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Phase II trial of two different irinotecan schedules with pharmacokinetic analysis in patients with recurrent glioma: North Central Cancer Treatment Group results

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Abstract

Purpose—The aims of this trial were to assess the safety and efficacy of two different dosing schedules of irinotecan (CPT-11) in recurrent glioma patients, to assess irinotecan pharmacokinetics in patients on enzyme-inducing antiepileptic drugs (EIAEDs) and steroids, and to correlate with toxicity and response to treatment.

Methods—Sixty-four recurrent glioma patients were included in this study. Schedule A patients received irinotecan weekly (125 mg/m²/w) for four out of six weeks. Schedule B patients received irinotecan every three weeks at a dose of 300 mg/m². A 20% dose reduction was implemented for patients who had received prior nitrosureas. Treatment was continued until unacceptable toxicity, tumor progression or patient withdrawal.

Results—There was no difference in confirmed responses between the two groups (6.3%). PFS at 6 months was 6.25% (2/32 patients) on schedule A and 18.75% (6/32 patients) on schedule B but median OS (5.1 versus 5.5 months), and survival at one year (19%) was similar for both arms. The most common grade 3–4 toxicities on schedules A/B were: thrombocytopenia (15.6%/21.9%), diarrhea (6.3%/12.5%) and nausea and vomiting (0%/15.7%). One toxic death due to infection in the absence of neutropenia occurred in schedule B. EIAEDs reduced SN-38 and CPT-11 area under the curve and increased CPT-11 clearance. This effect was more prominent in schedule A patients. Steroids did not alter CPT-11 pharmacokinetics in either schedule.

Conclusions—Single agent irinotecan has modest activity in patients with recurrent gliomas, independently of the administration schedule. Irinotecan administration on an every 3 week schedule resulted in longer PFS-6, at the expense of more toxicity. EIAEDs alter CPT-11 pharmacokinetics in this group of patients, and should be taken into consideration when determining optimal dosing.

Keywords

Enzyme-inducing antiepileptic drugs; Dexamethasone; Irinotecan; Pharmacokinetics; Recurrent gliomas

Introduction

Recurrent gliomas are associated with significant morbidity and mortality and most patients will eventually succumb to their disease [1]. Treatment options for recurrent disease are limited and with few exceptions have limited impact on duration and quality of the patients' life [2, 3].

Irinotecan (CPT-11) is a semisynthetic derivative of camptothecin that is hydrolyzed after administration by carboxylesterases to its more active metabolite SN-38. The parent molecule is metabolized by cytochrome P450 3A4 to form the metabolite APC (7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxy-campto-thecin) and SN-38 is conjugated with glucuronic acid by glucuronosyl transferase UGT1A1 to form SN-38 glucuronide (SN-38G). Irinotecan's mechanism of action, i.e., inhibition of topoisomerase-I, a nuclear enzyme that plays a critical role in DNA replication and transcription [4,5] differs from other chemotherapy agents employed in glioma treatment. In addition, its lipophilic nature and its low molecular weight result in excellent CNS penetration. Both single agent trials [6–12] and combination studies of CPT-11 with BCNU [13–15], temozolomide [16,17], topoisomerase-II inhibitors [18] and celecoxib [19] in recurrent malignant gliomas have resulted in variable response rates varying from 7% to 21%. Recently, the addition of the antiangiogenic monoclonal antibody bevacizumab to CPT-11 has resulted in a 40–63% response rate with a 6-month progression free survival (PFS6) of 38–46% and acceptable toxicity [20–22] thus potentially opening new directions in recurrent glioma treatment. This wide variability of antitumor activity in response to irinotecan or irinotecan containing regimens could be explained on the basis of pharmacokinetic variations: first, a significant percentage of glioma patients receive concurrently anticonvulsants and corti-costeroids that induce hepatic enzymes involved in the metabolism or excretion of the CPT-11 [23]; furthermore the different administration schedules that have been employed could have affected the antitumor efficacy, since camptothecins are specific for the S-phase of the cell cycle [24].

The primary objective of this multicenter phase II trial was to evaluate the efficacy and toxicity of two different administration schedules of CPT-11 in recurrent glioma patients. Secondary goals include pharmacokinetic analysis of the impact of enzyme-inducing antiepileptic drugs (EIAEDs) and steroids and its association with toxicity and response to therapy.

