

Two Studies Evaluating Irinotecan Treatment for Recurrent Malignant Glioma Using an Every-3-Week Regimen

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Two studies were performed to evaluate the safety, tolerability, and efficacy of irinotecan (CPT-11) in the treatment of adults with malignant glioma. Patients with progressive or recurrent malignant gliomas were enrolled. In the first study, CPT-11 was administered once every 3 weeks as a 90-minute intravenous infusion at a dose of 300 mg/m². After 2 treatments, doses were increased to 350 mg/m² in those patients without Grade 3/4 toxicities. Dose modifications were made for toxicities. All 14 patients who enrolled (11 males and 3 females) were treated with CPT-11 and were assessable for survival, response, and toxicity. The majority of patients (86%) had prior surgery. Two patients had a confirmed partial response (PR), and 2 patients (14%) had stable disease (SD). Median survival was 24 weeks; median time to tumor progression (TTP) was 6 weeks. The primary hematologic toxicity was Grade 3/4 neutropenia, which was observed in 14% of patients. Infrequent Grade 3/4 nonhematologic toxicity was observed, possibly due to the concomitant use of anticonvulsants that might have altered pharmacokinetics. The second study evaluated the potential underdosing observed in patients who did or did not receive enzyme-inducing antiepileptic drugs (EIAED) by implementing an inpatient dose escalation design. In this open-label study, treatment of patients with recurrent malignant glioma (rMG) was started at 300–400 mg/m² of CPT-11 every 3 weeks and, depending on individual safety and efficacy evaluation, escalated by steps of 100 mg/m² in subsequent courses. Thirty-five patients (median age, 43 years; gender, 11F and 24M; histology, 26 glioblastoma multiforme and 9 anaplastic glioma) have completed at least two cycles of chemotherapy and are evaluable for toxicity and response. Dose-limiting toxicity (DLT) was reached in 12 patients at doses ranging from 400–1700 mg/m². Preliminary efficacy data show that 3 patients exhibited PR and 15 patients exhibited SD. Median TTP was 2.7 months, and median survival was 8.5 months. Patients who did not receive anti-convulsants achieved higher peak concentrations, relative to dose, of the active metabolite SN-38 than did patients in the EIAED group. This study confirmed the activity of CPT-11 in malignant glioma and indicated that the maximum tolerated dose (MTD) for patients with rMG was considerably higher than expected but still possessed significant variability. A higher level of efficacy for CPT-11 may be observed if an MTD can efficiently be established for each patient. *Cancer* 2003; **97(9 Suppl):2381–6**. © 2003 American Cancer Society.

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At a dose of 125 mg/m² weekly for 4 weeks followed by a 2-week rest, irinotecan (CPT-11) possesses activity in the treatment of recurrent malignant glioma.¹ It was thought that an every-3-week dosing schedule might provide equal benefits and also, because of the decreased number of patient visits, be tolerated better by patients with brain tumors. We enrolled adult patients with recurrent malig-

nant glioma in a study (Study 1) in which the primary objective was to determine the efficacy and safety of CPT-11 at a starting dose of 300 mg/m² given every 3 weeks.²

Use of CPT-11 following the dosing regimen of 300–350 mg/m² every 3 weeks was feasible and demonstrated activity against recurrent malignant glioma; however, there was significant variability in toxicities within the patient population.² Other studies have reported that the use of a p450 enzyme-inducing antiepileptic drug (EIAED) or dexamethasone may play a critical role in the metabolism of CPT-11 and therefore may influence its efficacy.^{1,3} However, it is also noteworthy that in Study 1, some patients on EIAED required dose de-escalation predominantly due to hematopoietic toxicities. This effect may be the result of prior chemotherapy exposure and bone marrow suppression, or there may be unique interpatient pharmacogenetic differences with regard to CPT-11 metabolism. If higher doses can be tolerated in patients with malignant glioma, they have the potential to yield improved responses. The second part of this paper describes a study (Study 2) that employed the same enrollment criteria and aimed to define further the interpatient differences in CPT-11 toxicity and the effect of anticonvulsants via an inpatient dose escalation (Cloughesy TF, Filka E, Kuhn J, et al. Unpublished data). From this study, we hoped to gain insight that would allow us to define an effective dosing of CPT-11 for this patient population.

