

Phase I Clinical and Pharmacokinetic Study of Irinotecan in Adults with Recurrent Malignant Glioma¹

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ABSTRACT

Purpose: A preliminary evaluation of the efficacy of irinotecan in patients with malignant glioma demonstrated modest activity. A markedly lower than expected incidence of drug-related toxicity was also noted. This was consistent with pharmacokinetic data indicating that the total body clearance (CL) of irinotecan in this patient population was considerably greater than in colorectal cancer patients. Concomitant medications used chronically in brain cancer patients, especially glucocorticoids and anticonvulsants that induce hepatic enzymes involved in the metabolism or excretion of drugs, were believed to be the cause of the alteration in pharmacokinetic behavior. A Phase I study was therefore undertaken in patients with recurrent malignant gliomas to independently determine the maximum tolerated dose (MTD) of irinotecan in patients stratified according to the use of enzyme-inducing anticonvulsants (EIAs).

Experimental Design: Patients with recurrent malignant gliomas received irinotecan as a weekly 90-min i.v. infusion for four consecutive weeks, with additional cycles of treatment repeated every 6 weeks. The starting dose was 125 mg/m²/week for both groups of patients (+/–EIA). Groups of ≥3 patients were evaluated at each dose level, and the modified continual reassessment method was used for dose adjustments. The plasma pharmacokinetics of irinotecan, its active metabolite, 7-ethyl-10-hydroxy-camptothecin (SN-38), and the glucuronide conjugate of SN-38, SN-38 glucuronide, were determined in all patients during treatment with the first weekly dose.

Results: Forty patients were enrolled into the study and treated with a total of 135 cycles of irinotecan. The MTD was determined to be 411 mg/m²/week in the +EIA cohort and 117 mg/m²/week in the –EIA cohort for the weekly × 4 every 6 weeks schedule. Pharmacokinetic studies showed that the CL of irinotecan was distinctly dose dependent in the patients receiving EIAs, decreasing from ~50 liters/h/m² at the lower dose levels (125–238 mg/m²) to a mean ± SD value of 29.7 ± 9.0 liters/h/m² (n = 7) at the MTD. The grand mean CL for a group of 13 patients who were not taking EIAs, 18.8 ± 10.6 liters/h/m², was significantly different from the mean CL at the MTD of the +EIA cohort (P = 0.033). Mean values of the AUC of SN-38 (P = 0.4) and SN-38 glucuronide (P = 0.55) were not significantly different at the MTDs for the two cohorts of patients.

Conclusions: The MTD of irinotecan was 3.5 times greater in patients with malignant glioma who were concurrently receiving EIAs than in those who were not. This study has also served to confirm that the concomitant administration of EIAs results in marked enhancement in the CL of irinotecan. These findings have important implications for subsequent clinical trials to further evaluate irinotecan in brain cancer patients and underscore the importance of assessing the potential for pharmacokinetic interactions between concurrent medications and chemotherapeutic agents.

INTRODUCTION

Inhibitors of topo I,³ a nuclear enzyme involved in the replication, recombination, and transcription of DNA, are one of the most promising classes of antineoplastic agents introduced into the clinic during the past decade (1). The lead compound of this class, camptothecin, is an alkaloid produced by a Chinese bush that was discovered in the 1960s by the NCI drug screening program (2). Topo I reduces the torsional stress in supercoiled DNA by creating transient breaks in a single strand of DNA, allowing replication to proceed (3). Camptothecin and its structural analogues bind to and stabilize the topo I–DNA complex (4). Although this inhibits religation of the parent DNA, collision of the DNA replication fork with the ternary drug–topo I–DNA complex produces an irreversible double-strand break, which ultimately leads to cell death by an apoptotic pathway (5). Cells in S phase are particularly susceptible to the camptoth-

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³ The abbreviations used are: topo I, topoisomerase I; AUC, area under the plasma-concentration curve from time 0 to infinity; CYP450, cytochrome P₄₅₀; MTD, maximum tolerated dose; MRI, magnetic resonance imaging; CT, computed tomography; EIA, enzyme-inducing anticonvulsant; NCI, National Cancer Institute; CL, total body clearance; CNS, central nervous system; NPC, 7-ethyl-10-(4-amino-1-piperidino)-carbonyloxycamptothecin; DLT, dose-limiting toxicity; SN-38, 7-ethyl-10-hydroxy-camptothecin; SN-38G, SN-38 glucuronide.

ecins because ongoing DNA synthesis is required to induce the sequence of events resulting in cytotoxicity (6).

A reversibly hydrolyzable α -hydroxy- δ -lactone ring proved to be a critical structural element for the biological activity of camptothecin (1). Because of the poor solubility of the active form of the compound, with an intact lactone ring, the more water soluble carboxylate salt of camptothecin was used for the initial Phase I clinical trials performed in the early 70s. Clinical trials to evaluate the efficacy of camptothecin sodium were abandoned because of severe and unpredictable toxicity, notably nausea, vomiting, hemorrhagic cystitis, and myelosuppression (7–9). The identification of analogues with properties that were more suitable for clinical development was subsequently pursued. Irinotecan is perhaps the most promising camptothecin analogue that has been clinically evaluated to date. It is actually a water soluble prodrug designed to facilitate parental administration of the potent SN-38, a 1000-fold more potent inhibitor of purified topo I than irinotecan (10–12). Water solubility is conferred by a dibasic bispiperidine substituent, linked through a carbonyl group to the C-10 hydroxyl group, which is enzymatically cleaved on presentation to the systemic circulation.

