Published in final edited form as:
J Neurooncol. 2009 December ; 95(3): 393–400. doi:10.1007/s11060-009-9937-x.

Phase II trial of temozolomide (TMZ) plus irinotecan (CPT-11) in adults with newly diagnosed glioblastoma multiforme before radiotherapy

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Abstract

This phase II trial evaluated efficacy and safety of temozolomide (TMZ) in combination with irinotecan (CPT-11) before radiotherapy in patients with newly diagnosed glioblastoma multiforme

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(GBM). Prior to radiotherapy, patients were treated with a maximum of three 6-week cycles of TMZ and CPT-11. Patients received TMZ at a dose of 200 mg/m^2/day on days 1–5 and CPT-11 on days 1, 8, 22, and 29, with a dose adjustment for enzyme-inducing antiepileptic drug use. The primary end point was objective response rate (ORR). Secondary end points included progression-free survival (PFS), overall survival (OS), safety, and tumor O^6-methylguanine-DNA methyltransferase (MGMT) expression. Of the 42 patients treated, 8 (19%) patients achieved a partial response. Median PFS and median OS were 3.1 and 13.8 months, respectively. Grade 3 or 4 AEs were documented in 36% of patients, most of which were hematologic (29%). Twenty-four percent of patients had grade 3 or 4 non-hematologic AEs, with gastrointestinal AEs being the most common (12%) Two patients died, one of intracranial hemorrhage and one of treatment-related renal failure. Low MGMT expression, compared with high MGMT expression, showed no significant difference in ORR (25 vs. 8%), median PFS (14 vs. 5 months) or OS (21 vs. 15 months). Although TMZ plus CPT-11 is at least comparable in efficacy to TMZ alone, this combination appears more toxic and poorly tolerated. The lack of correlation of activity with MGMT expression is intriguing, but needs further evaluation in subsequent trials.

Keywords

Temozolomide; Glioblastoma multiforme; Irinotecan; Radiotherapy; Newly diagnosed

Introduction

The diagnosis of malignant glioma (MG) can be likened to a death sentence, with a median survival in the United States of less than 2 years [1]. Currently, the only FDA-approved therapies for treatment of MG are the alkylators carmustine (BCNU), lomustine (CCNU), temozolomide (TMZ) and carmustine implantable wafers—Gliadel®. These therapies have shown to prolong survival, but the fact remains that most patients will die of their disease. Clearly, novel therapeutic agents and strategies are needed.

The inter- and intra-tumoral heterogeneity of gliomas suggests that a combination regimen may be efficacious in producing lasting anti-tumor effect and overcoming drug resistance. However, the main challenge in the development of combination regimens is the lack of active agents. TMZ [2–4] and irinotecan (CPT-11) [5–9] each have demonstrated clinical activity when administered separately to patients with MG. TMZ and CPT-11 are ideal candidates for combination chemotherapy because they exert their antitumor effects through interactions with different targets and have different organ toxicities. CPT-11 is a topoisomerase I inhibitor with dose-limiting toxicity (DLT) of diarrhea [10,11]. TMZ is an alkylating agent with DLT of myelosuppression [12].

Not only do TMZ and CPT-11 demonstrate antitumor activity when administered separately, but in preclinical studies this antitumor activity was synergistic when TMZ was administered within 5 days preceding the administration of CPT-11 [13,14]. This synergy was produced because O^6 alkylation of guanine by TMZ induces topoisomerase I-DNA covalent complexes, thereby decreasing the topoisomerase I-mediated DNA religation and enhancing CPT-11 activity [15].

Initial exploration of combination TMZ and CPT-11 was recently pursued in a phase I trial in adults with recurrent MG [16]. TMZ was administered at a dose of 200 mg/m^2/day on days 1–5, and CPT-11 was administered as a 90-min infusion during weeks 1, 2, 4, and 5 of each 6-week cycle. The maximum tolerated dose (MTD) of CPT-11 for patients concurrently receiving and not receiving enzyme-inducing antiepileptic drugs (EIAEDs) was 325 and 125 mg/m^2, respectively. The DLTs were hematologic, gastrointestinal, and hepatic. A second phase I trial

was conducted by the North American Brain Tumor Consortium (NABTC) in which patients, all of whom were receiving EIAEDs, received TMZ at a dose of 150 mg/m^2/day on days 1–5, and CPT-11 was administered as an IV infusion of days 1 and 15 of each cycle [17]. The MTD of CPT-11 was 500 mg/m^2. The DLTs were hematologic and gastrointestinal.