Patients and methods

Eligibility criteria

Patients were eligible for inclusion in this study if they had a recurrent glioma with histologic confirmation at initial diagnosis and/or on recurrence to include astrocytoma, oligodendroglioma, mixed glioma, or gliosarcoma. Pathology material was reexamined at the time of study entry by the same neuropathologist (B.W.S.) to confirm histologic diagnosis. Patients had to be 18 years of age or older; have an Eastern Cooperative Group (ECOG) performance status (PS) of 0, 1 or 2; absolute neutrophil count and platelet count greater than 1,500/mm³ and 100,000/mm³ respectively, hemoglobin $\geq$ 9 g/dl, serum creatinine level $\leq$ 2 mg/dl, serum total bilirubin level $\leq$ 1.5 mg/dl and aspartate aminotransferase level less than 3 times the institutional upper normal limits. Patients had to be on a fixed dose of corticosteroids (or no corticosteroids) for at least 2 weeks prior to baseline scan. Up to one adjuvant

chemotherapy regimen and one regimen for recurrent disease was allowed. At least 8 weeks should have elapsed from completion of RT, and at least 4 weeks from last chemotherapy administration (6 weeks for nitrosourea containing regimens). Exclusion criteria included prior use of CPT-11, topotecan or 9-aminocamptothecin. Other contraindications included pregnant or nursing women, uncontrolled infection, myocardial infarction within the previous 6 months, congestive heart failure requiring therapy, history of Gilbert's syndrome and the presence of other active malignancy. The study was approved by the institutional review boards, and all patients signed an informed consent form prior to enrolment.

Treatment schedule

Patients received irinotecan according to one of two different schedules. The two schedules (A and B) opened sequentially to accrual. Patients in schedule A received irinotecan at a dose of 100 mg/m² if they have had prior treatment with nitrosoureas or 125 mg/m² (if no prior nitrosoureas) by 90-min intravenous infusion every week for 4 weeks with a two week rest period between courses. Patients in schedule B received irinotecan at a dose of either 250 mg/m² (prior nitrosoureas) or 300 mg/m² (no prior nitrosoureas) by 90 min intravenous infusion every 3 weeks. If dose limiting toxicities (DLTs) were encountered, irinotecan dose was decreased by 50 mg/m² in subsequent cycles until toxicities decreased to grade 2 or lower. The following criteria met the study definition of DLT: grade 4 neutropenic fever, grade 4 non-hematologic toxicities and lack of recovery to baseline from previous toxicities. Grade 4 diarrhea, nausea and vomiting were considered dose-limiting if they occurred despite optimal supportive treatment. The irinotecan dose was decreased by 25 mg/m² until toxicities decreased to grade ≤ 1 , if patients experience $\geq$ grade 2 hematologic or non-hematologic toxicity. Grade 2/3 diarrhea, nausea and vomiting resulted in dose modification, only if they occurred despite optimal supportive treatment.

Treatment evaluation

Patients were assessed clinically and by imaging before every treatment, i.e., every 6 weeks for schedule A and every 3 weeks for schedule B. At each evaluation the patient's objective status was defined as a function of the neurologic exam status and imaging results.

Response definition

Measurable disease was defined as a tumor visible on CT scan or MRI that could be easily measured by the products of perpendicular cross-sectional diameters. Evaluable disease was defined as tumor visible on CT scan or MRI but not amenable to bi-dimensional measurements because of tumor geometry. The MacDonald criteria for response assessment were employed to assess response in patients with measurable disease [25]. Complete response (CR) was defined as a total disappearance of all evidence of tumor with the patient no longer receiving corticosteroids. Partial response (PR) was defined as $\geq 50\%$ reduction in the product of perpendicular diameters of contrast enhancing mass with no new lesions and the patient receiving stable or decreased corticosteroid dose. Progression was defined as $\geq 25\%$ increase in the product of perpendicular diameters of contrast enhancement or mass or appearance of new lesions. For patients with evaluable disease, regression was defined as unequivocal reduction in size of contrast enhancement or decrease in mass effect as determined by primary physician and quality control physicians and no new lesions, with the patient receiving stable or decreased steroid dose. Stable disease was defined as failure to qualify for CR, PR or tumor progression.

Pharmacokinetic analysis

Specimen collection—Blood samples (7 ml) were drawn via venipuncture or indwelling intravenous cannula into heparin-containing tubes from the arm contralateral to the infusion

line at the following times: prior to the first irinotecan infusion; at the end of the infusion, and 1, 2, 4 and 24 h following the end of the infusion. If a heparin lock was used, 1 ml of whole blood was withdrawn and discarded prior to sample collection. Collection tubes were immediately placed into a slurry of ice water, the plasma was separated by centrifugation ($1000\text{--}1200 \times g$ for 20 min) and transferred into plastic tubes. The plasma specimens were stored at -70°C until assay for CPT-11 and SN-38, SN-38G and APC.

Specimen analysis—Plasma samples were assayed for CPT-11, SN-38 and APC using validated, sensitive and specific isocratic high-performance liquid chromatography methods. In brief, the plasma specimen was mixed with the internal standard camptothecin in acidified acetonitrile to precipitate plasma proteins, and incubated for 15 min at 40°C to convert the analytes to their respective lactones. After addition of tri-ethylamine buffer (pH 4.2), the sample was centrifuged and the supernatant was transferred to an amber vial for injection (40 μl) onto the HPLC system.

Chromatographic separation was achieved using a Zor-bax-C8 column (MacMod) and a mobile phase consisting of 28:72 (v/v) acetonitrile: 0.025 M TEA buffer (pH 4.2). The fluorescence detector was operated at an excitation wavelength of 372 nm; the CPT-11 was monitored at an emission wavelength of 425 nm; SN-38 was monitored at 535 nm.