A wide variety of dosing regimens has been evaluated in Phase I and II clinical trials of irinotecan in patients with systemic malignancies, as recently reviewed (1). The drug is currently approved for the treatment of colorectal cancer. The recommended dosing regimen in the United States is 125 mg/m² given as a 90-min i.v. infusion once weekly for 4 of 6 weeks (13). Chronic diarrhea is the most prevalent DLT of irinotecan. It is ameliorated with only partial success by the concurrent and prophylactic use of loperamide. Acute diarrhea, which responds to treatment with i.v. atropine, may also occur within a few h of irinotecan administration. Myelosuppression, particularly neutropenia, can also be severe but is often short in duration.

The results of a Phase II trial of irinotecan in patients with recurrent malignant gliomas were recently reported (14). Administration of the drug according to the approved regimen afforded a partial response rate of 15% and stable disease rate of 55%. Toxicity was considerably less than expected from experience with the treatment regimen in colorectal cancer patients. Furthermore, pharmacokinetic studies indicated that the AUC for both irinotecan and SN-38 was significantly lower than historical values in patients with extraneural primary malignancies. This finding suggested that the use of anticonvulsant drugs, which are known to induce hepatic CYP450 enzymes, could be responsible for the enhanced elimination of irinotecan in these patients, similar to the interaction described previously for 9-aminocamptothecin and paclitaxel (15, 16). A Phase I trial was clearly necessary to determine the MTD for irinotecan in this patient population and further assess the nature of the effect of concomitant anticonvulsants on the pharmacokinetic behavior of the drug.

PATIENTS AND METHODS

Patient Selection. Adult patients (age \geq 18 years) were required to have documented progressive or recurrent malignant gliomas, including the histological diagnosis of glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, or anaplastic mixed oligoastrocytoma. All of the following

conditions were required for entry into the study: (a) measurable disease by contrast-enhanced MRI or CT scans; (b) a Karnofsky performance status of \geq 60%; (c) receiving a stable or decreasing dose of corticosteroids for \geq 1 week; (d) a stable or improving neurological examination; and (e) previous treatment with not more than one chemotherapy regimen. The minimum time intervals between previous treatment of the malignancy and entry into this study were 3 months for radiation and 3 weeks for chemotherapy, unless the regimen included a chloroethylnitrosourea, in which case the interval was 6 weeks. Full recovery from the effects of any earlier intervention was required. Eligibility also required demonstrating adequate results from hematological studies (absolute neutrophil count \geq 1,500/ μ l; platelet count \geq 100,000/ μ l), renal function assessment (serum creatinine \leq 1.7 mg/dl), and the analysis of hepatic function (total bilirubin $<$ 1.5 mg/dl; aspartate aminotransferase and alanine aminotransferase less than four times the upper limit of normal). Factors resulting in exclusion from the study included: (a) a concurrent malignancy, except for basal cell carcinoma of the skin or cervical carcinoma *in situ*; (b) previous treatment with a topo I inhibitor; or (c) pregnancy or nursing, because of the risk of exposing the fetus or infant to the effects of chemotherapy. All pretreatment and eligibility evaluations were performed within 14 days of initiating therapy. The study protocol was reviewed and approved by the institutional review board governing each site participating in the study. Signature of a written informed consent document, satisfying all federal and institutional requirements, by each patient was required as a condition of registering for participation in the study.

Drug Administration and Dose Escalation. Patients were placed into one of two treatment groups depending on the use of anticonvulsants. Group A comprised patients taking anticonvulsants that are known inducers of CYP450 enzymes (+EIA), which included phenytoin, carbamazepine, phenobarbital, pyrimidone, and felbamate. Group B included patients who were either not being treated with anticonvulsants or were receiving anticonvulsants that did not induce CYP450 (–EIA), such as gabapentin and lamotrigine. The use of valproate was not permitted because of the potential for enhanced diarrhea resulting from diminished glucuronidation of SN-38 (17, 18). Treatment was intended to be delivered on an outpatient basis except when precluded by the condition of the patient.

Irinotecan hydrochloride (Pharmacia & Upjohn, Kalamazoo, MI) was administered weekly as a 90-min i.v. infusion for four consecutive weeks followed by a 2-week break period. This 6-week course was considered to be one cycle of treatment. Patients were premedicated with a serotonin agonist antiemetic, most commonly ondansetron or granisetron, and observed for \geq 1 h after completing the administration of irinotecan. The occurrence of acute diarrhea during this period prompted intervention with atropine, usually at a dose of 1 mg, by i.v. injection. Patients were instructed to take loperamide p.o. on the onset of diarrhea at home. The regimen consisted of an initial dose of 4 mg, followed by 2 mg every 2 h until the diarrhea resolved for a minimum of 12 h. The use of hematopoietic growth factors on a prophylactic basis was not permitted.

The initial dose level for both groups was 125 mg/m² weekly for 4 weeks. The continual reassessment method was used to escalate the dose (19). Three patients were entered into

each dose level and monitored for treatment-related toxicities, as described in the following section. Once all three patients had completed the first cycle of treatment with the starting dose, and they continued to satisfy all eligibility criteria for continued therapy or were removed from the study because of disease progression, all available dose and toxicity data were used to fit a logistic dose-response model. Only the toxicity associated with the first cycle of treatment was used for the dose-finding determination. The dose associated with a toxicity rate of 30% was calculated from the model, although the new dose was restricted to 150% of the previous dose, to prevent the dose from being escalated too rapidly without a reasonable degree of clinical certainty concerning the safety of the recommended dose level. Three additional patients were treated at the new dose level, and the entire modeling process was repeated, including an estimation of the MTD. The process was terminated when the recommended dose remained within 10% of the preceding dose for two consecutive iterations.

