimated to theoretical quality control standard concentrations, averaged 96% to 99% for CPT-11 [98%–101% for APC] and 96% to 101% for SN-38.

Pharmacokinetic Analyses. CPT-11, APC, SN-38, and SN-38G plasma concentrations were analyzed by non-compartmental methods. The time intervals relative to the start of the CPT-11 infusion and the actual sample times were used for the calculations of the time-to-peak curve and the plasma AUC. The maximal plasma concentration for CPT-11 was defined as the concentration achieved at the end of the 90-min infusion. The maximal plasma concentrations for APC, SN-38, and SN-38G were determined by visual inspection of each individual's plasma concentration-versus-time profile. Elimination rate constants were estimated by linear regression of the last 2 data points on the terminal log linear portion of the concentration-time curve. The terminal half-life ($t_{1/2}$) was calculated by dividing 0.693 by the elimination rate constant. The AUC was calculated by using the linear trapezoidal rule up to the last measurable data point (for AUC_{0-24}), then extrapolated to infinity (AUC). The systemic clearance for CPT-11 was determined by dividing the dose (in milligrams freebase of CPT-11 per meter squared) by the AUC. A metabolic ratio, estimated as the ratio of $\text{AUC}_{\text{SN-38}}$ or $\text{AUC}_{\text{SN-38}} + \text{AUC}_{\text{SN-38G}}$ to $\text{AUC}_{\text{CPT-11}}$, was used as a measure of the relative extent of the conversion of CPT-11 to SN-38. The relative extent of metabolism of CPT-11 to APC was estimated as $\text{AUC}_{\text{APC}}/\text{AUC}_{\text{CPT-11}}$ and the relative extent of glucuronidation of SN-38 as the ratio of $\text{AUC}_{\text{SN-38}}$ to $\text{AUC}_{\text{SN-38G}}$.

Statistical Considerations

The primary end points for this study were to describe toxicity and pharmacokinetics of CPT-11 in a dose-escalating phase 1 study and to define a recommended phase 2 dose. The dose for patients on EIAED therapy was escalated as described earlier, and the DLT, MTD, and safety were evaluated. When the dose escalation scheme described was used, the probability that the dose would be escalated to the next level, based on the true rate of DLT at the current dose, is given by the following:

	True Toxicity at a Given Dose					
	10%	20%	30%	40%	50%	60%
Probability	0.91	0.71	0.49	0.31	0.17	0.08

Thus, if the true underlying proportion of DLT was 50% at any dose, there was a 17% chance of escalating to the next higher dose.

Pharmacokinetic variables for all compounds are reported as mean values \pm SD. The relationships between the CPT-11 dose administered (mg/m^2) and AUCs were analyzed by Spearman's correlation coefficient and linear regression analysis. Interpatient differences in the kinetics were assessed by the coefficient of variation, expressed as the ratio of the SD to the observed mean. Differences between the 2 groups with respect to the kinetic variables were evaluated by using an unpaired 2-tailed *t* test. Two-tailed probability values of less than 0.05 were regarded as statistically significant. Kinetic variables were also compared to those obtained from the Mayo Clinic trial that included 6 patients with non-CNS malignancies who received $340 \text{ mg}/\text{m}^2$ of CPT-11 (Pitot et al., 2000). Relative metabolic ratios were then compared with those reported in 3 recent trials.

Results

Patient Characteristics

A total of 48 patients were enrolled in the phase 1 study (group B, Table 1). Three patients did not receive any drug, and 2 patients were ineligible, but treated. These 2 patients are included in the toxicity assessments. The median age was 47 years (range 19–77). The majority (37/48) of patients had recurrent GBM, and most had been treated with 1 or more prior chemotherapy regimens. Patients enrolled in the phase 2 study (group A) will be described in more detail in a separate report dealing with response to CPT-11. However, the median age was 53 years, and 75% were patients with recurrent GBM, treated with no more than 1 prior chemotherapy regimen.