PATIENTS AND METHODS

Patient Selection

Both studies utilized the same patient selection criteria. Patients age \geq 18 years were enrolled if they met the following criteria: 1) they had histologically confirmed primary malignant glioma that was determined by contrast-enhanced magnetic resonance imaging (MRI) to be progressive or recurrent; 2) they had undergone radiotherapy or chemotherapy \geq 4 weeks and surgical resection \geq 10 days before study treatment; 3) their Karnofsky performance status (KPS) was 60–100%; 4) they exhibited adequate organ function as documented by an absolute neutrophil count $>$ 1500 mm⁻³, platelet count \geq 100,000 mm⁻³, hemoglobin concentration \geq 9.0 g/dL, total bilirubin within normal limits, both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) \leq 3 times the upper limit of normal, and serum creatinine \leq 2.0 mg/dL.

Patients were not eligible for either study if they experienced any of the following: 1) previous CPT-11 or topotecan treatment; 2) any active or uncontrolled infection; 3) psychiatric disorders that could interfere with consent or follow-up; 4) history of myocardial

infarction within the previous 6 months or congestive heart failure that required therapy; 5) history of prior malignancy, except for adequately treated basal cell or squamous cell carcinoma or cervical carcinoma in situ, or any other cancer from which the patient has been disease-free for at least 5 years; 6) pregnancy or lactation; 7) any severe or concurrent disease that would make the patient inappropriate for study entry.

Before the initiation of any study procedures, all patients were required to provide written informed consent as approved by local institutional review boards.

Treatment Plan

CPT-11 (Pharmacia & Upjohn, Inc., Kalamazoo, MI) was supplied in 2 mL vials containing 40 mg of drug or 5 mL vials containing 100 mg of drug. CPT-11 was diluted to a total volume of 500 mL with 5% dextrose in water.

Study 1: 300 mg/m² every 3 weeks

CPT-11 was administered as a 90-minute intravenous (IV) infusion once every 3 weeks at a starting dose of 300 mg/m². After 2 treatments, doses were increased to 350 mg/m² in those patients without Grade 3/4 toxicities.

Dose modifications were made for toxicity. If dose-limiting toxicities (DLTs) occurred, the dose was decreased by 50 mg/m² until the toxicities decreased to Grade 2 or lower. The following were considered to be DLTs: neutropenic fever, Grade 4 thrombocytopenia, Grade 4 diarrhea (despite intensive loperamide treatment), other nonhematologic Grade 3/4 toxicities (except nausea/vomiting), and lack of recovery to baseline from previous toxicities.

Study 2: 350–400 mg/m² every 3 weeks with inpatient dose escalation

CPT-11 was administered as a 90-minute IV infusion once every 3 weeks at a starting dose of 350–400 mg/m². After each treatment, doses were increased by 100 mg/m² for patients who were receiving EIAED and who did not experience Grade 3/4 toxicities. Doses were increased by 50 mg/m² for patients who were not receiving anticonvulsants or were on non-EIAED, and who did not experience Grade 3/4 toxicities.

Dose modifications were made for toxicity. If DLT occurred, the dose was decreased by 100 mg/m² or 50 mg/m², depending on whether the patient was receiving anticonvulsants, and the next course was delayed until the toxicities decreased to Grade 2 or lower. The following were considered to be dose-limiting toxicities: neutropenic fever, Grade 4 thrombocytopenia, Grade 4 diarrhea (despite loperamide treatment),

other nonhematologic Grade 3/4 toxicities (except nausea/vomiting), lack of recovery to baseline from previous toxicities, and patient refusal to dose-escalate due to toxicities.