Patients continued to receive the same dose of irinotecan in the absence of major toxicities, as defined in the following section. Before retreatment, full recovery from any nonhematological toxicity, an absolute neutrophil count $\geq 1,500/\mu\text{l}$ and platelet count $\geq 100,000/\mu\text{l}$, was required. Chemotherapy was discontinued on evidence of a deterioration in neurological status, need for an increased glucocorticoid dosage, disease progression, or the appearance of new lesions on serial magnetic resonance or CT scans. Patients experiencing a major toxicity during the first cycle of therapy were permitted to receive additional treatment with a 25% reduction in the dose of irinotecan. Additional decreases in the dose, in this same manner, were permitted because of the occurrence of a major toxicity after treatment with a reduced dose. The maximum number of dose reductions permitted was three; thus, the development of a major toxicity after the third dose reduction resulted in removal from the study.

Evaluations for Toxicity and Response. The toxicity data required for continual reassessment method modeling were based on the incidence of major adverse events, as defined below. Toxicities were classified and graded according to the United States NCI's common toxicity criteria. Major hematological toxicities included: (a) absolute neutrophil count $< 500/\mu\text{l}$ for ≥ 3 days; (b) febrile neutropenia; (c) platelet count $< 25,000/\mu\text{l}$; and (d) a delay in starting the next cycle of treatment by > 7 days to allow complete recovery from toxicity. A complete blood count with differentials and platelet count was performed 7 days after initiating treatment and twice a week thereafter. In the event of a major hematological toxicity, these tests were repeated every other day until evidence of recovery, as indicated by an absolute neutrophil count $\geq 1,500/\mu\text{l}$ and platelet count $\geq 100,000/\mu\text{l}$. Nonhematological toxicities of grades 3 and 4 severity, with the exception of nausea and vomiting without adequate antiemetic prophylaxis or diarrhea without adequate antidiarrheal medications, were considered to be major toxicities. In addition, chronic renal, pulmonary, some neurological toxicities, such as alterations in mental status, and cardiac toxicities of grade 2 severity were considered to be major adverse events. Unresolved major nonhematological toxicity that delayed the subsequent course of chemotherapy by > 7 days was also to be considered a major adverse event. The

development of seizures, progression or worsening of preexisting neurological deficits, deep venous thrombosis, or pulmonary emboli were not dose-limiting considerations unless the investigator believed that the event was attributed to the study drug and not the underlying CNS malignancy.

MRI or CT images with volumetric analysis and neurological examinations were used to determine the response to therapy. Brain imaging studies to provide a baseline measurement of the tumor volume were performed not > 2 weeks before beginning treatment. Measurements were repeated after completing every second cycle of therapy. A complete response required the complete disappearance of all measurable tumor, withdrawal from glucocorticoid therapy, and a stable or improving neurological examination for a minimum of 6 weeks. A partial response was indicated by a reduction in tumor volume by $\geq 50\%$, with a stable or decreasing dose of glucocorticoids, and stable or improving neurological examination for a minimum of 6 weeks. Progressive disease was indicated by continued neurological abnormalities not explained by causes unrelated to tumor progression (*e.g.*, anticonvulsant or corticosteroid toxicity, electrolyte abnormalities, hyperglycemia, and others) or an increase in tumor volume $> 25\%$. Stable disease was defined by a clinical status and radiographic tumor measurement that did not meet the criteria for a complete response, partial response, or progressive disease. Survival was measured from the time of entry into the study.

Pharmacokinetic Studies

Sample Collection. Sampling to characterize the plasma pharmacokinetics of irinotecan was performed during treatment with the first weekly dose of the first cycle of therapy. Blood specimens (7 ml) were drawn from a peripheral vein in the arm contralateral to the site of drug administration and collected directly in tubes containing freeze-dried sodium heparin anticoagulant before dosing, coincident with the end of the 90-min infusion of irinotecan, then at 6 and 24 h after the end of the infusion (20). Sample tubes were mixed by inversion and placed on wet ice until centrifuged ($1000 \times g$, 10 min, 4°C) within 15 min. Plasma was transferred into a polypropylene cryovial and stored at -70°C until assayed.

Analytical Methods. The total concentration (*i.e.*, lactone plus carboxylate forms) of irinotecan and SN-38 in plasma specimens was determined by reversed phase high-performance liquid chromatography with fluorescence detection. Analytical reference samples of irinotecan hydrochloride trihydrate and SN-38 were very generously provided by Pharmacia & Upjohn, Inc. Camptothecin was obtained from the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, NCI (Bethesda, MD). Study samples were thawed at ambient temperature and prepared for chromatographic analysis as described previously, with minor modifications (21). Briefly, to 100 μl of plasma, 5 μl of a 2 $\mu\text{g}/\text{ml}$ solution of camptothecin in methanol-10 mM acetic acid, which served as the internal standard, and 200 μl of acetonitrile-methanol (1:1, volume for volume) were added. The mixture was mixed vigorously by vortexing and centrifuged for 3 min at $12,000 \times g$. The clear, protein-free supernatant was removed and diluted with an equivalent volume (200 μl) of potassium phosphate buffer (0.1 M, pH 2.0). A 250- μl aliquot of

the resulting solution was loaded onto a 3.9-mm (internal diameter) \times 15-cm NovaPak C₁₈ (5- μ m particle size) analytical column (Waters Corp., Milford, MA), preceded by a 3.2 mm \times 1.5-cm Brownlee RP-18 NewGuard (7- μ m particle size) pre-column (Alltech Associates, Deerfield, IL) and a 0.5- μ m in-line filter. Chromatography was performed at ambient temperature using a mobile phase composed of acetonitrile-potassium phosphate buffer (0.1 M, pH 4.0; 22:78, volume for volume) containing 0.05 mM tetrabutylammonium hydrogen sulfate delivered at 1.0 ml/min. The chromatographic conditions were adapted from analytical methods reported previously for the drug (21, 22). Elution of the analytes and internal standard was monitored using an HP 1046A programmable fluorescence detector with an xenon-arc flash lamp, fitted with a 2 \times 2-mm excitation slit (25-nm bandwidth), 4 \times 4-mm emission slits (50-nm bandwidth), a 305-nm cutoff filter, and a 5- μ l flow cell. Additional detector parameters were set as follows: (a) radiation source flash frequency, 220 Hz; (b) excitation wavelength, 223 nm; (c) emission wavelength, 520 nm; (d) photomultiplier gain, 15; and (e) response time, 4 s.

