

Phase II Trial of Irinotecan plus Celecoxib in Adults with Recurrent Malignant Glioma

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BACKGROUND. In the current study, the authors report a Phase II trial of irinotecan (CPT-11), a topoisomerase I inhibitor active against malignant glioma (MG), with celecoxib, a selective COX-2 inhibitor, among MG patients with recurrent disease. **METHODS.** Patients with MG at any type of recurrence received CPT-11, administered as a 90-minute intravenous infusion on Weeks 1, 2, 4, and 5 of each 6-week cycle plus celecoxib, which was administered continuously at a dose of 400 mg twice a day. CPT-11 was given at a dose of 350 mg/m² for patients receiving enzyme-inducing antiepileptic drugs (EIAEDs) and at a dose of 125 mg/m² for those patients not receiving EIAEDs. Assessments were performed after every cycle. The primary endpoint was radiographic response and the secondary endpoints were progression-free survival (PFS), overall survival (OS), and therapeutic safety.

RESULTS. Thirty-four of the 37 patients enrolled in the current study (92%) were diagnosed with recurrent GBM and 3 patients (8%) were diagnosed with recurrent anaplastic astrocytoma (AA). Twenty-one patients were receiving EIAEDs and 16 patients were not. The median follow-up time was 76.9 weeks. Concomitant CPT-11 plus celecoxib was found to be well tolerated and safe. Hematologic toxicities of \geq Grade 3 (according the second version of the Common Toxicity Criteria of the National Cancer Institute) reportedly complicated 8.6% of treatment courses. Grade 3 diarrhea, the most commonly reported nonhematologic toxicity, occurred with equal frequency (8%), regardless of whether the patient was receiving EIAED. Six patients (16%), all whom were diagnosed with recurrent GBM, achieved an objective radiographic response whereas an additional 13 patients (35%) achieved stable disease. The median PFS was 11.0 weeks and the 6-month PFS was reported to be 25.1%. The median OS was 31.5 weeks.

CONCLUSIONS. The results of the current study confirm that CPT-11 plus celecoxib can be safely administered concurrently at full dose levels, and that this regimen has encouraging activity among heavily pretreated patients with recurrent MG. *Cancer* 2005;103:329-38. © 2004 American Cancer Society.

KEYWORDS: irinotecan (CPT-11), celecoxib, COX-2, malignant glioma.

Recurrence is nearly universal for patients with malignant glioma (MG) after conventional therapy comprised of surgical debulking, external beam radiotherapy, and chemotherapy, and is typically accompanied by progressive physical and mental debilitation, culminating in death. Available salvage therapies after disease progression are ineffective, with a median progression-free survival of only 9 weeks for patients with World Health Organization (WHO) Grade 4 tumors such as glioblastoma multiforme (GBM) and 12 weeks for patients with WHO Grade 3 tumors, including anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and anaplastic oligoastrocytoma (AOA).¹ The role of chemotherapy for patients with MG re-

mains controversial. Regimens such as procarbazine, lomustine, and vincristine (PCV) are reported to improve the outcome for some patients with WHO Grade 3 tumors,²⁻⁵ but fail to increase the survival of patients with GBM beyond that of radiotherapy alone.⁶ Other studies ascribe a modest survival advantage to chemotherapy.⁷⁻¹¹ Our center and others have attempted to improve the outcome for patients with MG by investigating additional, rationally designed chemotherapy regimens.

Irinotecan (CPT-11), a water-soluble derivative of camptothecin extracted from the Chinese tree *Campotheca acuminata*, inhibits topoisomerase-I, an essential enzyme for DNA transcription, replication, and repair.¹² CPT-11 has substantial activity against a broad panel of central nervous system (CNS) xenografts.^{13,14} In a Phase II trial of CPT-11 for patients with MG at first recurrence, 15% of patients achieved a partial response (PR), whereas 55% achieved stable disease (SD) for > 12 weeks.¹⁵ Additional clinical studies have confirmed the activity of CPT-11 in the treatment of MG.¹⁶⁻²²

Expression of cyclooxygenase (COX)-2, the inducible isoform of prostaglandin H synthase, is associated with a broad range of malignancies including carcinomas of the lung, prostate, esophagus, ovary, breast, skin, stomach, pancreas, and head and neck.²³⁻³² COX-2 is widely expressed in gliomas, with increased expression noted among high-grade tumors.^{24,33} In addition, COX-2 expression is associated with poorer survival.³² Selective inhibitors of COX-2, such as celecoxib, have antitumor activity against a variety of human tumors in preclinical models including gliomas.^{33,34} COX-2 inhibitors also have been shown to inhibit tumor endothelial cell proliferation and function³⁵⁻³⁷ and therefore may contribute to tumor control via antiangiogenic mechanisms. Furthermore, preclinical studies demonstrate that celecoxib enhances the antitumor activity of CPT-11.³⁸ Results from a recent clinical trial support the belief that celecoxib can augment the activity of chemotherapy.³⁹

We previously demonstrated that CPT-11 can be safely combined with additional chemotherapeutic agents for patients with MG.³⁹ In the current study, we report a Phase II study that was designed to determine the efficacy of CPT-11 plus celecoxib in this patient population.