Toxicity

The dose of CPT-11 ranged from 350 to $800 \text{ mg}/\text{m}^2$. Dose-limiting toxicity was grade 3 diarrhea despite maximal loperamide support and was noted in 2/6 patients at a dose of $800 \text{ mg}/\text{m}^2$. A third patient treated at this dose also had grade 3 diarrhea but did not receive maximal loperamide support. The recommended phase 2 dose is $750 \text{ mg}/\text{m}^2$. No treatment-related deaths were reported. Table 2 describes the most common types of toxicity reported in the study.

There were 42 patients evaluable for response by MRI. All had progressed at the time of this report. Although it was not a response study, there were no reports of any patients who had an objective response ($>50\%$ decrease in size of tumor). The median progression-free survival time measured from the date of registration into the study was 6 weeks (6 weeks for GBM and 9 weeks for non-GBM). Ten patients were progression-free for 13 weeks or longer, and 3 patients were progression free for 6 months or longer.

Table 1. Characteristics of the 48 group B patients enrolled and receiving EIAEDs

Characteristic	Median (range), Percentage, or Number
Median Age (years)	47 (19–77)
Karnofsky Performance Status (%)	
100	11.3
90	25.8
80	30.6
70	21.0
60	11.3
Sex M:F (%)	66.1:33.9
Histology (number of patients)	
Glioblastoma multiforme	37
Anaplastic astrocytoma	7
Anaplastic oligodendroglioma	1
Anaplastic mixed glioma	1
Oligodendroglioma	2
Prior Chemotherapy Regimens (%)	
None	17.7
One	58.2
Two	24.2

Table 2. Reported grade 3 toxicity in cycle 1, indicating definite relationship to drug¹

Toxicity	Dose, m^2 (No. of patients treated)							
	450 (6)	500 (3)	550 (3)	600 (6)	650 (6)	700 (3)	750 (6)	800 (6)
Diarrhea	0	0	0	1	0	0	1	3
Granulocytopenia ²	0	2	0	0	1	0	0	0
Lymphocytopenia	0	0	0	1	1	0	0	0
Leukopenia	0	0	0	0	0	0	0	1
Nausea	0	0	0	0	1	0	0	0

¹ There were no instances of grade 4 toxicity reported.

² Grade 3 but not dose limiting.

Pharmacokinetic Results

Blood samples were obtained from patients during their first course of treatment. Sixteen patients were nonevaluable because of incomplete sample collections. Pharmacokinetic variables were characterized for 56 patients: 22 patients in group A (non-EIAEDs), who were treated with $350 \text{ mg}/\text{m}^2$ of CPT-11, and 34 patients in group B (EIAEDs), who were treated with doses ranging from 350 to $800 \text{ mg}/\text{m}^2$.

The pharmacokinetic characteristics for CPT-11, APC, SN-38, and SN-38G are summarized in Tables 3 and 4. Comparisons between the 2 groups at the $350\text{-mg}/\text{m}^2$ dose level are displayed in Table 5, which also includes