The concentration of SN-38G was determined indirectly by measuring the total concentration of SN-38 liberated by hydrolysis with β -glucuronidase (18). A solution of Type B-1 β -glucuronidase from bovine liver (Sigma, St. Louis, MO) in ammonium acetate buffer (0.1 M, pH 5.0) was prepared daily as needed. Study samples and plasma calibration standards (50 μ l) were pipetted into polypropylene microcentrifuge tubes, treated with 50 μ l of the β -glucuronidase solution, and incubated for 2 h in an Eppendorf model 5436 Thermomixer (Brinkmann Instruments, Westbury, NY) set at 37°C with moderate agitation. Thereafter, the samples were prepared for chromatographic analysis as described above. The molar concentration of SN-38G in study samples was calculated as the difference between the molar concentration of total SN-38 when measured after enzymatic hydrolysis and directly.

Each study sample was independently assayed in duplicate, on different days, together with a series of eight plasma calibration standards containing irinotecan hydrochloride trihydrate at concentrations ranging from 10.9 to 1091 ng/ml and SN-38 at concentrations from 2.9 to 117 ng/ml. Values of the parameters describing the best-fit lines determined by weighted linear regression were used to calculate the concentration of each analyte in the study samples. Specimens with an estimated concentration above the upper limit of the standard curve were reassayed in duplicate on appropriate dilution with drug-free plasma. Study samples were also reassayed in cases where the two initial determinations differed from their average by >10%. Accuracy and precision of the analytical method were assessed from the mean value and coefficient of variation, respectively, of the interpolated concentrations from a set of four standard curves that were independently prepared and assayed on different days during a single week. Both parameters were \leq 10% at all concentrations except for the lower limit of the standard curves. Accuracy expressed as the percentage of difference between the mean calculated and nominal concentration was 11.9% for irinotecan (10.9 ng/ml) and 16.2% for SN-38 (2.9 ng/ml). Corresponding values of the precision were 4.3% for irinotecan and 7.0% for SN-38.

Table 1 Patient characteristics (n = 40)

	No. of patients
Age (yr)	
Median	45
Range	22–74
Sex	
Male	25
Female	15
Karnofsky performance status	
<70%	3
70–80%	14
90–100%	21
Histological diagnosis	
Glioblastoma multiforme	34
Anaplastic astrocytoma	5
Anaplastic oligodendroglioma	1
Concomitant medications	
Group A	
No. of patients	31
Decadron	25
Phenytoin	20
Carbamazepine	9
Phenobarbital	2
Group B	
No. of patients	9
Decadron	4
Gabapentin	2
No anticonvulsants	7

Data Analysis. Actual sample times were calculated from the beginning of the irinotecan infusion to the sample collection time. Individual patient plasma concentration time curves were analyzed by noncompartmental methods using routines supplied in the WinNonlin Version 1.1 software package (Scientific Consulting, Apex, NC; Ref. 23). AUC was estimated using the logarithmic-linear trapezoidal algorithm to the last data point, with extrapolation to time infinity using the estimated value of the slope of the terminal logarithmic-linear disposition phase. The administered dose was converted from milligrams of irinotecan hydrochloride trihydrate to nanomoles per meter squared body surface area for calculating CL. Estimated values of the pharmacokinetic parameters at each dose level are reported as the geometric mean \pm SD of the values for the individual patients (24, 25). SDs for the geometric mean values were estimated by the jackknife method (26). Parametric statistical tests (*i.e.*, single factor ANOVA, Student's *t* test) of pharmacokinetic variables were performed after logarithmic transformation of the data. All tests were two sided, and a value of $P < 0.05$ was the criteria for significance.

RESULTS

Phase I Clinical Trial. A description of the characteristics of the 40 patients enrolled into the trial is provided in Table 1. Most of the patients (71%) on the study had glioblastoma multiforme, and the majority (55%) had a good to excellent performance status (Karnofsky Performance Status $>$ 80). A total of 135 cycles of weekly irinotecan was administered. As shown in Table 2, DLT was not observed in patients taking EIAs until the dose of irinotecan was escalated to 444 mg/m². Two patients experienced a DLT at this dose level, one with grade 3 abdominal cramping and the other patient with grade 4 diarrhea.

Table 2 Toxicity observed during the first cycle of treatment

Dose level (mg/m ²)	No. of patients evaluated	No. of patients					
		Grades 3–4 nonhematologic toxicity	Febrile neutropenia	Grade 4 neutropenia	Platelet count < 25,000/μl	Treatment delay > 7 days	DLT (% of patients)
+EIA cohort							
125	3	0	0	0	0	0	0
144	3	0	0	0	0	0	0
189	3	0	0	0	0	0	0
238	3	0	0	0.5 ^a	0	0	17
267	3	0	0	0	0	0	0
296	3	0	0	0	0	0	0
344	3	0	0	0	0	0	0
411	6	1	1	0	0	0	17
444	3	2	0	0	0	0	67
–EIA cohort							
125	3	3	0	0	0	0	100
112	3	0	0	0	0	0	0
117	3	0	0	0	0	0	0

^a A value of 0.5 for DLTs was used for the CRM model because of insufficient data to verify neutropenia.