MATERIALS AND METHODS

Protocol Objectives

The objectives of the current study were to define the activity of CPT-11 plus celecoxib in the treatment of adults with recurrent MG and to further define the toxicity of this regimen.

Patient Eligibility Criteria

Patients were required to have a histologically confirmed diagnosis of MG (GBM, AA, AO, or anaplastic oligoastrocytoma) that was recurrent as defined by the presence of unequivocal progressive disease (PD) after prior radiotherapy or chemotherapy. Eligible patients also were required to be at least 18 years of age, have measurable tumor on contrast-enhanced magnetic resonance imaging (MRI) obtained within 2 weeks of study initiation, have a Karnofsky performance status (KPS) \geq 60%, and be receiving treatment with a stable corticosteroid dose for at least 1 week prior to the initiation of therapy. Additional enrollment criteria included hematocrit > 29%; an absolute neutrophil count > 1000 cells/ μ L; a platelet count > 100,000 cells/ μ L; and a serum creatinine level, blood urea nitrogen, serum aspartate aminotransferase level, and bilirubin < 2.0 times the institutional upper limit of normal. At least 3 weeks were required between prior surgical resection and enrollment into the study, and at least 6 weeks were required between prior radiotherapy or chemotherapy and enrollment unless there was unequivocal progression of the tumor. All patients were informed of the investigational nature of the study and provided informed consent as approved by the Duke University Medical Center Institutional Review Board.

The following patients were excluded: pregnant or nursing women; those with reproductive potential and not using an effective contraceptive method; patients with PD after prior treatment with CPT-11; patients with an allergy to sulfa-derived medications, nonsteroidal antiinflammatory medications, or aspirin; those with an acute infection requiring intravenous antibiotics; and patients who underwent prior stereotactic radiosurgery, radiation implants, or radiolabeled monoclonal antibody therapy, unless there was unequivocal radiographic evidence of PD (such as a new or distant lesion) or biopsy-proven confirmation of recurrent tumor.

Treatment design

CPT-11 was given during Weeks 1, 2, 4, and 5 of each 6-week treatment cycle at a dose of 350 mg/m² for patients receiving EIAED and at a dose of 125 mg/m² for those patients not receiving EIAED. Celecoxib was administered orally at a dose of 400 mg on a continuous basis twice daily. Patients received up to eight treatment cycles unless unacceptable toxicity or tumor progression occurred.

Dose modification and retreatment criteria

Toxicity was graded according to the second version of the National Cancer Institute Common Toxicity Crite-

ria (NCI 2004). CPT-11 was reduced by 20% for any nonhematologic toxicity \geq Grade 3 or for any Grade 4 hematologic toxicities. The criteria for retreatment included an absolute neutrophil count > 1000 cells/ μ L; a platelet count $> 100,000$ cells/ μ L; and serum aspartate aminotransferase, total bilirubin, and creatinine levels < 2.0 times the upper limit of normal. All other toxicities were required to resolve to $< \text{Grade 1}$ for retreatment.

Patients were removed from study if they demonstrated evidence of PD at any time after the initiation of the study; Grade 4 nonhematologic toxicity; or more than two dose reductions because of toxicity; non-compliance; or voluntary withdrawal.

Supportive Care

Antiemetic therapy with ondansetron and dexamethasone was given before each weekly dose of CPT-11. Atropine (1 mg intravenously) was administered for acute cholinergic symptoms and loperamide was prescribed for late diarrhea as previously described.⁴⁰ Hematopoietic growth factors and blood products were administered as indicated for Grade 4 hematologic toxicity.

Evaluations Prior to and during Therapy

Patients underwent physical and neurologic examinations and MRI scans within 3 weeks of enrollment in the study and before every 6-week cycle. A complete blood count with differential was performed weekly, and a serum biochemistry profile was assessed every 6 weeks. A urinalysis was performed prior to the first treatment cycle, along with a β -human chorionic gonadotropin test in women of reproductive potential.