Supportive care

All patients were allowed necessary supportive care during therapy. Cholinergic symptoms that occurred during or shortly after administration of CPT-11 could be treated with IV atropine (0.25–1 mg IV or as needed). Dexamethasone (10 mg IV) was administered as part of the pretreatment antiemetic regimen unless a relative or absolute contraindication to corticosteroid use was identified. Additional antiemetic agents, such as lorazepam, ondansetron, granisetron, and prochlorperazine, were allowed. Loperamide was provided as a therapeutic agent for delayed diarrhea. Patients were instructed to take 4 mg at the onset of diarrhea and then 2 mg every 2 hours around the clock until they were diarrhea-free for at least 12 hours. During the night, patients were allowed to take 4 mg every 4 hours. Routine prophylactic use of granulocyte–colony-stimulating factor was not recommended; however, it was allowed at the investigator's discretion. Methylphenidate (10–40 mg/d) was administered in divided doses for fatigue or asthenia.

Patients could be removed from the study for the following reasons: 1) documented disease progression following one or more courses of treatment; 2) unacceptable toxicity that did not respond to dose modifications; 3) withdrawal of patient consent; 4) intercurrent, non–cancer-related illness that prevented continuation of therapy or regular follow-up; 5) changes in the patient's condition that, in the investigator's opinion, rendered the patient unsuitable for further treatment; or 6) failure to recover from CPT-11 toxicities to Grade 1 or lower or to baseline by 5 weeks after the previous CPT-11 treatment.

Study Evaluations

Four weeks before treatment, a medical history was taken, and a chest X-ray was performed. Pretreatment baseline tumor measurements were made by MRI within 4 weeks of treatment. Surgery was performed on patients for whom it was indicated for best clinical care, and postsurgical baseline measurements of tumor size were made by MRI (with and without contrast) within 72 hours after surgery. When surgery was performed immediately before the initiation of therapy, all patients who were eligible for surgery showed evidence of progression by MRI and were enrolled and gave signed consent before surgery. Two patients in Study 1 and 4 in Study 2 were found not to have an evaluable tumor on the postoperative MRI scan.

Seven days before treatment, patients underwent

a physical examination (including determination of KPS, weight, and vital signs), a neurological examination, and a laboratory evaluation (complete blood count [CBC] with differential, platelet count, serum electrolytes and chemistries, and pregnancy testing for women of childbearing potential).

At the beginning of each treatment course (Week 1), patients underwent a physical examination (including adverse event evaluation and determination of KPS, weight, and vital signs), a neurological examination, and a laboratory evaluation (CBC with differential, platelet count, and serum electrolytes and chemistries).

During Weeks 2 and 3 of each treatment cycle, patients had a CBC with differential. At 6 and 12 weeks after the first dose, and at least every 9 weeks thereafter until progression, brain MRIs were performed with and without contrast. At the end of the study, a physical examination was performed, and the extent of the tumor was reevaluated with and without contrast. Adverse events were recorded for at least 30 days after the last treatment.

Tumor response was assessed according to modified World Health Organization criteria—i.e., complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR was defined as the disappearance of all enhancing tumor on consecutive MRI scans at least 1 month apart, with the patient neurologically stable or improved and no longer receiving steroids. PR was defined as $\geq 50\%$ reduction, maintained for at least 1 month, in the size (calculated as the product of the largest perpendicular diameters) of enhancing tumor, with the patient neurologically stable or improved and receiving stable or reduced steroid treatment. SD was divided into 2 categories—one in which any change in tumor size that did not qualify as CR, PR, or PD lasted for ≥ 6 months and one in which such changes lasted for ≤ 6 months. PD was defined as $\geq 25\%$ increase in the size (calculated as the product of the largest perpendicular diameters) of enhancing tumor or any new tumor on an MRI scan, or the deterioration of the patient's neurological condition accompanied by stable or increased steroid treatment. Patients who had a CR or PR underwent a repeat tumor assessment after 4–6 weeks to confirm the initial response. After response confirmation, disease was reassessed at least every 9 weeks (or sooner if clinically indicated). In addition, time to tumor progression (TTP, time from the start of therapy to the first documentation of PD) and survival (time from the start of therapy to death) were measured.

The response of patients on whom surgery was performed immediately before treatment and who had no contrast-enhancing residual disease was

placed into one of two categories: PD (as described above, but also including SD < 6 months) and SD > 6 months. This categorization was used to define more effectively the positive responders among patients who did not exhibit disease that was evaluable by postoperative MRI.