Table 3. Pharmacokinetic parameters of CPT-11¹

Group	Dose (mg/m ²)	No. of Patients	Cp _{max} (µg/ml)	t _{1/2} (h)	AUC ₀₋₂₄ (µg × h/ml)	AUC ² (µg × h/ml)	CL (liters/h/m ²)	CV ³ (%)
A	350	22	3.3 (0.50)	6.7 (1.30)	17.3 (5.22)	18.4 (5.73)	18.2 (5.86)	32.2
B	350	2	2.4 (0.50)	7.5 (0.57)	9.2 (0.14)	9.7 (0.07)	31.6 (0.07)	0.22
B	400	3	2.7 (0.50)	7.7 (0.88)	10.7 (3.34)	11.2 (3.62)	33.8 (12.6)	37.1
B	450	5	3.3 (0.50)	5.9 (0.34)	12.5 (2.81)	12.7 (2.84)	31.9 (6.78)	21.3
B	500	3	4.2 (0.55)	5.3 (0.54)	19.3 (0.59)	19.7 (0.61)	22.1 (0.67)	3.00
B	550	2	3.9 (0.07)	5.4 (1.27)	16.2 (4.24)	16.5 (4.10)	29.9 (7.42)	24.8
B	600	4	4.0 (0.43)	6.1 (0.75)	16.8 (2.34)	17.1 (2.51)	31.1 (4.80)	15.4
B	650	4	4.4 (1.39)	6.4 (0.40)	19.5 (4.89)	20.4 (4.99)	29.1 (6.84)	23.5
B	700	3	5.6 (1.74)	6.2 (3.08)	25.6 (7.01)	26.9 (7.97)	24.1 (7.68)	31.9
B	750	4	4.3 (1.03)	5.4 (0.93)	21.2 (5.80)	21.6 (5.83)	33.1 (9.31)	28.1
B	800	4	6.0 (1.28)	6.0 (0.63)	27.3 (3.50)	27.9 (3.81)	25.3 (3.23)	12.8

Abbreviations used are as follows: AUC, area under the curve; CL, systemic clearance; Cp_{max}, maximal plasma concentration; CV, coefficient of variation; t_{1/2}, terminal half-life (harmonic mean).

¹ Values reported are means (± SD) unless otherwise indicated.

² Average percent extrapolation between the AUC₀₋₂₄ and AUC (3%).

³ Percent CV related to CL.

the pharmacokinetic characteristics from the Mayo Clinic trial that included 6 patients with non-CNS malignancies who received 340 mg/m² of CPT-11 (Pitot et al., 2000). Overall, the kinetic variables in patients receiving no anticonvulsants or steroids in our trial are similar to those of non-CNS malignancy patients. Unfortunately, kinetic characteristics were available for only 2 patients in the EIAED group at the 350-mg/m² dose level. However, a comparison of the kinetics of the 2 groups revealed that the peak concentrations and AUCs of CPT-11 and SN-38 were substantially decreased in the EIAED-treated patients. Although not as substantial, a quantitative decrease in peak concentrations and AUCs for APC and SN-38G was also observed. CPT-11 clearance values (29.3 ± 7.11 l/h/m², n = 34) for the EIAED group were increased 2-fold compared to those for the non-EIAED group (14.2 ± 4.12 l/h/m², n = 7) or by 1.5-fold compared to those for patients receiving only dexamethasone and/or non-EIAEDs (20.1 ± 5.72 l/h/m², n = 15).

The EIAED patients were empirically categorized into 4 groups (phenytoin, carbamazepine, phenobarbital, and combination EIAEDs) for the purposes of comparison (Table 6). The non-EIAED drugs, particularly gabapentin, had a small but statistically significant effect on the clearance of CPT-11 when compared to the clearance values for patients not receiving steroids or antiepileptic agents. Six patients were receiving valproic acid in combination with a non-EIAED. For those patients receiving valproic acid, CPT-11 clearance values (19 ± 2.98 l/h/m²) were unchanged compared to the clearance values for the other group A patients (18 ± 16.69 l/h/m², P = 0.73). However, SN-38 AUCs (185 ± 49.94 ng × h/ml) were significantly lower for the patients receiving valproic acid compared to the SN-38 AUCs (552 ± 306 ng × h/ml,

P = 0.01) for patients receiving other non-EIAEDs ± steroids. SN-38G AUCs of the 2 groups were not different (1113 ± 395 vs. 1713 ± 1182 ng × h/ml, P = 0.24). Likewise, there was no difference in the AUC values for CPT-11 and SN-38 for those patients receiving dexamethasone alone compared to the no-anticonvulsant group.