We now report a phase II clinical trial in patients with newly diagnosed glioblastoma multiforme (GBM). This trial was designed to determine the efficacy and toxicity profile of CPT-11 in combination with TMZ.

Materials and methods

Patients

Patients were eligible if they were newly diagnosed with GBM that had been histopathologically confirmed by central review. Patients were required to be at least 18 years old and have a Karnofsky performance score ≥ 70%. Patients were required to have measurable disease on contrast-enhanced magnetic resonance imaging (MRI) performed within 14 days before drug administration. Those who had undergone resection must have had an MRI exam within 14 days after surgery. Although surgical resection was not required, if one was performed, patients were required to be treated within 42 days of the surgery or biopsy. Additional enrollment criteria included adequate pretreatment bone marrow function (total granulocyte count ≥ 1,500 cells/μl, platelets ≥ 100,000 cells/μl), renal function (serum creatinine ≤ 1.5 mg/dl), and hepatic function (serum SGOT and total bilirubin ≤ 2.5 × upper limit of normal). Patients of reproductive potential were required to take effective contraceptive measures for the duration of the study. All patients were informed of the investigational nature of the study and were required to provide signed an informed-consent form as approved by the Duke University Health System Institutional Review Board.

Patients were excluded if they had been treated previously with chemotherapy, biologic therapy, radiation therapy, stereotactic radiosurgery, or brachytherapy. The following patients were also excluded from the study: pregnant women, potentially fertile women or men who were not using an effective contraception method, patients with an active infection requiring antibiotics, patients with a known diagnosis of HIV, and patients taking immunosuppressive agents other than corticosteroids.

Study design and treatment

This was a single-institution, non-randomized, two-stage, phase II clinical trial. Patients were treated on a 6-week (42-day) cycle. Treatment cycles were repeated up to a maximum of 3 cycles or until occurrence of either unacceptable toxicity or evidence of disease progression. At the end of the 3rd cycle or if cycles were stopped early for toxicity or progression, the subject would undergo radiation therapy.

TMZ was administered orally at 200 mg/m^2 in a fasting state 1 h prior to the CPT-11 infusion. TMZ was administered on day 1 of the treatment cycle and every 24 h thereafter for 5 days, with treatment cycles repeated every 6 weeks (42 days).

CPT-11 was administered intravenously in a fasting state over 90 min. CPT-11 began 1 h after TMZ administration on day 1 of the treatment cycle. CPT-11 was administered on days 1, 8, 22, and 29 of the 6-week (42-day) treatment cycle. The dose of CPT-11 for patients receiving EIAEDs, including phenytoin, phosphenytoin, carbamazepine, oxcarbamazepine, phenobarbital or primidone, was 325 mg/m^2, and for those patients not receiving EIAEDs, the CPT-11 dose was 125 mg/m^2.

Surveillance and follow-up

The baseline examination included central review of tumor tissue, MRI, complete blood count (CBC), a blood chemistry test, and a physical examination including a comprehensive neurologic examination. During therapy, weekly CBCs were obtained. Prior to subsequent cycles of chemotherapy, patients were required to repeat the CBC, blood chemistry test, physical and neurologic examination, and neuro-imaging.

Toxicity was graded according to the third version of the National Cancer Institute Common Toxicity Criteria. Dose reductions, delays, and discontinuations were applied according to the package inserts for TMZ and CPT-11. TMZ and CPT-11 were not restarted until the ANC $\geq$ 1,500/mm^2 and platelet count $\geq$ 100,000/mm^3. CPT-11 was not restarted until treatment-related diarrhea was fully resolved.

Objective assessments of overall response by the treating physicians were based on tumor assessment from MRI scans (CT if MRI was medically contraindicated) interpreted in the light of corticosteroid use, as suggested by Macdonald et al. [18], with appropriate support from the neurologic examination. Responses must have been confirmed on two sequential MRIs at least 1 month apart.