All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (Version 1).

Statistical Analysis

All eligible patients who received at least one course of chemotherapy were evaluable for efficacy. Patients who were removed from the study during the first course because of PD or serious drug-related events were also considered evaluable for efficacy. Patients who were removed from the study during the first course of treatment for other reasons (e.g., patient request or non-drug-related toxicity) were considered unevaluable for efficacy.

TTP and survival were analyzed by the Kaplan-Meier method.

Patients who received any chemotherapy in this study were evaluable for safety. Adverse events were tabulated by frequency of occurrence.

RESULTS

Patient Characteristics

Table 1 lists details regarding patient characteristics for each study.

Treatment Administration

Study 1

Fourteen patients received a combined total of 50 courses of treatment. The median number of courses administered was 2 (range, 1–9). Doses ranged from 250–350 mg/m². Overall, eight doses (distributed among four patients) were delayed. Four doses were delayed due to Grade 2 neutropenia and leukopenia, 3 were delayed due to Grade 2 neutropenia, and 1 was delayed due to Grade 2 thrombocytopenia.

Study 2

Thirty-five patients received a combined total of 213 courses of treatment. The median number of courses administered was 5 (range, 1–17). Doses ranged from 300–1700 mg/m². Overall, 1 dose was delayed in 1 patient due to Grade 2 diarrhea, Grade 3 nausea, and weight loss. Six patients who did not receive anticonvulsants or who received non-EIAED underwent 19 total courses of treatment, with doses ranging from 300–550 mg/m². Five patients who received EIAED were treated with doses of \geq 1200 mg/m². Given the extremely high doses of CPT-11 that were adminis-

TABLE 1
Baseline Patient Characteristics

Characteristic	Study 1 <i>n</i> (%)	Study 2 <i>n</i> (%)
Patients	14	35
Median age (yrs) [range]	39.5 [18–64]	43 [20–69]
Gender		
Male	11 (79)	24 (69)
Female	3 (21)	11 (31)
Baseline performance status (Karnofsky)		
90–100	6 (42)	17 (49)
70–80	4 (29)	11 (31)
50–60	4 (29)	7 (20)
Prior debulking surgery		
With	12 (86)	16 (46)
Without	2 (14)	19 (54)
Histology		
Glioblastoma multiforme	12 (86)	26 (74)
Anaplastic astrocytoma	2 (14)	3 (9)
Anaplastic mixed glioma	0 (0)	4 (11)
Anaplastic ependymoma	0 (0)	1 (3)
Aggressive gemistocytic astrocytoma	0 (0)	1 (3)
Anticonvulsants		
None	0 (0)	3 (9)
EIAED	13 (93)	29 (82)
Non-EIAED	1 (7)	3 (9)

EIAED: enzyme-inducing antiepileptic drugs.

Study 1 data from Cloughesy TF, Filka E, Gillian N, et al. Irinotecan treatment for recurrent glioma using an every three week regimen. *Am J Clin Oncol*. 2002;25:204–208.²

Study 2 data from Cloughesy TF, Filka E, Kuhn J, et al. Unpublished data.

tered on these occasions, the infusion duration was extended to up to 2.75 hours. In addition, atropine (0.25 mg IV push) was used as a premedication, rather than “as needed,” when these higher doses of CPT-11 were administered.

Efficacy

Tumor responses for Studies 1 and 2 are shown in Table 2. All enrolled patients were evaluable for response.

Safety

Study 1

Safety results are summarized in Table 3. There were no drug-related deaths. Grade 3/4 adverse events were infrequent and were limited to nausea (*n* = 1), vomiting (*n* = 1), and neutropenia (*n* = 2). Three patients developed prolonged neutropenia that resulted in the limiting of dose escalation to 350 mg/m² or the required dose reduction to 250 mg/m².