The relationship between CPT-11 dose and systemic exposure (AUC) was relatively linear (r² = 0.64, P = 4.53E⁻⁰⁶) over the dosage range of 350 to 800 mg/m². Likewise, the clearance of CPT-11 was dose independent (r² = 0.035). However, no proportionate increase was observed in the SN-38 or SN-38G AUC nor in the dose-normalized AUCs with increasing dosages of CPT-11 (r² = 0.04). Additionally, there was a poor linear relationship between CPT-11 dose and APC systemic exposure (r² = 0.35). The pharmacodynamic assessment of correlation between (a) CPT-11, APC, and SN-38 systemic exposure, (b) NCI grade of diarrhea, and (c) percent change in neutrophil count showed no correlations in either of the treatment groups.

At the MTD of 750 mg/m², the AUC for CPT-11 (21.6 µg × h/ml) matched the AUC (18 µg × h/ml) in the group of patients receiving no anticonvulsants treated with 350 mg/m² of CPT-11. The mean percent change in neutrophil count (nadir-baseline count/baseline count) was 62.4% (±27%) for the non-EIAED group (350 mg/m²) and 58.2% (±18%) for the EIAED group treated with 750 mg/m² of CPT-11. There was considerable variability observed for the SN-38 AUCs at all of the dose levels. The mean AUC for SN-38 at the MTD was not statistically different from the SN-38 AUC at the 350-mg/m² dose level for the non-EIAED patient group.

Table 4. Pharmacokinetic parameters of CPT-11 metabolites*

Metabolite Profile	CPT-11 Dose (mg/m ²)					
	350 (group A)	350 (group B)	400	450	500	550
APC						
t _{max} (h)	3.16 (0.93)	2.00 (0)	2.5 (0.87)	1.95 (0.33)	2.25 (0.25)	2.59 (0.12)
C _{pmax} (ng/ml)	527 (284)	414 (30.4)	729 (283)	644 (301)	1106 (610)	1006 (33.9)
t _{1/2} (h)	6.5 (1.52)	7.6 (1.13)	7.8 (1.62)	6.5 (0.80)	5.2 (0.41)	5.8 (0.71)
AUC ₀₋₂₄ (μg × h/ml)	4.8 (2.91)	3.1 (0.28)	5.6 (3.15)	4.3 (2.35)	8.0 (2.86)	7.6 (0.71)
AUC (μg × h/ml)	5.3 (3.27)	3.4 (0.28)	6.2 (3.76)	4.6 (2.54)	8.3 (2.89)	7.9 (0.85)
AUC _{APC} / AUC _{CPT-11} (%) [#]	28.8	35.1	55.4	36.2	42.1	47.9
SN-38						
t _{max} (h)	1.78 (0.55)	1.13 (0.53)	2.00 (0.87)	1.45 (0.44)	1.67 (0.14)	1.59 (0.12)
C _{pmax} (ng/ml)	41.1 (26.6)	21.5 (7.35)	32.9 (24.1)	20.6 (12.8)	33.2 (5.64)	22.8 (1.13)
t _{1/2} (h)	14.9 (7.92)	16.0 (4.03)	23.1 (9.33)	11.6 (3.22)	8.5 (0.51)	11.1 (1.48)
AUC ₀₋₂₄ (ng × h/ml)	314 (220)	123 (38.9)	212 (182)	136 (90.7)	211 (64.8)	133 (24.0)
AUC (ng × h/ml) ²	558 (602)	168 (33.9)	365 (377)	166 (127)	229 (76.6)	156 (23.3)
AUC _{SN-38} / AUC _{CPT-11} (%) [#]	3.1	1.7	3.3	1.3	1.2	1.0
AUC _{SN-38} + AUC _{SN-38G} / AUC _{CPT-11} (%) [#]	11.8	11.0	21.1	7.6	7.6	7.3
SN-38G						
t _{max} (h)	2.11 (0.63)	1.90 (0.14)	1.86 (0.62)	1.41 (0.38)	1.92 (0.14)	1.84 (0.12)
C _{pmax} (ng/ml)	120 (61.4)	115 (32.5)	207 (105)	105 (33.1)	179 (37.5)	173 (42.4)
t _{1/2} (h)	15.1 (6.31)	16.3 (8.13)	17.5 (9.40)	12.3 (2.80)	9.1 (1.98)	9.5 (0.92)
AUC ₀₋₂₄ (ng × h/ml)	1099 (663)	690 (154)	1355 (824)	625 (295)	1134 (181)	944 (295)
AUC (ng × h/ml)	1589 (1045)	894 (134)	1997 (1695)	793 (437)	1270 (168)	1052 (308)
AUC _{SN-38} / AUC _{SN-38G} (%) [#]	35.1	18.8	18.3	20.9	18.0	14.7