The MTD was determined to be 411 mg/m² for the +EIA cohort. In contrast, patients not taking EIAs experienced DLT, grade 3 nonhematological toxicity (diarrhea in 2 patients and neuropathy in 1 patient) at a dose of 125 mg/m². As a consequence, the MTD was determined to be 117 mg/m² in the absence of EIAs, which is lower than the starting dose. Thus, the MTD of irinotecan in glioma patients receiving EIAs was 3.5 times greater than for patients who were not concurrently taking EIAs.

Four patients had centrally reviewed radiographic partial responses as detected by serial measurements of gadolinium-enhanced MRI scans. No complete responses were seen. Six patients also showed disease stabilization for a minimum of two cycles. There was evidence of tumor progression in 26 patients during the first evaluation performed after completing the second cycle of therapy. Four patients failed to complete the first cycle of treatment and were considered to be unsuitable for evaluating response. Interestingly, all 4 patients showing an objective response were in the +EIA cohort ($n = 29$ evaluable for response), with 2 treated at intermediate dose levels of 189 mg/m² (1 patient) and 238 mg/m² (1 patient) and the other two at the MTD of 411 mg/m². There were no responders in the –EIA cohort, although only 9 patients were enrolled in this group, because only three dose levels were required to establish the MTD. Thirty-eight of the 40 patients have died, the 2 surviving patients were followed for 17.5 and 34.5 months, and the total follow-up was 36.6 person-years. Median overall survival as estimated by the Kaplan-Meier technique was 7.4 months (95% confidence interval = 5.6, 12.4 months) from the time of entry into the study (Fig. 1).

Pharmacokinetics. Mean pharmacokinetic parameters for irinotecan, SN-38, and SN-38G estimated by noncompartmental analysis are summarized in Table 3 for the +EIA cohort and in Table 4 for the –EIA group. In addition to the 40 patients enrolled into the Phase I trial, pharmacokinetic sampling was also performed in 4 patients treated at the 117 mg/m² MTD for the –EIA cohort in the subsequent Phase II trial. Data from these patients have also been included in Table 4. The grand

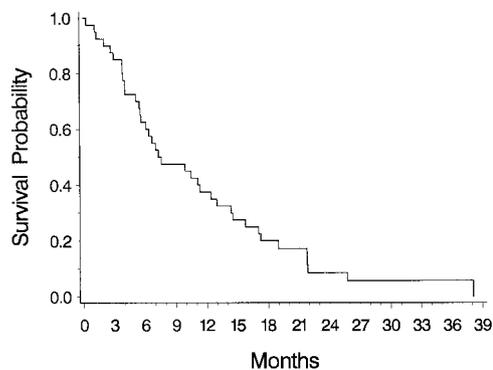


Fig. 1 Kaplan-Meier survival curve for all patients enrolled in the Phase I study. Survival was measured from the time of entry into the study.

mean CL of total irinotecan for the entire cohort of 13 patients in the –EIA group, who were treated with doses ranging from 112 to 125 mg/m², was 18.8 ± 10.6 liters/h/m². Mean CL values determined at each dose level for the –EIA patients were not significantly different ($P = 0.18$), although the range of doses evaluated differed by only 12%. In contrast, in the +EIA cohort, there was evidence of a statistically significant difference among the mean CL values of irinotecan determined at the nine dose levels, ranging from 125 to 444 mg/m² ($P = 0.0065$). As illustrated in Fig. 2A, the CL of irinotecan was significantly correlated with the administered dose ($r = -0.71$, $P = 0.032$) in the +EIA cohort, decreasing from ~ 50 liters/h/m² in patients treated at the lower dose levels (125–238 mg/m²) to 29 liters/h/m² at the higher doses. In addition, there was a significant difference ($P = 0.025$) between the mean CL of irinotecan determined at the 411 mg/m² MTD for patients receiving EIAs (29.7 ± 9.0 liters/h/m², $n = 7$) as compared with the 117 mg/m² MTD for patients not receiving EIAs (14.8 ± 9.8 liters/h/m², $n = 7$). The influence of different anticonvulsants on the pharmacokinetics of irinotecan could not be discerned because of the

Table 3 Pharmacokinetic parameters of irinotecan and metabolites in patients receiving enzyme-inducing anticonvulsants^a

Dose (mg/m ²)	No. of patients	C _{max}			AUC (μM·h)			Irinotecan clearance (liter/h/m ²)
		Irinotecan (μM)	SN-38 (nM)	SN-38G (nM)	Irinotecan	SN-38	SN-38G	
125	3	1.5 ± 0.4	37 ± 7	370 ± 68	4.5 ± 0.6	0.13 ± 0.07 ^b	2.7 ± 0.7	41.0 ± 5.7
144	3	0.9 ± 0.4	24 ± 8	355 ± 37	4.3 ± 0.8	0.15 ± 0.05 ^b	2.2 ± 0.2	50.2 ± 9.6
189	3	1.4 ± 0.6	30 ± 21	225 ± 53	5.9 ± 0.7	0.19 ± 0.09	1.7 ± 0.3	47.2 ± 5.5
238	3	1.7 ± 0.2	30 ± 3	285 ± 61	6.4 ± 0.7	0.17 ± 0.03	2.1 ± 0.3	54.7 ± 6.2
267	3	3.0 ± 1.0	40 ± 3	254 ± 97	12.7 ± 5.6	0.26 ± 0.09	1.9 ± 0.8	31.0 ± 12.3
296	3	2.2 ± 0.3	42 ± 12	429 ± 122	12.3 ± 3.4	0.59 ± 0.65	2.9 ± 1.5	35.3 ± 10.1
344	3	2.9 ± 0.5	38 ± 5	253 ± 212	12.6 ± 1.9	0.33 ± 0.10	2.0 ± 2.1	40.3 ± 6.1
411	7	5.5 ± 3.2	56 ± 32	247 ± 222	20.4 ± 5.9	0.33 ± 0.11	1.7 ± 1.9	29.7 ± 9.0
444	3	4.8 ± 0.8	67 ± 9	223 ± 87	23.3 ± 5.3	0.41 ± 0.08	1.7 ± 0.4	28.2 ± 6.2

^a Mean ± SD at each dose level based on measurement of the total plasma concentration (lactone + carboxylate) of each compound.