Response Evaluation

Response determination, performed by the study investigators, was based on neurologic examination and comparison of the baseline contrast-enhanced MRI scan with those performed before each cycle. A complete response (CR) was defined as the disappearance of all enhancing tumor from baseline on consecutive MRI scans at least 6 weeks apart, combined with the discontinuation of corticosteroids and the achievement of neurologic stability or improvement. A PR was defined as a $\geq 50\%$ reduction from baseline in the size (measured as the product of the largest perpendicular dimensions) of enhancing tumor maintained for at least 6 weeks with a stable or improved neurologic examination and a stable or reduced corticosteroid requirement. A minor response was defined as a $> 25\%$ but $< 50\%$ reduction from baseline in the size of the enhancing tumor on the MRI scan, neurologic stability, and a stable or reduced corticosteroid dose.

PD was defined as a $> 25\%$ increase in the size of the enhancing tumor from baseline or any new tumor detected on MRI scan. SD was defined as any clinical status not meeting the criteria for CR, PR, or PD for more than one course of therapy. Patient response was defined based on the best response achieved at any point while the patient was enrolled on the clinical trial.

Statistical Analysis

The primary goal of the current study was to evaluate the response rate of CPT-11 plus celecoxib in the treatment of patients with recurrent or progressive MG. Given a 15% response rate for CPT-11 alone,¹⁵ we employed a 2-stage "minimax" Phase II design to differentiate between a 5% and 20% response rate among eligible patients treated in the current study.

Eighteen patients were treated in the first stage with a plan to terminate the study if none of the patients responded to treatment. If any of the 18 initial patients responded to treatment, 14 patients would be added. The treatment regimen would be considered worthy of further evaluation if ≥ 4 of the total 32 patients responded.

The following characteristics were true of this study design: 1) the probability of erroneously concluding a treatment was active ($P \geq 0.2$) when it actually was ineffective ($P \leq 0.05$) was < 0.1 (i.e., $\alpha = 0.1$); and 2) the probability of erroneously concluding that the treatment was ineffective ($P \leq 0.05$) when it actually was active ($P \geq 0.2$) was 0.1 (i.e., $\beta = 0.1$). Under the null hypothesis, the probability of early termination was 0.40.

Time to tumor progression (TTP) and overall survival (OS) were measured from the date of the administration of the first cycle of treatment and analyzed using the Kaplan–Meier method, including 95% confidence intervals (95% CIs).^{41,42} Relative to the progression-free survival (PFS) and OS, the log-rank test was used to compare subgroups defined by the following patient characteristics: age (< 50 years vs. ≥ 50 years), KPS ($< 90\%$ vs. $\geq 90\%$), and histology (GBM vs. AA/AO), and whether patients received concurrent use of EIAEDs.

RESULTS

Patient Characteristics

Thirty-seven patients with recurrent MG were enrolled at the Duke University Medical Center between October 2002 and July 2003 (intent-to-treat [ITT] population). One patient who withdrew consent prior to the initiation of treatment was not evaluable for response. Twenty-one patients (57%) were receiving EIAEDs whereas 16 patients (43%) were not. Patient

TABLE 1
Patient Characteristics at Study Enrollment

Characteristic	No EIAED (n = 16)	Treated with EIAED (n = 21)	All Patients (n = 37)
Age (yrs)			
Median	51.5	49	50
Range	37–68	34–64	34–68
Gender			
Male	11 (69%)	16 (76%)	27 (73%)
Female	5 (31%)	5 (24%)	10 (27%)
Histology			
GBM	15 (94%)	19 (90%)	34 (92%)
AA	1 (6%)	2 (10%)	3 (8%)
KPS			
100%	1 (6%)	3 (14%)	4 (11%)
90%	7 (44%)	8 (38%)	15 (41%)
80%	2 (13%)	5 (24%)	7 (19%)
70%	5 (31%)	5 (24%)	10 (27%)
60%	1 (6%)	0	1 (3%)
Surgery			
STR	0	1 (5%)	1 (3%)
Biopsy	0	1 (5%)	1 (3%)
None	16 (100%)	19 (90%)	35 (94%)
Prior XRT	15 (94%)	20 (95%)	35 (94%)
Prior ChemoRx	15 (94%)	21 (100%)	36 (97%)
Median no. of prior chemo agents (range)	3 (0–4)	2 (0–5)	3 (0–5)
Median no. of prior recurrences (range)	1 (1–4)	2 (1–3)	1 (1–4)

EIAED: enzyme-inducing antiepileptic drug (phenytoin, carbamazepine, and phenobarbital); GBM: glioblastoma multiforme; AA: anaplastic astrocytoma; KPS: Karnofsky performance status; STR: subtotal resection; XRT: external beam radiotherapy; Chemo: chemotherapy.

characteristics did not appear to differ based on EIAED status (Table 1). Twenty-seven patients (73%) were male. The median age of the patients was 50 years (range, 34–68 years). Thirty-four patients had GBM (92%) and 3 patients (8%) had AA. All patients had a KPS > 60%.