MGMT analysis

Immunohistochemistry was performed according to published methodology [19]. Briefly, tissue sections were incubated with monoclonal antibodies (MT3.1; Oncogene Research Products). Cytoplasmic-only and granular nuclear reactivity were considered negative. High expression was defined as $\geq$ 20% of tumor cell nuclei expressing detectable O^6-methylguanine-DNA methyltransferase (MGMT) protein; low expression was defined as less than 20% of nuclei expressing detectable MGMT.

Statistical analysis

Among patients newly diagnosed with GBM and treated with TMZ, Gilbert reported a response rate of 42% (95% confidence interval: 26, 59%) [20]. 39% of these patients have had only a biopsy at initial diagnosis. Given our expectation that significantly more than 39% of patients enrolled on the study would have only a biopsy a response rate on the low side of the confidence interval was used as a benchmark for hypothesis testing. More specifically, if the true response rate with CPT-11 plus TMZ was 26% or greater, there would be interest in formally incorporating this treatment regimen into a randomized phase III study. However, if the true response rate was 10% or less, there would definitely be no interest in further pursuing the new treatment regimen. Therefore, the study was designed to differentiate between a 10% (null hypothesis) and 26% response rate (alternative hypothesis). The study was conducted as a two-stage study with 21 and 20 patients in the first and second stage. If 3 or more of the first 21 patients responded to treatment, the second stage of patient accrual commenced. If 7 or more of the 41 patients (i.e., both stages combined) responded to treatment, the decision was made that the treatment regimen was worthy of further investigation. Otherwise, the treatment regimen was determined unworthy of further investigation. The type I and II error rate for this study was 0.10.

Efficacy (and safety) analyses included all patients who received at least one dose of drug. The number and proportion of patients who achieved an objective response (complete response [CR] or partial response [PR]) was summarized. PFS, defined as the time between study entry and the first occurrence of disease progression, disease, or death, and OS, defined as the time between study entry and death, were summarized by using the Kaplan–Meier method [21]. The logrank test was used to compare patient subgroups defined by MGMT status with respect to PFS and OS. Categorical data were analyzed by Fisher's exact test.

Toxicity prevalence was summarized by type and maximum grade experienced according to the National Cancer Institute's Common Toxicity Criteria version 3.0.

Results

Patient characteristics

Patient demographics and baseline disease characteristics are outlined in Table 1. A total of 42 patients (28 men and 14 women) were enrolled between March 2006 and July 2007 and received treatment.

Eighteen patients (43%) completed 3 cycles of TMZ and CPT-11. Twenty-two (52%) patients discontinued therapy because of disease progression (n = 15), or AEs (n = 7) after 1 or 2 cycles and went on immediately to radiotherapy plus adjuvant TMZ (75 mg/m^2/day for 42 days).

Response

The overall response rate was 19% (95% confidence interval: 8, 31%), which included 4 PRs during the first stage and 4 PRs during the second stage of the study. With 8 responders overall, the study's null hypothesis that the study's null hypothesis is rejected indicating that the treatment regimen is worthy of further investigation within this particular patient populations. The response rate in patients undergoing biopsy alone was 17%. In addition, 20 (50%) patients had stable disease (SD). Seven of these patients, who initially demonstrated an objective response or SD, progressed before completing all 3 cycles of TMZ and CPT-11.

Survival

Forty of the 42 patients progressed or died of their disease. Two patients were censored after loss to follow-up; one after completing two cycles and another after completing the entire treatment regimen. Median follow-up was 19.3 months for the entire population. Median progression-free survival was 3.1 months (95% CI, 1.4–8.7 months). Median overall survival was 13.8 months (95% CI, 8.6– 16.8 months). The PFS data and OS data are illustrated by a Kaplan–Meier curve in Figs. 1 and 2, respectively.