CPT-11, APC and unconjugated SN-38 concentrations were determined by direct analysis of plasma. SN-38G concentrations were determined in a separate portion of each plasma sample in which SN-38G was hydrolyzed to SN-38 by incubation with β -glucuronidase. SN-38 concentrations determined following incubation of plasma with β -glucuronidase were labeled as “Total SN-38” (i.e., sum of unconjugated SN-38 and conjugated SN-38). Plasma concentrations of SN-38G were estimated as the difference between the Total SN-38 concentration and the SN-38 concentration.

Pharmacokinetic analysis—CPT-11, SN-38 and SN-38G plasma concentration data were analyzed by non-compartmental methods using the program WINNONLIN. The apparent terminal elimination rate constants (λ_z) were determined by linear least-squares regression through the 4 and 24 h plasma-concentration time points. The apparent elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. Area under the plasma concentration–time curves ($\text{AUC}_{0\text{--}24\text{h}}$) were determined using the linear trapezoidal rule from time zero to the 24 h sample time. Area under the plasma concentration–time curves through infinite time ($\text{AUC}_{0\text{--}\infty}$) were calculated by adding C_T/λ_z to $\text{AUC}_{0\text{--}24\text{h}}$. The CL of CPT-11 was calculated as $\text{dose}/\text{AUC}_{0\text{--}\infty}$, where dose is the administered dose of CPT-11 expressed in free base equivalents.

The pharmacokinetics for patients in cohort B were further compared to those from cancer patients treated on a previously completed phase I trial of irinotecan [26], who were not on EIAEDs. This phase I trial employed similar irinotecan regimens and pharmacokinetic assay methodology [26].

Statistical methods—The intervals to progression, treatment failure and death were calculated from the onset of treatment to the date of disease progression, treatment failure or death. Treatment failure was the occurrence of disease progression, appearance of unacceptable toxicity or refusal of the patient to continue treatment. The distributions of time to progression (TTP), time to treatment failure and time to death were estimated using the Kaplan-Meier method. The association of nominal risk factors with survivorship was assessed with log-rank tests. Duration of response for patients who responded to treatment was measured from the start of CPT-11 treatment to TTP. Multivariate analysis using Cox models was used to assess the importance of different prognostic variables in predicting response, TTP and OS. The two schedules were analyzed independently and no comparisons were made between each other.

Multivariate linear regression was used to explore the relationship between CPT-11, SN-38, SN-38G and APC AUC and CPT-11 clearance as dependent variables and age, gender, CPT-11 dose, use of steroids, use of any anticonvulsant, CBZ, DPH and PB as independent variables. Age was modeled as a continuous variable and the other independent variables were specified as indicator variables. The results shown are for forward stepwise regression modeling. Backward regression, models using the ranks of the dependent variables, and models using dose adjusted AUC provided consistent results.

Results

Patients

Sixty-four patients (32 per cohort) were enrolled in this trial by 15 NCCTG institutions. All patients were evaluable for toxicity, and all patients were included in the survival analysis. Thirty patients per cohort were evaluable for response. Table 1 lists demographic, histologic and prior treatment characteristics of these patients. The median age was 54.5 years for the whole population and the majority of tumors were pure astrocytomas. Fifty of the sixty-four patients (78.1%) had received prior nitrosureas, 43 of the 64 patients (67.2%) were on steroids treatment and 52 of the 64 patients (81.3%) were on EIAEDs.

Treatment delivery

Mean number of treatment cycles were 1.96 ± 2.42 (range 1–14) for schedule A and 3.71 ± 3.08 (range 1–12) for schedule B. Treatment discontinuation because of toxicity was similar in both groups (3.13%), 12.5% of the patients in schedule A refused continuing treatment, while only 3.13% of the patients refused to continue treatment on schedule B.

Response

The primary efficacy endpoint for this trial was confirmed objective response. This was similar in both arms: 2/32 patients (6.3%) in each cohort had partial responses. Of the responders one patient had an oligoastrocytoma, and three patients pure astrocytomas. Seven of 32 patients in cohort A and 25 of 32 patients in cohort B achieved stable disease as their best objective response (21.9% and 78.1% respectively, i.e., 32/64; 50% for the combined group). Twenty-one of the 32 patients (65.5%) in schedule A and 3 of the 32 patients (9.4%) in schedule B had progressive disease as their best objective responses (24/64; 37.5% for the combined group).

Toxicity

Most of the observed toxicity was mild (grade 1, 2). The incidence of grade 3 and 4 toxicity according to schedule is summarized in Table 2. The main toxicities were gastrointestinal and hematologic. The most common toxicity in schedule A was grade 3/4 thrombocytopenia (15.6%) followed by diarrhea (6.3%), infection, lethargy and transaminase elevation (3.1% each), nausea (34.4%) and leukopenia (21.9%). In schedule B the most common grade 3/4 toxicities were thrombocytopenia (22%) followed by nausea (9.4%), lethargy (9.4%), diarrhea (9.4%) and vomiting (6.3%).