Only one patient underwent resection prior to enrollment in the study. Excluding surgery, the mean number of prior treatments per patient was four (range one to six prior treatments). Thirty-six patients (97%) had failed prior chemotherapy and the mean number of prior chemotherapeutic agents per patient was 3 (range, 0–5 prior chemotherapy agents). The median time to study enrollment from the time of the original diagnosis was 10.3 months (range, 0.4–40.1 months) for patients with recurrent GBM and 15.0 months (range, 2.3–37.1 months) for patients with recurrent AA.

Toxicity

Ninety-three cycles of CPT-11 plus celecoxib were administered to the patients enrolled on the current

study. Overall, the regimen was well tolerated (Table 2). Grade 3 or 4 hematologic toxicities complicated 8 of the courses administered to patients not receiving EIAEDs (18.6%) and included neutropenia (Grade 3 [$n = 3$ patients] and Grade 4 [$n = 1$ patient]), thrombocytopenia (Grade 3 [$n = 3$ patients]), and anemia (Grade 3 [$n = 1$ patient]). It is interesting to note that hematologic toxicity of \geq Grade 3 was not observed among patients who were concurrently receiving EIAEDs. Therefore, hematologic toxicity of \geq Grade 3 complicated 8 of all administered courses (8.6%). The most common nonhematologic toxicity of \geq Grade 3 was diarrhea and was reported to occur during 7–8% of courses. One death occurred on study and involved a patient who developed *Klebsiella pneumoniae* sepsis with severe neutropenia and disseminated intravascular coagulation after receiving < 2 weeks of the first cycle of therapy.

Outcome

Confirmed objective responses were observed in 6 patients with recurrent tumors (Table 3), resulting in a response rate of 17% among evaluable patients. One CR was observed and included a patient with biopsy-proven recurrent GBM at the time of study enrollment who received prior therapy that included two previous resections (one with the implantation of carmustine-impregnated wafers), external beam radiotherapy, temozolomide (eight cycles), and lomustine (two cycles). This patient achieved a PR after three cycles of CPT-11 plus celecoxib, which converted to a CR after nine cycles (Fig. 1A). Treatment cycles were discontinued after 1 year and at the time of last follow-up, this patient continued to receive celecoxib alone for 4 months with no evidence of disease recurrence. Five patients, all of whom were diagnosed with recurrent GBM, achieved a PR, including four patients who were not receiving EIAEDs and one patient who was receiving EIAEDs (Fig. 1B,1C). The PRs were durable in 4 of these 5 cases (10.5 months, 16.5 months, 12.5 months, and 13.5 months, respectively). Thirteen patients (36%) achieved SD, including 1 patient with recurrent GBM who discontinued celecoxib after 2 weeks of therapy because of rash. At the time of last follow-up, this patient had remained off therapy for 3 months with no evidence of recurrence after the completion of 1 year of therapy on study. Seventeen patients (47%) developed PD, including 2 patients who came off study because of fulminant clinical decline after receiving only the first 2 weeks of therapy and 1 patient who died of overwhelming sepsis after only 2 weeks of therapy.

Table 4 summarizes the PFS and OS for patients treated on this study. With a median follow-up of 76.9

TABLE 2
Summary of \geq Grade 3 Toxicity

Toxicity	No EIAED (43 courses)			On EIAED (50 courses)			Total (93 courses)
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	
Diarrhea	3 (7%)	0	0	4 (8%)	0	0	7 (8%)
Hyponatremia	1 (2%)	1 (2%)	0	0	0	0	2 (2%)
Infection	1 (2%)	0	1 (2%)	0	1 (2%)	0	2 (2%)
Thrombosis	0	0	0	1 (2%)	1 (2%)	0	2 (2%)
Anemia	1 (2%)	0	0	0	0	0	1 (1%)
Neutropenia	3 (7%)	1 (2%)	0	0	0	0	4 (4%)
Thrombocytopenia	3 (7%)	0	0	0	0	0	3 (3%)

EIAED: enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine, and phenobarbital).

TABLE 3
Summary of Radiographic Response among Evaluable Patients

Response	No EIAED (n = 16)	Treated with EIAED (n = 21)	All (n = 37)
Complete	0	1 (5%)	1 (3%)
Partial	4 (25%)	1 (5%)	5 (14%)
Stable disease	5 (31%)	8 (38%)	13 (35%)
Progressive disease	7 (44%) ^c	10 (48%)	17 (46%) ^c
Nonevaluable	0	1 (5%) ^b	1 (3%)

EIAED: enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine; and phenobarbital).

^a Includes 1 patient who died of sepsis after < 2 weeks of Cycle 1 and prior to evaluation for response.

^b One patient withdrew consent prior to the initiation of therapy.