Abbreviations used are as follows: AUC, area under the curve; C_{pmax}, maximal plasma concentration; t_{max}, time to peak; T_{1/2} (h), terminal half-life (harmonic mean).

* Values reported are mean (± SD).

[#] Average % extrapolation between the AUC₀₋₂₄ and AUC (APC [7%]; SN-38 [46%]; SN-38G [27%]).

Discussion

The goals of this study were to define the toxicity and pharmacokinetics of CPT-11 in patients receiving EIAED therapy and to establish a recommended phase 2 dose. For patients receiving non-EIAEDs, a fixed dose of 350 mg/m² of CPT-11 was administered i.v. every 3 weeks. Dose escalations in the EIAED patient groups ranged from 350 to 800 mg/m². The DLT at the 800-mg/m² dose level was grade 3 diarrhea despite maximal doses of loperamide.

EIAEDs altered the pharmacokinetics of CPT-11 and its metabolites. At the comparative dose level of 350

mg/m², peak concentrations and the AUC of CPT-11, APC, SN-38, and SN-38G were substantially lower in the EIAED patient group. A moderate-to-fair linear relationship existed between CPT-11 dose and AUC over the dosage range of 350 to 800 mg/m². No relationship was observed between CPT-11 dose and the AUCs for SN-38 or SN-38G. The clearance of CPT-11 was dose independent. The clearance of CPT-11 in the EIAED group (29.3 ± 7.11 l/h/m²) was increased 1.6-fold compared to the clearance for the non-EIAED group (18.2 l/h/m²). The majority of the patients in the EIAED group were receiving phenytoin with or without dexamethasone. CPT-11 clearance values were highest among the patients

Table 4. Continued

CPT-11 Dose (mg/m ²)				
600	650	700	750	800
2.27 (0.27)	2.63 (1.53)	2.91 (0.37)	2.44 (0.66)	2.27 (0.43)
1532 (780)	1090 (382)	1461 (693)	1816 (1259)	1578 (557)
6.01 (1.50)	6.8 (1.03)	6.5 (4.17)	5.4 (0.67)	5.7 (0.98)
10.8 (3.9)	8.9 (2.89)	14 (7.73)	12.2 (6.64)	11.0 (3.72)
11.3 (3.8)	9.5 (3.02)	15.8 (8.44)	12.6 (6.93)	11.6 (4.19)
66.1	46.6	58.7	58.3	41.6
1.66 (0.24)	2.40 (1.69)	1.25 (0.43)	1.60 (0.63)	1.85 (0.46)
21.6 (8.36)	21.1 (8.91)	40.5 (20.5)	26.1 (5.09)	40.2 (14.2)
14.5 (8.26)	17.2 (16.8)	10.4 (11.0)	9.8 (3.44)	11.9 (6.98)
161 (46.6)	154 (65.2)	257 (145)	162 (45.4)	230 (48.2)
296 (161)	278 (167)	409 (304)	190 (58.6)	300 (95.3)
1.7	1.4	1.5	0.9	1.1
11.5	7.5	9.5	8.5	6.7
1.90 (0.27)	2.17 (0.88)	1.75 (0.25)	1.93 (0.41)	1.66 (0.14)
198 (71.5)	140 (60.2)	232 (110)	169 (76.6)	196 (66.1)
12.8 (5.71)	14.6 (8.58)	11.0 (4.75)	12.3 (3.89)	11.1 (3.16)
1422 (551)	870 (214)	1719 (1007)	1401 (1117)	1301 (404)
1671 (516)	1257 (361)	2145 (1379)	1640 (1234)	1570 (517)
17.7	22.1	19.1	11.6	19.1