Progression-free survival and overall survival

At the time of this report, sixty-three patients (98.4%) have died (100% of the patients in cohort A and 96.9% in cohort B) and all patients had disease progression. Eight patients (12.5%) were progression-free at six months (2/32 in cohort A and 6/32 in cohort B). The median TTP in cohorts A and B were 1.6 and 1.9 months respectively. The median survival in cohorts A and B were 5.1 and 5.5 months. The one-year survival estimate was 19% both for cohorts A and B.

Pharmacokinetic analysis

The pharmacokinetics of CPT-11 and its metabolites were characterized in both patient cohorts in order to establish the impact of anticonvulsant usage for each schedule. Information regarding use of enzyme inducing anticonvulsants and dexamethasone is summarized in Table 3. Two approaches were employed to analyze the pharmacokinetic data. First, data were grouped according to treatment with dexamethasone and treatment with EIAEDs (Table 4). In this approach, patients treated with DPH, CBZ or PB that are all known to induce the p450 system were considered as a single group. Second, data were grouped according to treatment with individual anticonvulsants (Table 5). Patients treated with anticonvulsants that were not known to induce the p450 system were included with the group that received no anticonvulsants.

CPT-11 plasma clearance for patients on schedule A varied over an 8-fold range (5.3–41.4 l/h/m², Table 4). The CPT-11 clearance value in the single patient who received no concurrent treatment (12.7 l/h/m²) and the mean value in patients receiving concurrent treatment with dexamethasone alone (12.1 ± 2.5 l/h/m²) were similar to the mean value previously reported for a group of GI patients [27] who did not receive concurrent anticonvulsants and dexamethasone (13.0 ± 5.6 l/h/m²). CPT-11 clearance was 75% higher in those glioma patients who received EIAEDs with or without dexamethasone (21.6 ± 9.7 l/h/m², Table 4). Exposure to the inactive CPT-11 metabolites APC and SN-38G were not substantially altered by dexamethasone and EIAEDs. SN-38 C_{max} and AUC values for patients that received EIAEDs were significantly lower than the values for the patient that did not receive dexamethasone or EIAEDs (Table 4). Indeed, our results in dexamethasone plus EIAEDs patients in low-dose regimen (100–125 mg/m²) are very similar to the other prior phase II trial with PK analysis [6].

Because there are known differences in the enzyme induction pattern for individual anticonvulsants, effects of dexamethasone and each anticonvulsant on CPT-11 and metabolite PKs were evaluated. CPT-11 clearance was increased by DPH and CBZ, but the increase was not statistically significant (Table 5). When compared with values for patients that received no EIAEDs, APC C_{max} and APC AUC values were higher in patients treated with PB, unchanged in patients treated with DPH, and lower in patients treated with CBZ. The difference in APC C_{max} and AUC values between the PB and CBZ treatment groups was statistically significant. SN-38 AUC, but not SN-38 C_{max}, significantly reduced by treatment with CBZ, DPH and PB. SN-38G C_{max} were similar among the CBZ, DPH and PB treatment groups. SN-38G AUC values for patients who received CBZ or DPH were 40% lower than the values for patients who received PB or no EIAEDs.

CPT-11 plasma clearance for patients in cohort B varied over a 4-fold range (10.1–36.9 l/h/m²). The mean CPT-11 clearance values in patients who received no concurrent treatment (15.3 ± 6.1 l/h/m²) and the mean value in patients receiving concurrent treatment with dexamethasone alone (13.9 ± 3.9 l/h/m²) were similar to the mean value previously reported for patients in a phase I trial [26] who did not receive concurrent anticonvulsants and dexamethasone (13.0 ± 3.8 l/h/m²). CPT-11 clearance was 75% higher in those glioma patients who received EIAEDs with or without dexamethasone (22.9 ± 7.2 l/h/m², Table 2). Dexamethasone and EIAEDs did not appear to substantially alter exposure to the inactive CPT-11 metabolite APC (Table 4). SN-38 and SN-38G C_{max} and AUC values were highest in patients that received dexamethasone alone. This difference was statistically significant when compared with the other treatment groups.

The effect of each anticonvulsant on CPT-11 clearance, parent drug or metabolite exposure use was also evaluated (Table 5). CPT-11 clearance was increased by CBZ and DPH. The difference between the group that received no EIAEDs and the group that received DPH was

statistically significant. APC exposure was not significantly altered by individual anticonvulsants, however, $C_{\max}$ and AUC values were highest in patients treated with PB. SN-38 $C_{\max}$ and AUC values were reduced by each of the anticonvulsants, and the difference for DPH was statistically significant. Similarly, SN-38G exposure was lower for patients in each anticonvulsant treatment group, but only DPH caused a statistically significant reduction of SN-38G exposure.

The effects of clinical and demographic covariates, prior nitrosoureas and anticonvulsants treatment on SN-38 AUC were evaluated by multivariate regression analysis (Table 6). The model for schedule A predicted that pretreatment bilirubin, steroids, CBZ, PB and DPH had a statistically significant effect on SN-38 AUC ($R^2 = 0.6952$, $P = 0.0001$). Age, prior nitrosoureas CPT-11 dose [17] and gender had no effect on SN-38 AUC. The model for Cohort B predicted that CBZ and DPH had a statistically significant effect on SN-38 AUC ($R^2 = 0.3561$, $P = 0.0033$). Age, prior nitrosoureas, CPT-11 dose, gender, pretreatment bilirubin, steroids, and PB had no effect on SN-38 AUC.