^c Includes 2 patients who discontinued therapy after < 2 weeks of Cycle 1 because of fulminant tumor progression.

weeks (95% CI, 69.0–86.0 weeks), the median TTP for all patients was 11.0 weeks (95% CI, 6.3–14.7 weeks). Patients with GBM had a median TTP of 11.1 weeks (95% CI, 6.3–15.6 weeks) compared with only 7.0 weeks (95% CI, 5.6–14.7 weeks) for patients with AA (Fig. 2A). The unexpectedly low median PFS reported among patients with AA reflects the impact of early disease progressions occurring during Cycle 1 in this relatively small patient subset. The probability of remaining progression-free at 6 months and 12 months for patients with GBM was 27.5% (95% CI, 15.5–48.6%) and 15.7% (95% CI, 7.1–34.6%), respectively. The median OS for all patients was 31.5 weeks (95% CI, 20.1–57.0 weeks), including 31.1 weeks (95% CI, 20.1–57.0 weeks) for those with GBM and 55.0 weeks (95% CI, 18.4–not estimable [NE] weeks) for those with AA (Fig. 2B). The 1-year survival probability for patients with recurrent GBM was 21% (95% CI, 11–44%).

Correlation of outcome was assessed relative to patient age, KPS, use of EIAEDs, and the number of prior chemotherapy agents. None of these treatment variables was found to be correlated with PFS, al-

though age and KPS were found to be correlated with OS (Table 5).

DISCUSSION

Historically, the benefit of chemotherapy in the treatment of patients with MG has been a subject of much controversy. However, recent growing evidence supporting the value of chemotherapy for such patients has emerged. First, tumors with chromosomal 1p and 19q loss exhibit particular chemosensitivities and patients with such tumors may achieve prolonged disease-free survival with chemotherapy.^{3,5} Second, a recent Phase III, multicenter, international study confirmed that temozolomide plus radiotherapy provides a survival advantage for patients with newly diagnosed GBM compared with the use of external beam radiotherapy alone.¹¹ However, given that nearly all patients with MG ultimately develop a disease recurrence, and that salvage therapies to date have been reported to have extremely limited therapeutic benefit, additional, innovative therapies are desperately needed for patients diagnosed with these tumors.

Extensive laboratory efforts over the past 30 years have led to the identification and functional evaluation of critical components of multiple signal transduction pathways that underlie much of the phenotype of neoplastic cells. Based on these findings, a unique, exciting genre of therapeutic agents targeting key cell signaling pathway components has emerged. COX-2 is currently a therapeutic target of significant interest in cancer therapy because, as the enzyme responsible for catalyzing the rate-limiting conversion of arachidonic acid to prostaglandins, it influences multiple key signaling pathways affecting cellular processes such as mitogenesis, cellular adhesion, invasion, angiogenesis, and apoptosis.^{43,44} The goal of the current study was to evaluate the activity of a regimen