receiving phenytoin or carbamazepine (30.1 and 28.1 l/h/m², respectively) and were lowest among those receiving phenobarbital (23.6 l/h/m²). The relative influence of individual anticonvulsant agents and their dose effect on the pharmacokinetics of CPT-11 in glioma patients are also being evaluated in a larger database from 4 NCI-sponsored trials in glioma patients (Reid et al., 2001). As was observed in our study, the findings from the larger database suggest that the AUCs for CPT-11 and SN-38 were not altered by dexamethasone, a reported inducer of CYP3A4 and glucuronosyl transferase activity (McCune et al., 2000; Sutherland et al., 1993). Likewise, other covariates including age and gender did not influence

CPT-11 or SN-38 AUCs. We also observed that the non-EIAEDs, especially gabapentin, appeared to have a small but statistically significant effect on CPT-11 clearance. Preclinical data (Gupta et al., 1997) indicated that we might observe an increase in SN-38 exposure in those patients receiving valproic acid due to the inhibition of UGT1A1 conjugation of SN-38. We actually observed the opposite effect. For the small number of patients receiving valproic acid in combination with another non-EIAED, SN-38 AUCs were comparatively lower. Additionally, the grade of diarrhea and the percent change in neutrophil counts in the valproic acid group were similar to those of the other group A patients. The same

Table 5. Pharmacokinetic comparisons between patients on EIAEDs and patients not on EIAEDs receiving CPT-11 at the 350-mg/m² dose level*

PK Parameter	EIAED group B	Non-EIAED group A	
	n = 2	None (n = 7)	± Steroid (n = 15)
CPT-11 (Freebase)			
Cp _{max} (μg/ml)	2.4 [#]	3.7 (3.4) [§]	3.1 [#]
t _{1/2} (h)	7.5	6.8 (12) [§]	6.7
AUC (μg × h/ml)	9.7 [#]	22.9 (23) [§]	16.2 [#]
CL (l/h/m ²)	31.6 [#]	14.2 (12) [§]	20.1 [#]
APC			
Cp _{max} (ng/ml)	414	619 (ND)	484
t _{1/2} (h)	7.6	6.7 (ND)	6.4
AUC (μg × h/ml)	3.4	6.2 (ND)	4.6
SN-38			
Cp _{max} (ng/ml)	21.5 [#]	63.8 (56) [§]	30.5 [#]
t _{1/2} (h)	16.0	16.2 (21) [§]	14.3
AUC (ng × h/ml)	168 [#]	768 (714) [§]	319 [#]
SN-38G			
Cp _{max} (ng/ml)	115	145 (168) [§]	109
t _{1/2} (h)	16.3	13.8 (17) [§]	15.8
AUC (ng × h/ml)	894	1944 (2329) [*]	1424

Abbreviations used are as follows: APC, 7-ethyl-10[4-N-(5 aminopentanoic acid)-1-piperidine]-carbonyloxycamptothecin; AUC, area under the curve; CL, systemic clearance; Cp_{max}, maximal plasma concentration; EIAED, enzyme-inducing antiepileptic drug, ND = not done; PK, pharmacokinetic; t_{1/2}, terminal half-life.

*Mean values for 2 patients receiving EIAED therapy; 7 patients who did not receive EIAED medications, non-EIAED medications, or steroids; and 15 patients who received non-EIAED medications with or without steroids.

[#]P < 0.05 versus group A patients receiving no steroids.

[§]Non-CNS malignancy patients (340 mg/m² CPT-11 every 3 weeks, n = 6) from Mayo Clinic Study (Pitot et al., 2000).