Discussion

Development of effective treatment regimens for recurrent disease remains a significant challenge in the management of patients with malignant gliomas. Limited success in this setting can be due to limitations in drug delivery or to tumor resistance to standard cytotoxic therapies.

Following original observations demonstrating activity of CPT-11 in preclinical models [28, 29], a phase I trial determined that maximal tolerated dose (MTD) for patients with recurrent malignant gliomas treated on EIAEDs was 410 mg/m²/week, but as low as 115 mg/m²/week for patients not on EIAEDs [23].

In this phase II trial of CPT-11 in adult recurrent glioma patients, the objective response rate (RR) was very low (6.3%). Although the RR observed in this trial is consistent with rates reported in other studies (0–15%) [6–12] and the percentage of patients with SD was around 50%, time to progression (TTP) and survival was worse than previously reported: the median TTP was only 1.6 months for the weekly schedule and 1.9 months for the once every three weeks schedule. PFS at 6 months (PFS6) were 6% and 19% for schedules A and B respectively (13% for the whole group). Median OS were 5.1 and 5.5 months for schedules A and B respectively and 1-year survival was 19% for both groups, lower than OS in prior phase II trials. In other trials of weekly CPT-11 administration, median TTP was reported to be 3 to 7.3 months with a 56% PFS6, and median OS was 10.4–10.75 months [6,10]. In trials employing the once every three weeks administration schedule, PFS6 was 0% [7], 0% [8], 26% [9] and 17.6% [12], median TTP was 0.75 months [7], 1.5 months [8] and 2.1 months [9], and median OS of was 4 months [7], 6 months [8] and 8.5 months [9]. Better results especially in some of the trials of weekly CPT-11 administration can be explained because of differences in eligibility criteria (78% of our patients had prior chemotherapy exposure) and the possible impact of EIAEDs on active drug metabolites.

Although weekly administration schedules appear to have a higher median TTP and median OS than intermittent high-dose schedules in prior phase II studies, no significant difference in outcome between the two schedules was observed in our study.

The most frequent dose-limiting toxicities of single agent CPT-11 in previous clinical trials using weekly or every-three-weeks schedules have been diarrhea and neutropenia [6,8–10, 12]. In our trial no grade 3/4 neutropenia or leucopenia was observed. In contrast, five patients (15.6%) had grade 3/4 thrombocytopenia in schedule A and seven patients (21.9%) developed grade 3/4 thrombocytopenia in schedule B. This high-frequency of thrombocytopenia could be explained because of prior myelosuppressive treatments containing nitrosoureas (75% in

cohort A and 81.3% in cohort B), as compared to 48% [6] and 15% [8] in another phase II trials. Similarly to our results, Chamberlain et al observed an incidence of 23% of thrombocytopenia in a group of patients, 95% whom were pretreated with nitrosureas [7].

The interaction between CPT-11 and EIAEDs as a whole was reported in a phase II study of CPT-11 in glioma patients [30]. Increased CPT-11 clearance and reduced exposure to CPT-11, its active metabolite SN-38, and the inactive metabolites SN-38G and APC were associated with concurrent treatment with EIAEDs. Therefore, pharmacokinetic studies are extremely important with CPT-11: first, glioma patients often require dexamethasone to treat edema and P450 inducing anticonvulsants such as DPH, CBZ and PB for seizure management. These drugs are well known for producing drug interactions [31,32] that are usually due to induction of drug metabolism enzymes. For example, each of the drugs induce CYP3A4-catalyzed inactivation of CPT-11 to APC. DPH, CBZ and PB induce UGT, which catalyzes the inactivation of SN-38 by glucuronidation. Dexamethasone induces carboxylesterases, which catalyzes the activation of SN-38. DPH and CBZ induce CYP2C9, which catalyzes the metabolism of DPH. Second, similar efficacy with decreased toxicity has been seen in the weekly schedule against the three week schedule in colorectal cancer patients treated with CPT-11 [27,33]. Indeed, CPT-11 clearance in glioma patients who were not administered EIAEDs was similar to that found for other cancer patients administered similar doses and schedules of the drug [6,33]. Although it is often not appropriate to compare pharmacokinetic data across studies performed at different times, CPT-11 analysis for each of these studies was performed in the same laboratory using identical methodology. Third, some interpatient pharmacogenetic differences could occur with regard to CPT-11 metabolism such as genetic polymorphisms in UGT and CYP2C9. They result in populations of patients that may be classified as slow or rapid metabolizers for these reactions.