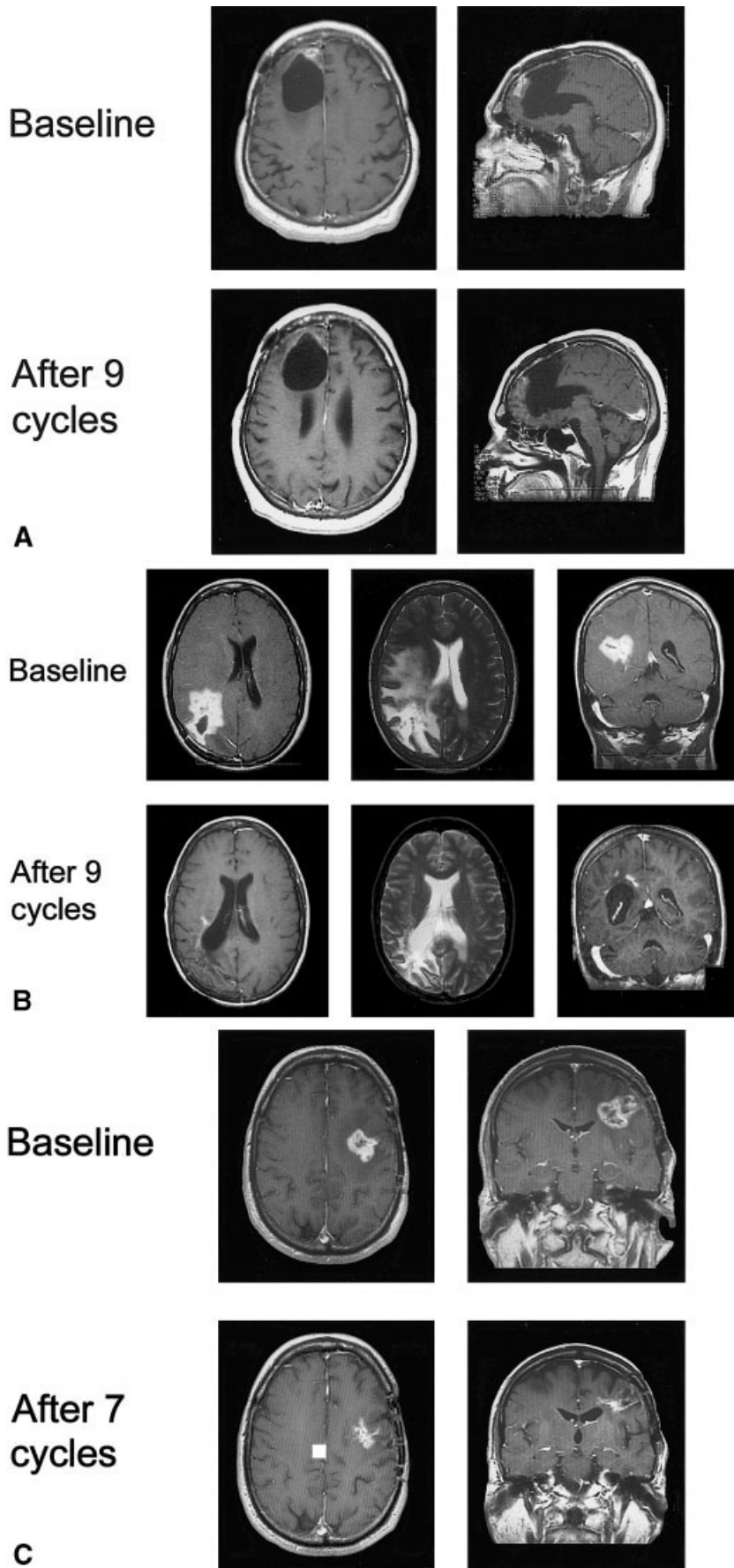


FIGURE 1. T1-weighted magnetic resonance imaging scan of representative responses to irinotecan plus celecoxib. (A) A patient with recurrent glioblastoma multiforme (GBM) who achieved a complete response. (B,C) Two patients with recurrent GBM who achieved partial responses.

TABLE 4
Median TTP (Weeks), 6-Month PFS (%) and OS (Weeks) with 95% CI

	No.	TTP (95% CI)	6-mo PFS (95% CI)	OS (95% CI)
All ^a	36	11.0 (6.3–14.7)	25.1 (14.1–44.9)	31.5 (20.1–57.0)
GBM	33	11.1 (6.3–15.6)	27.5 (15.5–48.6)	31.1 (20.1–57.0)
AA	3	7.0 (5.6–14.7)	0	55 (18.4–NE)
No EIAED	16	11.1 (6.6–42.6)	32.0 (15.0–68.4)	25.2 (14.9–58.9)
Treated with EIAED	20	9.0 (5.7–14.7)	20.0 (8.32–48.1)	32.6 (20.1–70.7)

TTP: time to tumor progression; PFS: progression-free survival; OS: overall survival; 95% CI: 95% confidence interval; GBM: glioblastoma multiforme; AA: anaplastic astrocytoma; NE: not estimable; EIAED: enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine, and phenobarbital).

^a Excludes one patient who withdrew consent prior to receiving therapy on study.

comprised of CPT-11, a traditional cytotoxic agent targeting topoisomerase-1, plus the selective COX-2 inhibitor celecoxib in the treatment of patients with recurrent MG.

Friedman et al. first demonstrated the activity of CPT-11 against MG in a Phase II study using a dosing regimen employed at the time for colorectal carcinoma patients.¹⁵ In that study, 60 patients with recurrent MG at first recurrence received 125 mg/m² of CPT-11 weekly for the first 4 weeks of each 6-week cycle. Evaluations, including MRI scans, were performed after every cycle. The overall ITT response rate was 15%, whereas an additional 55% of patients achieved SD for > 2 courses. It is interesting to note that pharmacokinetic analysis of patients enrolled on that study revealed significantly lower CPT-11 and SN-38 exposures compared with patients treated on the same dosing schedule with colorectal carcinoma.¹⁵ The concurrent use of EIAEDs is postulated to be responsible for the enhanced metabolism of CPT-11 observed among MG patients.^{15,19,21}

Thereafter, Phase I studies were performed to establish the maximum tolerated dose (MTD) of CPT-11 for patients with MG based on the concurrent use of EIAEDs. Gilbert et al. established the MTD of CPT-11 to be 117 mg/m²/dose for patients not receiving EIAEDs and 411 mg/m²/dose for patients receiving EIAEDs using the 4-times-weekly-every-6-weeks dosing schedule.²¹ Using a once-every-3-weeks dosing schedule, Prados et al. established the MTD of CPT-11 to be 350 mg/m² for patients not receiving EIAEDs and 750 mg/m² for patients receiving EIAEDs.²²