Study 2

Safety results are summarized in Table 4. There were no drug-related deaths. DLT developed in 12 patients

TABLE 2
Efficacy Results

End point	Result Study 1 (n = 14)	Result Study 2 (n = 35)
Objective response rate (%)	2 (14)	3 (9)
Partial response (%) ^a	2 (14)	3 (9)
Stable disease (%)	1 (7)	15 (43)
Progressive disease (%)	11 (79)	17 (48)
Median time to tumor progression (range)	6 wks (1–31 wks)	2.1 mos (0.1–27 wks)
6-month time to tumor progression (%)	14 (100)	26 (74)
Median survival (range)	24 wks (1–81 wks)	8.5 mos (0.1–27 wks)
1-year survival (%)	14 (100)	34 (97)

^a Response was confirmed \geq 4–6 weeks after first indication of partial response.

Study 1 data from Cloughesy TF, Filka E, Gillian N, et al. Irinotecan treatment for recurrent glioma using an every three week regimen. *Am J Clin Oncol*. 2002;25:204–208.²

Study 2 data from Cloughesy TF, Filka E, Kuhn J, et al. Unpublished data.

TABLE 3
Study 1: Highest Grade of Nonhematologic and Hematologic Adverse Events by Patient

Adverse event	Grade 0 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)
Late diarrhea	9 (64)	5 (36)	0 (0)
Vomiting	8 (57)	5 (36)	1 (7)
Nausea	9 (64)	4 (29)	1 (7)
Neutropenia	7 (50)	5 (36)	2 (14)
Thrombocytopenia	10 (71)	4 (29)	0 (0)
Anemia	1 (7)	13 (93)	0 (0)

Data from Cloughesy TF, Filka E, Gillian N, et al. Irinotecan treatment for recurrent glioma using an every three week regimen. *Am J Clin Oncol*. 2002;25:204–208.²

TABLE 4
Study 2: Highest Grade of Nonhematologic and Hematologic Adverse Events by Patient

Adverse event	Grade 0 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)
Late diarrhea	10 (29)	23 (65)	2 (6)
Vomiting	18 (51)	15 (43)	2 (6)
Nausea	12 (34)	20 (54)	3 (9)
Abdominal cramping	14 (40)	19 (54)	2 (6)
Asthenia/fatigue	11 (31)	14 (40)	10 (29)
Neutropenia	19 (54)	13 (37)	3 (9)
Thrombocytopenia	24 (69)	11 (31)	0 (0)
Anemia	4 (11)	31 (89)	0 (0)

Data from Cloughesy TF, Filka E, Kuhn J, et al. Unpublished data.

(Table 5) at a wide range of doses (400–1700 mg/m²). Eight patients developed asthenia, 2 with abdominal cramping; 1 patient developed Grade 3 diarrhea; and 1 patient developed Grade 4 neutropenia.

DISCUSSION

Study 1 evaluated a CPT-11 dose of 300 mg/m² administered once every 3 weeks; it was hoped that this dosing regimen would be more “patient-friendly” than the regimen of 125 mg/m² every week for 4 weeks followed by a 2-week rest period. It was anticipated that the higher dose might prove more beneficial to glioma patients by resulting in higher peak plasma levels; however, the efficacy results in Study 1 are consistent with those seen previously.¹ The response rate was 14% (95% confidence interval, 2–43%), and median survival was 24 weeks. Toxicities were similarly low. Grade 3/4 neutropenia occurred in only 2 patients (14%). Nausea and vomiting occurred in only 1 patient (7%), and there were no cases of late Grade 3/4 diarrhea. No pharmacokinetic analysis was performed in our study. However, the toxicity data

once again suggest that concurrent use of anticonvulsants and dexamethasone results in lower than desired plasma levels of CPT-11 and SN-38 and in decreased toxicity.

These results suggest that a CPT-11 dosing regimen of 300–350 mg/m² every 3 weeks is feasible and has activity against recurrent malignant glioma, but that the maximum tolerated dose has not yet been reached. It is noteworthy that in Study 1, some patients receiving EIAED required CPT-11 dose de-escalation predominantly due to hematopoietic toxicities. This effect may stem from prior chemotherapy exposure, or there may be unique interpatient pharmacogenetic differences with regard to CPT-11 metabolism. If higher doses could be tolerated, improved responses in this patient population could result. The data from this study left unanswered questions regarding a tolerable dose for patients who are taking enzyme-inducing medication. These questions were the impetus for the implementation in Study 2 of an every-3-week inpatient CPT-11 dose-escalation de-