While it is now possible to predict the qualitative nature of a metabolism-based drug interaction, it is much more difficult to predict the quantitative impact of the interaction due to the multiplicity of effects of each of these drugs. Since the metabolism phenotype of each anticonvulsant is different, we sought to evaluate the effect of individual drugs on CPT-11 pharmacokinetic by exploring relationships between treatment with individual anticonvulsants and exposure to CPT-11 and its metabolites in this phase II study. The effect of dexamethasone was difficult to establish in this group of patients. When data were grouped according to treatment with dexamethasone and treatment with EIAEDs, dexamethasone did not appear to affect AUC values of CPT-11 and its metabolites as might have been predicted by its known effect on carboxylesterase and CYP3A. CPT-11 AUC was higher for patients treated with dexamethasone, the increase in APC AUC was small and the lower SN-38 AUC was inconsistent with the recent observation that dexamethasone induces carboxylesterase. There may be several reasons for these observations. First, small and unbalanced groups were used to explore the effects of dexamethasone and anticonvulsants on CPT-11 pharmacokinetics, a problem often associated with performing such correlative studies in a chemotherapy treatment trial. Larger numbers of patients would be useful in assessing the role of individual anticonvulsants. Second, the administered dexamethasone doses were lower than those that induce CYP3A4 or carboxylesterase. The dose response relationship for enzyme induction by dexamethasone has not been established. Third, the peripheral edema, electrolyte imbalances and/or fat redistribution caused by dexamethasone may have a greater effect on the pharmacokinetics of concomitant medications than the induction or inhibition of metabolism.

Consistent with data from other clinical trials, CPT-11 pharmacokinetics in glioma patients were altered by EIA-EDs. However, this study further identified CPT-11 dose-dependent differential effects of individual anticonvulsants on CPT-11 pharmacokinetics. The magnitude and direction of the effect was dependent on the specific anticonvulsant. For example, large differences between APC AUC values were observed in cohort A patients administered lower

doses of CPT-11, but not in cohort B patients administered higher doses of CPT-11 (Table 6). In contrast, such a difference was not observed when APC AUC data were grouped according to treatment with dexamethasone and EIAC (Table 4). As expected for CYP3A4 induction, PB increased APC AUC, and CBZ was associated with a 2-fold reduction in APC AUC.

All EIAEDs caused reduction of SN-38 AUC, with the greatest magnitude change produced by DPH. However, this reduction was not accompanied by a concomitant increase in SN-38G AUC that would be predicted by induction of UGT. Clearly, as suggested by the modest correlation coefficients, other factors contribute to the disposition of CPT-11 and its metabolites in glioma patients. As for dexamethasone, the difficulty in defining relationships between CPT-11 pharmacokinetics and anticonvulsant use might include small patient population, different anticonvulsant doses, dose response relationships, enzyme polymorphisms, and other disease-related factors.

Variability in the accessibility of the active form of the drug to the tumor could account for the modest RRs noted in these studies. Variations in schedule administration were small, since the AUC for SN-38 is only 3% of the AUC CPT-11 in patients in cohort A without concurrent dexamethasone and 1.5% in cohort B patients with same characteristics. No differences were shown in patients with concurrent dexamethasone in both cohorts. Four-fold decrease in SN-38:CPT-11 AUC ratio have been described in a clinical trial comparing a continuous low-dose i.v. infusion of CPT-11 over 14 days with short i.v. infusions, supporting the concept of the carboxylesterase activity and saturation [34]. This means that only a relatively small fraction of the dose is ultimately converted to the active metabolite of the drug.

Although combination of other chemotherapy agents with CPT-11 does not appear to increase its activity, the addition of bevacizumab to CPT-11 has significantly improved antitumor activity, including RRs, as well as PFS and OS [20–22]. Bevacizumab is a humanized monoclonal antibody that inhibits human VEGF, a key driving force of glioma angiogenesis [35]. Although the mechanism of this effect has not been completely elucidated, one hypothesis is that bevacizumab improves CPT-11 delivery because it decreases interstitial pressure and hypoxia resulting to tumor resistance to cytotoxic therapy. The clinical efficacy of the CPT-11/bevacizumab combination has resulted in increased use of irinotecan in the management of recurrent glioma patients.

In summary, the low response rate and survival outcome measures in our study, independently of CPT-11 administration, indicates low activity of single agent CPT-11 in the treatment of recurrent gliomas. Impact of EIAEDs as well as dexamethasone on CPT-11 pharmacokinetics appears to be decreased in the once-each-three weeks schedule, although this did not translate into outcome differences.