Table 6. Influence of anticonvulsants on CPT-11 clearance

Group A (non-EIAED group, n = 22)	Mean (±SD) CL (l/h/m ²)
Steroid + Non-EIAEDs (n = 11)	21.2 (±5.74)
Steroid only (n = 4)	17.0 (±5.05)
None (n = 7)	14.2 (±4.12)
Group B (EIAED group, n = 34)	
Phenytoin ± Steroid ± Non-EIAEDs (n = 17)	30.1 (±7.40)
Carbamazepine ± Steroid ± Non-EIAEDs (n = 9)	28.1 (±7.92)
Phenobarbital ± Steroid ± Non-EIAEDs (n = 2)	23.6 (±0.99)
Combination EIAEDs (n = 6)	30.9 (±5.82)

Abbreviations used are as follows: CL, systemic clearance; EIAED, enzyme-inducing antiepileptic drug.

observation has been recently reported by other investigators (Raymond et al., 2003). Neither SN-38 exposure nor toxicity was increased in patients with glioblastoma who were treated with 350 mg/m² of CPT-11 while receiving concomitant valproic acid.

The relative metabolism ratios observed in our trial are compared with those reported in 3 recent clinical trials in Table 7. The analytical procedures and sampling schedules were similar with a few noted exceptions. Investigators at the Mayo Clinic (Pitot et al., 2000) and the Rotterdam Cancer Institute (de Jonge et al., 2000) conducted their phase 1 dose-escalating trials in patients with non-CNS malignancies, in which CPT-11 was administered on an every-3-week schedule. Within comparative patient groups, the ratios are remarkably similar. Changes in the metabolic ratios are subject to metabolism as well as elimination and therefore are not a direct measure of conversions. However, the metabolic ratios viewed within the context of the metabolism and elimination of CPT-11 and SN-38 can provide speculative mechanisms by which EIAEDs influence the disposition of CPT-11 and its metabolites. EIAEDs increased the clearance of CPT-11. Increased conversion of CPT-11 to its predominant metabolite, APC, by induction of CYP3A4 is suggested by the APC-to-CPT-11 ratio of 48.8 in the EIAED groups versus 28.8 in the non-EIAED group. Enhanced elimination of CPT-11 via biliary transport mechanisms could have also occurred. The low SN-38-to-CPT-11 ratio of 1.5 for the EIAED group versus 3.1 for the non-EIAED group suggests a decreased conversion of CPT-11 to SN-38, consistent with the 1.9-fold decrease in CPT-11's AUC in the EIAED group. Saturation of the high-affinity, low-K_m carboxylesterase with the higher doses of CPT-11 could have also accounted for the lower SN-38 AUCs. Additionally, enhanced elimination of SN-38 by one or more pathways, such as biliary elimination (MRP2, MXR) or glucuronidation, is also a plausible explanation. The comparatively low ratio of SN-38 to SN-38G of 18.0 in the EIAED group versus 35.1 in the non-EIAED group is suggestive of increased glucuronidation of SN-38 by the inducible UGT1A1. In conjunction, we observed approximately the same metabolic ratio for both the EIAED group and the non-EIAED group for the combined SN-38 + SN-38G-to-CPT-11 ratio, consistent with a decreased SN-38, increased SN-38G, and decreased CPT-11 in the EIAED group. EIAEDs appear to influence multiple pathways relevant to CPT-11 and SN-38 disposition.

Our pharmacokinetic results are somewhat in contrast with the recently reported phase 1 escalation trial in glioma patients treated with CPT-11 using the weekly schedule (Gilbert et al., 2003). Dose escalations ranged from 125 to 444 mg/m² for patients receiving EIAEDs. CPT-11 clearance values were found to be dose dependent. At the reported MTD of 411 mg/m², however, the mean clearance value for CPT-11 (29.7 l/h/m²) was virtually identical to our observed mean CPT-11 clearance value (29.3 l/h/m²) and to the clearance value that Friedman et al. (1999) reported (30.4 l/h/m²). Similarly to the finding in our study, no relationship was found between