Follow-up Phase II studies incorporating the MTDs established by the Phase I studies cited above were recently completed. Among 18 patients with recurrent MG who were treated on a Phase II study using the 4-times-weekly-every-6-weeks dosing schedule, 1 patient achieved a CR whereas 5 patients achieved SD.²⁰ Using the once-every-3-week dosing

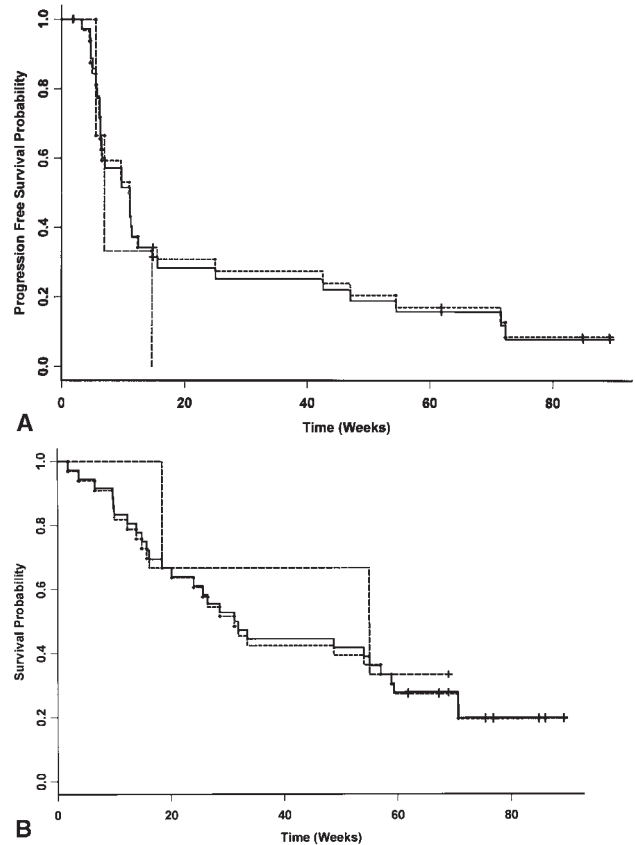


FIGURE 2. Kaplan–Meier estimates stratified by histology of (A) time to tumor progression and (B) overall survival. Dotted line: glioblastoma multiforme (GBM); dashed line: non-GBM; solid line: all patients.

schedule, Cloughesy et al. noted that 3 of 35 patients with recurrent MG achieved a PR (9%) whereas 15 patients (43%) achieved SD.¹⁹ Although the results of these studies further support the activity of CPT-11 for the treatment of MG, regimens incorporating CPT-11 in combination with additional agents currently are being evaluated and the preliminary results are encouraging.^{45,46}

COX-2 represents an attractive therapeutic target in the treatment of MG for several reasons. First, COX-2 directly affects prostaglandin levels that in turn have been linked with several key components of tumor cell biology including mitogenesis, adhesion and invasion, immune surveillance, and apoptosis.^{43,44} Second, COX-2 is widely expressed in glioma specimens,^{32,47–49} with an increased extent of expression noted by immunohistochemistry in MG compared with low-grade glioma or normal brain tissue.^{24,32,33} Furthermore, increased COX-2 expression predicts poor prognosis in general among patients with glial tumors and in particular among those with GBM.²⁴ The value of targeting COX-2 has been demonstrated

TABLE 5
Correlation between Outcome and Patient Characteristics

Group	No. ^a	Median (in wks)	95% CI	P value
OS				
Age (yrs)				0.0096
<50	17	58.9	(25.6–NE)	
≥50	19	24.0	(12.3–48.7)	
No. of prior chemoRx agents				0.3013
<2	10	29.5	(14.9–57.0)	
≥2	26	31.5	(18.4–70.6)	
KPS				0.0423
<90%	17	25.6	(9.9–57.0)	
≥90%	19	54.0	(20.1–NE)	
PFS				
Age (yrs)				0.0770
<50	17	11.4	(7.0–54.4)	
≥50	19	6.4	(5.7–11.3)	
No. of prior chemoRx agents				0.3077
<2	10	5.6	(4.7–47.0)	
≥2	26	11.1	(6.6–14.7)	
KPS				0.2439
<90%	17	10.4	(5.7–11.4)	
≥90%	19	11.1	(6.3–54.4)	

95% CI: 95% confidence interval; OS: overall survival; NE: not estimable; ChemoRx: chemotherapeutic; KPS: Karnofsky performance status; PFS: progression-free survival.