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Table 1
Baseline patient characteristics

Variable	Schedule A (N = 32) n (%)	Schedule B (N = 32) n (%)	Total (N = 64) n (%)
Age			
Median	55.5	53.0	54.5
Range	25–74	24–81	24–81
Mean ± SD	52 ± 14.5	51 ± 15.5	51.5 ± 14.9
Gender			
Female	14 (43.8%)	10 (31.3%)	24 (37.5%)
Male	18 (56.3%)	22 (68.8%)	40 (62.5%)
ECOG performance score			
0	4 (12.5%)	10 (31.3%)	14 (21.9%)
1	18 (56.3%)	14 (43.8%)	32 (50.0%)
2	10 (31.3%)	8 (25.0%)	18 (28.1%)
3	0	0	0
4	0	0	0
Steroids			
Yes	22 (68.8%)	21 (65.6%)	43 (67.2%)
No	6 (18.8%)	11 (34.4%)	17 (26.6%)
Missing	4 (12.5%)	0	4 (6.3%)
Anticonvulsants			
Yes	26 (81.3%)	26 (81.3%)	52 (81.3%)
No	6 (18.8%)	6 (18.8%)	12 (18.8%)
Prior Nitrosoureas			
Yes	24 (75.0%)	26 (81.3%)	50 (78.1%)
No	8 (25.0%)	6 (18.8%)	14 (21.9%)
Months since end of RT			
<6	5 (15.6%)	10 (31.3%)	15 (23.4%)
6–12	11 (34.4%)	8 (25.0%)	19 (29.7%)
>12	16 (50.0%)	14 (43.8%)	30 (46.9%)
Primary tumor resection			
None	0	0	0
Biopsy	11 (34.4%)	9 (28.1%)	20 (31.3%)
Subtotal	14 (43.8%)	14 (43.8%)	28 (43.8%)
Total	7 (21.9%)	9 (28.1%)	16 (25.0%)
Histology			
Astrocytoma	22 (68.8%)	18 (56.3%)	40 (62.5%)
Gliosarcoma	0	0	0
Oligodendroglioma	4 (12.5%)	5 (15.6%)	9 (14.1%)
Oligoastrocytoma	5 (15.6%)	8 (25.0%)	13 (20.3%)
Unknown	1 (3.1%)	1 (3.1%)	2 (3.1%)
Grade			
1	0	0	0
2	2 (6.3%)	6 (18.8%)	8 (12.5%)

Variable	Schedule A (N = 32) n (%)	Schedule B (N = 32) n (%)	Total (N = 64) n (%)
3	8 (25.0%)	6 (18.8%)	14 (21.9%)
4	21 (65.6%)	19 (59.4%)	40 (62.5%)
Unknown	1 (3.1%)	1 (3.1%)	2 (3.1%)

Observed toxicity according to schedule

	Schedule		B (N = 32)		All	
	A (N = 32)					
	N	%	N	%	N	%
Grade 3 heme	5	15.6	7	21.9	12	
Grade 3 non-heme	4	12.5	11	34.4	15	
Grade 4 non-heme	2	6.3	5	15.6	7	
Grade 5 non-heme			1	3.1	1	

Table 3
Baseline characteristics according to EIAEDS^a and dexamethasone use

Anticonvulsant treatment						
		None	CBZ	DPH	PB	Total
Schedule A	N	3	4	15	4	26
	Median age (years)	62	47	46	47	55
	Gender (M/F)	1/2	2/2	10/5	2/2	15/11
	CPT-11 dose (100/125)	2/1	2/2	10/5	4/0	18/8
	Steroids (Y/N)	2/1	3/1	12/3	3/1	20/6
Schedule B	N	8	7	12	3	30
	Median age (years)	52	44	54	43	50
	Gender (M/F)	2/6	6/1	9/3	3/0	20/10
	CPT-11 dose (250/300)	7/1	5/2	10/2	2/1	24/6
	Steroids (Y/N)	7/1	3/4	8/4	1/2	19/11

Abbreviations: CBZ carbamacepine, DPH phenytoin, PB Phenobarbital

^aCombinations of anticonvulsants were used in some patients

Table 4
Effect of dexamethasone and EIAEDs on the pharmacokinetics of CPT-11 and its metabolites

		Low CPT-11 dose (100/125 mg/m ²)				High CPT-11 dose (250/300 mg/m ²)			
		None (n = 1)	Dex alone (n = 3)	EIAED alone n = 4)	Dex + EIAED (n = 19)	None (n = 3)	Dex alone (n = 6)	EIAED alone (n = 9)	Dex + EIAED (n = 12)
CPT-11	C _{max}	1010	2090 ± 1490	1180 ± 590	2160 ± 3270	2200 ± 610	2630 ± 670	1990 ± 688	2380 ± 1110
	AUC	6710	7890 ± 2720	4930 ± 1380	5870 ± 4130	15,300 ± 5700	16,400 ± 3600	11,400 ± 4700	10,500 ± 3200
	Cl	12.7	12.1 ± 2.5	20.8 ± 5.6	21.7 ± 10.5	15.3 ± 6.1	13.9 ± 3.9	21.6 ± 8.2	23.9 ± 6.6
APC	t _{1/2}	5.3	6.5 ± 0.9	5.0 ± 0.3	5.3 ± 0.7	5.4 ± 0.4	6.3 ± 0.9	5.1 ± 0.5	5.1 ± 0.7
	C _{max}	153	142 ± 110	127 ± 12	162 ± 101	401 ± 39	380 ± 113	359 ± 134	432 ± 100
	AUC	1710	1860 ± 1610	1520 ± 297	1670 ± 1080	5010 ± 500	4720 ± 1580	4260 ± 1600	4610 ± 1740
SN-38	t _{1/2}	5.7	7.8 ± 2.1	5.5 ± 0.9	5.7 ± 0.9	6.0 ± 0.5	6.7 ± 2.3	6.0 ± 0.6	5.5 ± 1.1
	C _{max}	21.6	17.4 ± 2.3	11.1 ± 2.8	12.1 ± 5.0	25.7 ± 24.7	39.4 ± 24.4	15.9 ± 6.4	16.6 ± 4.4
	AUC	208	136 ± 34	85 ± 19	63 ± 33	232 ± 138	367 ± 218	150 ± 85	118 ± 44
SN-38G	t _{1/2}	17.1	17.5 ± 4.0	10.4 ± 1.7	14.5 ± 12.1	12.1 ± 2.2	19.0 ± 5.8	11.7 ± 3.0	11.1 ± 3.3
	C _{max}	34.4	64.5 ± 31.3	46.3 ± 14.1	57.7 ± 22.0	78.6 ± 30.4	137.3 ± 63.0	97.4 ± 18.0	90.9 ± 18.0
	AUC	418	692 ± 367	377 ± 160	422 ± 216	828 ± 288	1558 ± 720	839 ± 240	658 ± 171
	t _{1/2}	13.5	16.6 ± 9.4	9.9 ± 2.8	9.1 ± 2.0	13.0 ± 1.4	14.6 ± 3.6	9.7 ± 1.5	9.8 ± 3.9