^b Parameter could not be estimated in 1 patient (*n* = 2).

Table 4 Pharmacokinetic parameters of irinotecan and metabolites in patients who did not receive enzyme-inducing anticonvulsants^a

Dose (mg/m ²)	No. of patients	C _{max}			AUC (μM·h)			Irinotecan clearance (liter/h/m ²)
		Irinotecan (μM)	SN-38 (nM)	SN-38G (nM)	Irinotecan	SN-38	SN-38G	
112	3	1.3 ± 0.2	32 ± 13	150 ± 19	7.3 ± 1.6	0.18 ^b	2.3 ± 0.7	21.5 ± 4.8
117	7	2.3 ± 1.9	46 ± 28	206 ± 123	10.8 ± 6.9	0.45 ± 0.38	2.4 ± 2.0	14.8 ± 9.8
125	3	1.4 ± 0.2	51 ± 68	259 ± 173	5.8 ± 1.6	1.55 ± 0.01 ^c	2.6 ± 1.5	29.0 ± 6.2
Mean ± SD								18.8 ± 10.6

^a Mean ± SD at each dose level based on measurement of the total plasma concentration (lactone + carboxylate) of each compound.

^b Parameter could not be estimated in 2 patients (*n* = 1).

^c Parameter could not be estimated in 1 patient (*n* = 2).

dose-dependent CL of irinotecan, the small number of patients evaluated at each dose level, and a large majority of patients in the +EIA group (20 of 31) were treated with phenytoin. For the +EIA patients, the AUC of SN-38 increased linearly as the dose was escalated from 125 to 444 mg/m² (*r* = 0.68, *P* = 0.044), whereas the AUC of SN-38G was not significantly correlated with the dose (*r* = 0.45, *P* = 0.23; Fig. 2, B and C). A similar examination of the relationship between dose and AUC was not assessed for the -EIA group because of the narrow dose range evaluated. Mean values of the AUC of SN-38 (*P* = 0.40) and SN-38G (*P* = 0.55) were not significantly different at the MTDs for the two cohorts of patients. AUC values of both irinotecan and SN-38 were compared for patients with documented response, stable disease, and progressive disease. As illustrated in Fig. 3, there was no difference in the range or median values between the three response groups for either SN-38 or irinotecan.

DISCUSSION

Effectively treating primary brain tumors with cytotoxic chemotherapy has proven to be extremely challenging. One of the major concerns with the use of systemically administered chemotherapy is whether the extent of distribution of drug to the tumor is sufficient to achieve a therapeutic response. Although many anticancer drugs readily penetrate the visible tumor, where the blood-brain barrier is breached, achieving effective concentrations of these agents in the surrounding brain tissue that contains infiltrating tumor cells appears to be considerably more problematic. Therefore, the agents typically selected for clinical evaluation against malignant glial neoplasms are relatively low molecular weight, lipophilic molecules capable of

penetrating the blood-brain barrier by passive diffusion. In addition, the plasma pharmacokinetics of chemotherapeutic agents may be significantly altered in patients with brain tumors as a consequence of concurrent medications, such as anticonvulsants. Therefore, standard dosing regimens developed for patients with extraneural solid tumors may result in the under-treatment of brain cancer patients. Recent clinical studies have demonstrated that the major determinant of this effect is associated with the concurrent use of anticonvulsants and corticosteroids that induce hepatic CYP450 enzymes by this patient population, thereby resulting in enhanced clearance of drugs for which hepatic oxidative metabolism is an important route of elimination. For example, the MTD of paclitaxel was increased by 42% and that of 9-aminocamptothecin by 100% in brain cancer patients taking EIAs in comparison with those who were not (15, 16). The greater tolerability of both drugs was associated with a marked increase in their CL in patients concurrently receiving EIAs. Paclitaxel is extensively metabolized by CYP450 enzymes, and the existence of this interaction was not at all unexpected (27). In contrast, metabolism had not been identified previously as a significant elimination pathway for any of the camptothecins, and it is not entirely clear whether CYP450 induction is directly responsible for the observed changes in pharmacokinetic behavior.

There has been considerable interest in evaluating the clinical efficacy of camptothecin analogues against primary brain cancers. The investigational drug 9-aminocamptothecin showed no substantial activity against newly diagnosed or recurrent high-grade astrocytomas when given as a 72-h continuous i.v. infusion (28). Among the two clinically available

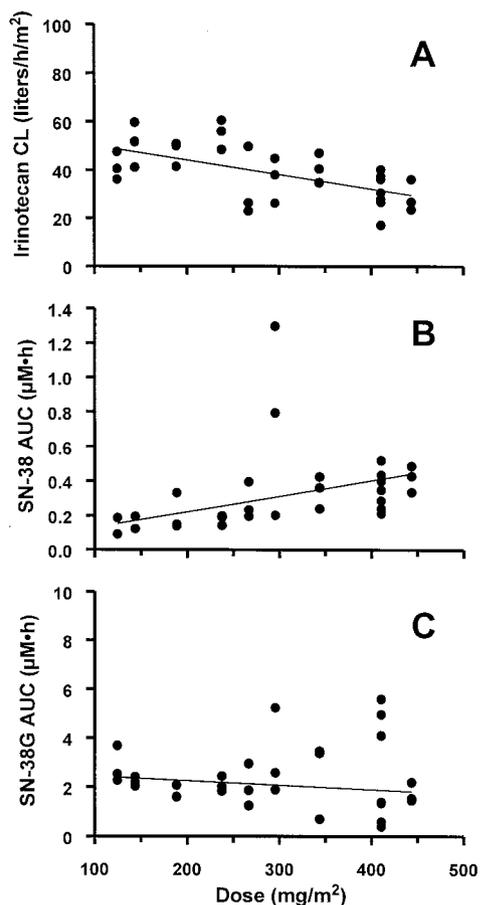


Fig. 2 Scatter plots depicting the CL of irinotecan (A) and AUC of SN-38 (B) and SN-38G (C) determined in individual patients who were receiving EIA drugs during treatment with irinotecan. The straight lines were generated from linear regression analysis of the mean parameter values for the group of patients evaluated at each dose level.