MGMT analysis

Twenty-five of 42 tumor samples were available for MGMT analysis. Of the 25 tumor samples available for MGMT analysis, low MGMT expression (<20% of tumor cells) was detected in 13 patients, and high MGMT expression was detected in 12 patients. Twenty-four of the 25 patients with a known MGMT level were assessable for response. The objective response rate (ORR) was 25% in 12 patients with low MGMT expression compared with 8% in 12 patients with high MGMT expression (Fisher's exact test *P*-value = 0.5901). The median PFS was 14 months for patients with low MGMT and 5 month for high MGMT (Logrank test *P*-value = 0.0643). The median OS was 21 months for patients with low MGMT and 15 months for patients with high MGMT levels (logrank test *P*-value = 0.3526). The difference in ORR, PFS, or OS for patients with low MGMT level compared to those with high MGMT level was not statistically significant.

Safety

All 42 patients were assessable for AEs with the treatment-related grades 3, 4, and 5 AEs detailed in Table 2. Grade 3 or 4 AEs were documented in 36% of patients. Twenty-nine percent of patients had any grade 3 or 4 hematologic AEs, 26% had grade 3 or 4 neutropenia, and 19% had grade 3 or 4 thrombocytopenia. Twenty-four percent of patients had any grade 3 or 4 non-hematologic AEs, with gastrointestinal AEs being the most common (12%), followed by infection (10%) and thrombosis (7%). The least common grade 3 or 4 AEs included pulmonary

AEs (5%), hypotension (5%), and elevated alanine transaminase (ALT) (2%). Two patients died of AEs, one of intracranial hemorrhage and one of renal failure as described below.

Dose reduction and treatment discontinuation

One patient (2%) required a dose reduction due to grade 3 diarrhea. Three patients (7%) required dose delays; grade 3 neutropenia-leukopenia-thrombocytopenia, grade 4 pulmonary infiltrates or pneumonitis, and grade 3 infection with grade 3 neutropenia-thrombocytopenia were responsible for each of these delays.

Seven patients (17%) discontinued therapy because of AEs as detailed in Table 3. Two patients discontinued therapy after experiencing grade 4 hematologic adverse events and clinically progressed while awaiting resolution of these events. Despite the absence of coagulation disorder or thrombocytopenia, one patient developed an intracranial hemorrhage and died on day 2 of the first treatment cycle. Four patients discontinued therapy after experiencing grade 4 hematologic adverse events along with gastrointestinal toxicities. Also, these four patients had a clinical course complicated by grade 3 or 4 infection, thrombosis, or hypotension. One of these four patients developed hypotension and died of renal failure. Thus, the combination of grade 3 or 4 hematologic AEs and grade 3 or 4 gastrointestinal AEs was near fatal or fatal in 4 (10%) patients.

Discussion

In the present study, TMZ in combination with CPT-11 demonstrated antitumor activity with a 19% ORR, whereby the study's null hypothesis was rejected indicating that the treatment regimen has anti-tumor activity and is worthy of further investigation. Three comparison studies investigating neoadjuvant TMZ using the standard 5-day regimen to treat GBM demonstrated response rates of 20% [22], 42% [20], and 52% [23]. Direct comparison of this study to the prior studies is difficult due to differences in the populations in terms of extent of resection, performance status, and other important variables although the vast majority (81%) of patients in our current trial only had a biopsy, putting this group at high risk for a bad outcome. Despite the differences in these populations, the results of the current study suggest an antitumor activity at least comparable to TMZ alone.

Combination TMZ and CPT-11 appears to be more toxic in comparison to TMZ alone. Two phase II trials performed by Friedman et al. [23] and Gilbert et al. [20] evaluated safety along with efficacy of neoadjuvant TMZ in MG. Also, a phase III trial performed by Stupp et al. [2] evaluated the safety and efficacy of adjuvant TMZ administered after radiotherapy. In all three studies, TMZ was administered on the same dosing regimen as performed in this study. When the hematologic toxicities are compared (Table 4), the combination of TMZ and CPT-11 appears to be more myelosuppressive than TMZ alone. With an increase in myelosuppression, it is not surprising that the occurrence of severe infection increased from 5 to 10% when CPT-11 was combined with TMZ. Although CPT-11 and TMZ are both associated with gastrointestinal adverse events, TMZ is most commonly associated with nausea/vomiting and constipation and CPT-11 is most commonly associated with diarrhea. When TMZ and CPT-11 were combined, grade 3 or 4 diarrhea occurred in 12% of patients, whereas grade 3 or 4 nausea/vomiting occurred in only 1% of patients with TMZ alone. It also appears that the combination of diarrhea or colitis/typhlitis associated with CPT-11 is a much more serious adverse event when combined with neutropenia and thrombocytopenia than nausea/vomiting or constipation associated with TMZ. Thus, the combination of TMZ and CPT-11 appears to be more toxic to both the hematopoietic and gastrointestinal system than TMZ alone.