Table 5
Effect of individual EIAEDs on the pharmacokinetics of CPT-11 and its metabolites

		Low CPT-11 dose (100/125 mg/m ²)				High CPT-11 dose (250/300 mg/m ²)			
		None (n = 4)	CBZ (n = 4)	DPH (n = 16)	PB (n = 3)	None (n = 9)	CBZ (n = 7)	DPH (n = 12)	PB (n = 2)
CPT-11	C _{max}	1820 ± 1330	780 ± 450	2440 ± 3500	1190 ± 600	2490 ± 650	2780 ± 1340	1920 ± 590	2030 ± 280
	AUC	7600 ± 2300	4000 ± 1840	6040 ± 4390	6190 ± 810	16,000 ± 4100	13,100 ± 5000	9100 ± 2200	13,500 ± 2500
	Cl	12.2 ± 2.0	27.6 ± 10.7	21.4 ± 9.8	14.3 ± 2.0	14.3 ± 4.4	19.6 ± 7.2	26.0 ± 6.3	15.9 ± 2.9
	t _{1/2}	6.2 ± 0.9	4.9 ± 1.0	5.4 ± 0.6	5.0 ± 0.6	6.0 ± 0.9	4.8 ± 0.5	5.3 ± 0.6	5.1 ± 0.4
APC	C _{max}	145 ± 90	93 ± 43	154 ± 87	247 ± 120	387 ± 92	365 ± 99	408 ± 122	484 ± 193
	AUC	1830 ± 1320	990 ± 590	1570 ± 860	2880 ± 1150	4820 ± 1280	4060 ± 1050	4490 ± 1890	5680 ± 2090
	t _{1/2}	7.3 ± 2.0	5.7 ± 0.9	5.7 ± 0.9	5.4 ± 0.2	6.5 ± 1.9	5.3 ± 0.5	5.8 ± 1.1	6.5 ± 1.1
	C _{max}	18.4 ± 2.8	11.7 ± 3.5	11.9 ± 5.4	12.0 ± 0.9	34.9 ± 23.9	19.2 ± 5.6	14.6 ± 4.8	16.6 ± 1.6
SN-38	AUC	154 ± 45	73 ± 38	60 ± 30	100 ± 14	322 ± 198	169 ± 86	106 ± 44	157 ± 2
	t _{1/2}	17.4 ± 3.3	9.4 ± 2.3	15.6 ± 13.1	10.5 ± 2.4	16.7 ± 5.8	10.4 ± 3.0	12.0 ± 3.4	10.8 ± 0.6
	C _{max}	57.0 ± 29.7	49.7 ± 11.7	55.8 ± 24.0	63.7 ± 13.2	117.7 ± 59.8	97.7 ± 15.3	91.6 ± 20.0	91.8 ± 19.0
	AUC	623 ± 330	330 ± 164	396 ± 201	622 ± 193	1310 ± 690	875 ± 248	631 ± 152	876 ± 127
SN-38G	t _{1/2}	15.9 ± 7.8	8.6 ± 2.3	9.3 ± 2.0	10.2 ± 2.9	14.1 ± 3.0	8.7 ± 1.7	10.3 ± 3.8	9.8 ± 1.6

Table 6
Multivariate regression models for SN-38 AUC_{0–24 h}

Variable	Cohort A		Cohort B	
	Parameter estimate	<i>P</i>	Parameter estimate	<i>P</i>
Intercept	126.9	0.0001	305.7	<0.0001
Steroids	−31.2	0.0462	—	—
Bilirubin	101.3	0.0298	—	—
CBZ	−78.5	0.0010	−137.0	0.0343
PB	−52.3	0.0275	—	—
DPH	−78.3	0.0002	−200.1	0.0009