camptothecins, topotecan appears to penetrate the blood–brain barrier more readily than irinotecan, as indicated by cerebral spinal fluid:plasma AUC ratios of 29–42% in pediatric patients receiving topotecan as a continuous i.v. infusion and 14% for the intact lactone form of irinotecan in nonhuman primates (29, 30). SN-38 was not measurable in the cerebral spinal fluid of nonhuman primates after administration of a dose of irinotecan that provided peak plasma levels of total irinotecan and SN-38, which were comparable with those achieved in humans with the standard 125 mg/m² dose (30). Treatment with topotecan as a 72-h continuous i.v. infusion at a rate of 0.87 mg/m²/day showed no objective activity in 28 adults with recurrent malignant glioma and partial responses in only 2 of 14 patients with newly diagnosed disease (31). A Phase II trial to assess the activity of topotecan in patients with recurrent glioma when given in the recommended manner, daily treatment with doses of 1.5 mg/m² as a 30-min i.v. infusion for five consecutive days repeated every 3 weeks, showed only modest activity with objective responses occurring in 2 of 31 (6%) patients (32). A more promising level of activity was recently reported for irinotecan against refractory malignant glioma, with partial re-

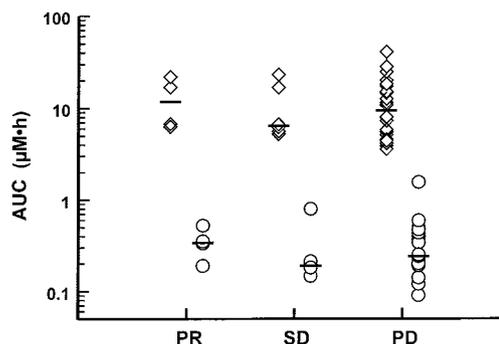


Fig. 3 Plot depicting the AUC values of irinotecan (\diamond) and SN-38 (\circ) in patients demonstrating a partial response (PR), stable disease (SD), or progressive disease (PD). Horizontal bars, the median AUC value for each group.

sponses occurring in 9 of 60 adult patients (15%) treated according to the recommended dosing regimen (14).

Several physicochemical and pharmacological factors could contribute to these seemingly conflicting findings. Topotecan is a substrate of P-glycoprotein, the transporter associated with the multidrug-resistance phenotype and an important component of the blood–brain barrier that impedes the distribution of several anticancer drugs into the brain (33–35). In contrast, SN-38 is not a P-glycoprotein substrate, and its cytotoxicity toward tumor cells is not notably diminished by multidrug-resistance overexpression (33), although the transporter has been implicated in the biliary excretion of the carboxylate form of irinotecan (36). Topotecan and irinotecan are both positively charged at physiological pH, and SN-38 is a neutral molecule. However, the fraction of topotecan bound to plasma proteins has been reported as ranging from 7 to 35%, in comparison with 30–43% for irinotecan and 92–96% for SN-38, based on total drug determinations (37, 38). Thus, the lower degree to which topotecan is bound to plasma proteins may account for its greater CNS penetration. Differences in the clinical activity between the two agents could be associated with the overexpression of P-glycoprotein by malignant gliomas (39).

The dosage and administration schedule of irinotecan approved for the treatment of colorectal cancer patients, 125 mg/m² once a week for 4 weeks followed by 2 weeks without drug, was used in the initial study to assess the clinical activity of irinotecan in brain cancer patients (14). The potential for enhanced clearance of irinotecan in patients receiving corticosteroids and EIAs on a continual basis, as reported in this previous study (14), could have been predicted from evidence indicating that hepatic metabolism by pathways other than conversion to SN-38 represented a prominent route of elimination for the compound. Two oxidative metabolites produced by the 3A4 isoform of hepatic CYP450, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino carbonyloxy]camptothecin and NPC, have been identified (40, 41). The existence of additional unidentified metabolites is suggested by a report that only 53% of the administered dose was recovered as unchanged irinotecan or its known metabolites in urine (28%) and feces (25%; Ref. 42). In addition, after i.v. administration of ¹⁴C-labeled irinotecan to patients, 64% of the radioactivity was found in the feces (43).