TABLE 5
Study 2: Dose-Limiting Toxicity

No. of patients	AE type	AE grade	Dose (mg/m ²)	Anticonvulsant
2	Abdominal cramping	3	400	CBZ
24	Abdominal cramping	3	800	DPH
33	Asthenia	3	450	None
8	Asthenia	3	500	PB
17	Asthenia	3	700	CBZ
1	Asthenia	3	750	DPH
11	Asthenia	3	800	DPH
29	Asthenia	3	800	CBZ
7	Asthenia	3	1100	DPH
12	Asthenia	3	1200	DPH/GAB
3	Diarrhea	2	650	PB
25	Neutropenia	4	1700	DPH

AE: adverse effect; CBZ: carbamazepine; DPH: phenytoin; PB: phenobarbital; GAB: gabapentin.
Data from Cloughesy TF, Filka E, Kuhn J, et al. unpublished data.

sign for 35 patients with recurrent malignant glioma. Maximum doses achievable, dose-limiting toxicities, and responses were evaluated in patients receiving EIAED compared with patients receiving non-EIAED or no anticonvulsants.

Doses ranging from 300–1700 mg/m² were administered every 3 weeks to patients in this study. Patients receiving EIAED were treated with higher doses of CPT-11 than those not receiving EIAED. The highest dose achieved among the patients not receiving EIAED was 550 mg/m², whereas the highest dose administered in the EIAED group was 1700 mg/m². Five patients who were treated with EIAED received doses \geq 1200 mg/m². Aside from DLT, the predominant reason for failure to achieve higher doses was early progression. Therefore, patients who were not treated with EIAED might have been able to receive higher doses of CPT-11 if more prolonged disease stabilization had occurred. Doses of CPT-11 \geq 800 mg/m² have not been reported previously in the literature.^{4–6}

Twelve patients developed DLT as defined by this study. Asthenia and gastrointestinal toxicity were the most common DLTs by a large margin. In some cases, asthenia was severe, leaving patients bedridden for 3–7 days. Methylphenidate appeared to alleviate the severity of asthenia. One patient not receiving EIAED developed dose-limiting asthenia at 450 mg/m². Nine patients receiving EIAED developed asthenia or gastrointestinal toxicity at doses varying from 400–1200 mg/m². This variation among the doses associated with DLT in patients who received EIAED is striking and cannot be explained by EIAED treatment alone. It is also noteworthy that 4 patients who were treated with EIAED received doses \geq 1200 mg/m² and did not

develop DLTs. Only one patient receiving EIAED experienced dose-limiting neutropenia; that event occurred at a dose of 1700 mg/m². The reason for the variability in doses associated with DLT in patients who received EIAED is unclear. Several classes of EIAED were used within this patient sample. The extent of prior chemotherapy also does not account for this variability. These interpatient differences may be due to the extent of enzyme induction caused by the anticonvulsants or by other unknown factors that lead to variability in CPT-11 clearance.

The response to therapy in this patient population was similar to previous CPT-11 studies, which employed a different dosing schema.¹ In Study 2 we observed an objective response rate of 9%, a median TTP of 12 weeks, a 6-month progression-free survival rate of 26%, a median survival of 36 weeks, and a 1-year survival rate of 34%. The Phase II study by Friedman et al.¹ reported an objective response rate of 15%, a median survival of 43 weeks, and a 1-year survival rate of 33%. There is no evidence that the intrapatient dose-escalation scheme evaluated in this study leads to an improved objective response rate.

Several questions about CPT-11 use in malignant gliomas remain to be answered. 1) What is the best dosing regimen? 2) Will a glioma trial in which all patients receive their MTD provide an improved outcome compared with the typical DLT reflected in pharmacokinetics? 3) Is interpatient variability in DLT reflected by pharmacokinetics? 4) Is interpatient variability in MTD an effect of EIAED, the individual's response to EIAED, or the individual's response to CPT-11? Ongoing National Cancer Institute Cancer Therapy Evaluation Program (CTEP)-sponsored glioma trials should answer some of these questions.

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