Table 7. Relative metabolic ratios of current trial compared with those of 3 recent trials

Ratio	Study Population (reference) Groups and Dose (mg/m ²)				Colorectal Cancer ¹ (n = 99) 125 q 3 weeks	Phase 1 ³ (n = 45) 175–300 q 3 weeks
	Gliomas ¹ EIAEDs (n = 32) 125 q week	Gliomas (current study) EIAEDs (n = 34) 350–800 q 3 weeks	Non-EIAEDs (n = 22) 350 q 3 weeks	Phase 1 ² (n = 34) 240–340 q 3 weeks		
SN-38/CPT-11	1.6	1.5	3.1	3.3	3.3	3.8
SN-38/SN-38G	17.9	18.0	35.1	31.9	27.9	*
(SN-38 + SN-38G)/ CPT-11	11.6	9.8	11.8	13.9	17.9	*
APC/CPT-11	Not Done	48.8	28.8	Not Done	Not Done	30.2

¹ Friedman et al. (1999)² Pitot et al. (2000)³ de Jonge et al. (2000)

*Different analytical procedure for determination of SN-38G.

CPT-11 dose and SN-38G AUC values. We observed no relationship between CPT-11 dose and SN-38 AUCs. In contrast, a fair relationship ($r^2 = 0.46$) between CPT-11 dose and SN-38 AUCs was reported by Gilbert et al. (2003). This latter observation again raises the issue of the saturability of the human carboxylesterase responsible for the conversion of CPT-11 to the active metabolite SN-38 (Slatter et al., 1997). Preliminary results from the pooled analysis of data from the 4 NCI-sponsored trials in glioma patients with CPT-11 doses ranging from 100 to 800 mg/m² indicated that SN-38 AUCs did not increase at doses greater than 350 mg/m² (Reid et al., 2001).

For patients receiving stable (2 weeks) doses of EIAEDs, the recommended phase 2 dose of CPT-11 is 750 mg/m² repeated every 3 weeks. The efficacy of CPT-11 is cur-

rently being evaluated in an NABTC phase 2 trial for glioma patients receiving EIAEDs. As a translational message, our NABTC experiences strongly suggest that the newer second-generation non-EIAEDs with little or no enzyme-inducing potential should be used when clinically indicated for patients with gliomas.

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Appendix

The North American Brain Tumor Consortium investigators and grant numbers for this study are presented in the table below.

Appendix Table. North American Brain Tumor Consortium investigators and funding under Prime Award CA 62399

Institution	Investigators	NABTC Grant	GCRC Grant
University of California at San Francisco	Michael Prados, M.D.* Susan Chang, M.D. M. Kelly Nicholas, M.D., Ph.D.	CA 62422	M01-RR00079
The University of Texas M.D. Anderson Cancer Center	W.K.A. Yung, M.D.* Kurt Jaeckle, M.D.	CA 62412	None
University of Texas Southwestern Medical Center	Karen Fink, M.D., Ph.D.*	CA 62455	M01-RR00633
The Dana Farber Cancer Center	Howard Fine, M.D.* Patrick Wen, M.D.	CA 62407	None
University of Pittsburgh	David Schiff, M.D.*	CA 62404	M01-RR00056
University of Texas Health Science Center at San Antonio	John Kuhn, Pharm.D.*	CA 62426	M01-RR0134
University of California, Los Angeles	Timothy Cloughesy, M.D.*	CA 62399	M01-RR0865
University of Michigan	Harry Greenberg, M.D.* Larry Junck, M.D.	CA 62399	M01-RR00042
University of Wisconsin	Minesh Mehta, M.D.* I.H. Robbins, M.D., Ph.D.	CA 62421	M01-RR03186

Abbreviations used are as follows: GCRC 5 General Clinical Research Center, NABTC, North American Brain Tumor Consortium.

* Principal Investigator. Dr. Fine is currently at the National Institutes of Health, and Dr. Schiff is at the University of Virginia.