The present study was undertaken to establish appropriate doses of irinotecan to further assess its efficacy against malignant gliomas and the influence of EIAs on the pharmacokinetics and metabolism of the drug. The MTD of irinotecan was found to be 3.5 times greater in brain cancer patients who were concurrently receiving EIAs (411 mg/m²/week) than in those who did not (117 mg/m²/week). Objective responses to therapy were documented in 4 of 29 evaluable patients concurrently receiving EIAs and in 0 of 7 evaluable patients in the -EIA cohort. The mean AUC of irinotecan at the MTD for patients receiving EIAs (20.4 ± 5.9 μM·h) was 89% greater than that observed at the MTD for the -EIA cohort (10.8 ± 6.9 μM·h). However, it does not appear likely that the lack of efficacy observed in -EIA patients is attributable to differences in systemic exposure to irinotecan or SN-38, because several responding patients in the +EIA group were treated at doses well below the MTD. Plausible alternative explanations include a statistical artifact resulting from the considerably smaller number of -EIA patients that were evaluated or an unknown pharmacodynamic interaction involving the EIAs. Nevertheless, greater systemic exposure to irinotecan could promote enhanced transport of the compound across the blood-brain or blood-tumor barriers. This could be therapeutically beneficial if the prodrug undergoes significant conversion to SN-38 in glioma cells. It has been reported that human tumor cell lines lacking carboxylesterase activity are unable to convert irinotecan to SN-38 and demonstrate reduced sensitivity to treatment with the prodrug *in vitro* (44, 45). However, because hepatic conversion most likely predominates *in vivo* (46), although a butyrylcholinesterase present in human serum also contributes to the activation of irinotecan (47), the importance of local carboxylesterase activity within cancer cells to achieving an antitumor effect is uncertain. In any event, a Phase II clinical trial has been initiated to determine the activity of irinotecan against refractory malignant glioma when administered at the MTD appropriate for the anticonvulsant therapy for each patient. The results of this study will be reported elsewhere.

This investigation has also served to further demonstrate that the plasma pharmacokinetics of irinotecan are markedly altered by the concurrent use of EIAs. A complete lack of toxicity in patients receiving EIAs who were treated with the standard 125 mg/m² dose of the drug is consistent with the lower than expected peak plasma concentrations and AUC of irinotecan and SN-38. The mean CL of total irinotecan in patients not receiving EIAs, 18.8 ± 10.6 liters/h/m², was very similar to the range of values reported previously in studies of patients with extraneural solid tumors (13, 48, 49). In addition, pharmacokinetic data determined for the group of 3 patients evaluated at the 125 mg/m² starting dose in the +EIA cohort were in good agreement with the parameter values reported previously for 32 glioma patients treated with this same dose (14). In this previous study, 29 of the 32 patients were receiving EIAs, and all were being chronically treated with dexamethasone. Pharmacokinetic data were obtained during the present clinical trial in patients receiving EIAs and chronic dexamethasone after treatment with irinotecan at a 3.6-fold range of doses from 125 to 444 mg/m². This provided an opportunity to acquire a greater understanding of the influence of EIAs on the disposition of the drug than permitted by a study restricted to a single

dose. The CL of irinotecan tended to decrease linearly with escalations in the dose; however, even at the highest dose level evaluated, the apparent CL was still significantly greater than in patients who were not receiving EIAs. Although the mean AUC of irinotecan determined at the MTDs was significantly greater for patients receiving EIAs, as noted above, the AUCs of SN-38 and SN-38G were not significantly different at the MTDs for the two cohorts of patients. This suggests that a greater fraction of irinotecan is eliminated by an alternative route, not leading to SN-38 formation, in patients receiving EIAs. Establishing whether concurrent treatment with EIAs results in enhanced formation of either of the two known oxidative metabolites of irinotecan (*i.e.*, 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin and NPC) would be of interest because both compounds are poor inhibitors of topo I, and only NPC is significantly converted to SN-38 by human carboxylesterases (40, 41). However, they were not measurable because of inadequate separation from polar fluorescent endogenous sample constituents by the chromatographic conditions used in the analytical method that was used for the quantitation of irinotecan and SN-38 in this study.

The level of activity observed in this Phase I trial and the initial clinical study warrants further investigation to fully explore the use of irinotecan for treating malignant gliomas. Variability in accessibility of the active form of the drug to the tumor could account for the modest response rates noted in these studies. Unlike small laboratory animals, in which ≥86% of the administered dose of irinotecan is converted to SN-38 (12), the AUC of SN-38 is only ~4% of the irinotecan AUC in humans, suggesting that only a relatively small fraction of the dose is ultimately converted to the active form of the drug (13). It is also possible that the human enzyme is saturable at physiologically achievable concentrations (50). A clinical trial using a continuous low-dose *i.v.* infusion of irinotecan over 14 days showed a marked increase in the SN-38:irinotecan AUC ratio compared with short *i.v.* infusions (16 *versus* 3–5%), supporting the concept of saturation of the carboxylesterase activity (51). Thus, bolus doses that provide greater plasma concentrations of irinotecan may not notably impact the relative amount of SN-38 formed. Such an effect was not observed in this study, because the AUC of SN-38 tended to increase in proportion to the AUC and C_{max} of irinotecan. Nevertheless, concern about the potential saturation of carboxylesterase activity during administration of relatively large, infrequent doses of irinotecan prompted investigations of a daily dosing regimen in a xenograft model and, recently, in a Phase I trial in children (52, 53). The xenograft model showed improved efficacy of repeated daily dosing, and the Phase I trial demonstrated good tolerance and tumor responses in a broad spectrum of cancers.

The critical issue of identifying a dosing strategy that maximizes the production and delivery of the intact lactone form of SN-38 to brain tumors remains to be determined. Characterizing the plasma pharmacokinetics of irinotecan during the Phase I trial in this unique patient population was an important first step in the clinical development of this drug for efficacious use against malignant brain tumors. The influence of various drug delivery techniques and effect of EIAs on the distribution of irinotecan and SN-38 to the CNS and brain tumors from the systemic circulation are important questions

that need to be addressed in patients. In addition to acquiring serial samples of cerebrospinal fluid, the clinical application of underused sampling techniques, such as microdialysis, to discern the time course of the concentrations of irinotecan and SN-38 in the extracellular fluid within brain tumors and surrounding normal tissue could greatly benefit the rational development of this agent for the treatment of malignant gliomas (54).

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Phase I Clinical and Pharmacokinetic Study of Irinotecan in Adults with Recurrent Malignant Glioma

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