^a Excludes one patient who withdrew informed consent prior to the initiation of the study regimen and did not receive treatment on study.

in gastrointestinal malignancies in which the inhibition of COX-2 reduces the number of preexisting adenomas in patients with familial adenomatous polyposis^{50,51} and reduces the risk of sporadic colorectal carcinoma.^{52,53} A recent prospective pilot study demonstrated that celecoxib can enhance the antitumor activity of chemotherapy. Among patients with newly diagnosed breast carcinoma, those treated with celecoxib plus chemotherapy were found to have a higher rate of clinical and pathologic response compared with those treated with chemotherapy alone.³⁹

Data from preclinical studies also demonstrate that targeting COX-2 may be of value in the treatment of MG. In vitro studies with GBM cell lines demonstrate that COX-2 inhibition can suppress cell proliferation, migration, and three-dimensional growth, while inducing apoptosis.³³ In vivo studies with 9L gliosarcoma cells that were orthotopically implanted in rats have demonstrated that the administration of the selective COX-2 inhibitor celecoxib reduces growth with increased apoptosis.³⁴

The results of the current study involving 37 patients with recurrent MG demonstrate that CPT-11 and celecoxib can be administered safely at full dose levels together and that this regimen has therapeutic benefit in this patient population. Furthermore, the

current results build on those of prior Phase II trials with CPT-11 in patients with recurrent MG.^{15,16,19,20}

In the current study, the regimen of CPT-11 plus celecoxib administered concurrently at full dose levels was found to be well tolerated. As reported in other Phase II studies incorporating the 4-times-weekly-every-6-weeks CPT-11 dosing schedule, and as noted in the Phase I study of Gilbert et al. for patients treated at the MTD dose level, significant hematologic toxicity was not a common finding.^{16,20,21,39} Specifically in the current study, Grade 3 and 4 neutropenia complicated 3 (3%) and 1 (1%) of all administered courses, whereas Grade 3 thrombocytopenia and Grade 3 anemia were noted after 3 (3%) and 1 (1%) of all administered courses, respectively.

As expected, diarrhea was the most common non-hematologic toxicity. In the current study, diarrhea did not exceed Grade 3 and occurred with approximately equal frequency regardless of EIAED use. It is interesting to note that the frequency of diarrhea observed in the current study was the same as that observed in a recently reported Phase II study combining CPT-11 with carmustine.³⁹ In that study, the dose of CPT-11 was 125 mg/m² for patients not receiving EIAEDs and 225 mg/m² for patients who were receiving EIAEDs. The fact that the frequency and severity of diarrhea was comparable among patients treated on both of these studies, despite the higher dose of CPT-11 administered to patients receiving EIAEDs in the current study, suggests that celecoxib may have attenuated the potential gastrointestinal toxicity associated with CPT-11. In fact, COX-2 inhibitors have been shown to decrease the severity of CPT-11-induced late diarrhea in a dose-dependent manner in preclinical models that is associated with a reduction in the levels of prostaglandin E₂ in the colon.³⁸ We note that other investigators have observed a higher rate of gastrointestinal toxicity among patients treated with CPT-11 than was reported in the current study.²⁰ This discrepancy is most likely attributable to a 15% lower CPT-11 dose for patients receiving EIAEDs in the current study and/or the gastrointestinal-protective effect of celecoxib. In addition, given the fairly small number of patients enrolled on these studies, it is possible that by chance, fewer patients who were heterozygous or homozygous for the UDP-glucuronosyltransferase 1A1 genetic variants associated with increased CPT-11-related gastrointestinal toxicity⁵⁴ were enrolled in the current study.

In the current Phase II study, CPT-11 plus celecoxib was associated with clear antitumor activity as measured by both radiographic response and PFS. Among 36 evaluable patients, 1 achieved a CR and 5 achieved a PR for an overall response rate of 17%. In a

previously reported Phase II study of the use of CPT-11 alone for patients with MG at first recurrence, the rate of radiographic response was 15%.¹⁵ The comparable rate of radiographic response observed in the current study, which allowed patients to enroll regardless of the number of prior disease recurrences or the degree of prior treatment, suggests that celecoxib may have contributed to the antitumor activity of CPT-11. Despite the overall heavy pretreatment of patients enrolled in the current study, the median PFS also was found to be slightly improved compared with that achieved with CPT-11 alone, again suggesting that celecoxib may have improved the activity of CPT-11. The 6-month PFS for patients with GBM observed on the current study was 27% and compared favorably with that achieved with temozolomide (21%), particularly given that the latter study again was limited to patients at the time of first recurrence.⁵⁵

The results of the current Phase II trial indicate that CPT-11 plus celecoxib can be administered safely together at full dose levels. In addition, despite the heavy degree of pretreatment for patients enrolled in the current study, the results further substantiate the activity of CPT-11 for patients with MG and suggest that celecoxib may augment this activity. Further studies of regimens incorporating CPT-11 plus celecoxib for patients with MG are warranted.

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