Perhaps combining these two drugs using a different TMZ dosing regimen may prove to be more efficacious with less toxicity. Of note, we may have reduced efficacy by increasing the

time between TMZ dosing from the standard 28 to 42 days, a step necessary to minimize toxicity. Continuous TMZ administered at 75 mg/m^2/day × 7 day/week for 4 to 6 weeks is one reasonable alternative dosing regimen and has been tested in chemonaive GBM patients receiving concomitant radiotherapy in two separate clinical trials, one a phase II study [24] and the other a phase III study [2]. This dosing regimen is hypothesized to be more effective than the standard regimen for two reasons. First, since MGMT seems to be a major mechanism of resistance to TMZ [23,25], prolonged TMZ exposure, which leads to MGMT consumption, albeit not shown in brain tumors, may possibly overcome inherent tumoral chemoresistance [26]. Second, since the synergy between TMZ and CPT-11 seems schedule dependent, occurring when TMZ is administered within 5 days preceding CPT-11 [13,14], daily TMZ administration for 4 to 6 weeks would ensure that TMZ would precede each dose of CPT-11 and thus optimize this synergy.

When TMZ and CPT-11 were combined in our study regimen, no correlation between MGMT protein expression and response was seen. Prior studies have explored the relationship between MGMT protein expression or promoter methylation status and response in newly diagnosed MG or GBM. In two trials where patients were treated with the standard TMZ regimen (200 mg/m^2/day for 5 days every 28 days), low MGMT expression [23] and methylation of the MGMT promoter [27] positively correlated with response. This same relationship was seen in a 7-day-on/7-day-off TMZ regimen (150 mg/m^2 on days 1–7 and days 15–21 every 28 days) [28]. In contrast to these three studies, when TMZ was administered on a 3-week-on/1-week-off regimen (75 mg/m^2/day for 21 days every 28 days), no relationship between MGMT promoter methylation status and response was seen [29]. Our study also found no statistically significant relationship between MGMT protein expression and response. This suggests that this combination has activity independent of tumor MGMT, an explanation finding support in the research performed by Houghton et al. [13] when he showed that the antitumor activity of TMZ combined with CPT-11 is independent of MGMT in CNS xenografts including GBM. However, the response rate in low MGMT expressing tumors was 25% compared to 8% in high expressors, suggesting that statistical significance may not have been seen due to low patient numbers. The low patient numbers might also explain the statistically insignificant but biologically interesting observation of a median PFS of 14 vs. 5 months in low versus high MGMT expressors. A phase I trial of TMZ, CPT-11, and O^6-BG (an MGMT depletor) has been conducted [30], and a phase II trial of this three-drug regimen is needed to elucidate the role of MGMT and its relationship to the antitumor activity.

The results of the current phase II trial indicate that although TMZ plus CPT-11 is at least comparable in efficacy to TMZ alone, this combination appears more toxic and less well tolerated. Although the median OS was only 13.8 months which is slightly lower than in the Stupp study using the TMZ arm (2) this may be explained by the observation that only 19% of our patients underwent an actual resection. MGMT tumor expression does not seem to be predictive of response, albeit with the caveat of low patient numbers as detailed above, presumably since CPT-11 activity is not affected by MGMT although we only could do MGMT assays on 60% of the samples, similar to the experience of Hegi et al. [25]. Further exploration of CPT-11 in combination with a continuous, low-dose TMZ regimen may improve the efficacy of this combination without an incremental increase in toxicity particularly using every 2 week CPT-11 similar to the NABTC trial [17]. Furthermore, the rationale supporting the benefit of neoadjuvant chemotherapy remains controversial.

Acknowledgments

This study was supported by NINDS Grant 5P50 NS20023-25, NIH SPORE Grant 5P50 CA108786-4, NIH Merit Award R37 CA 011898-38 and by funds from Pfizer Pharmaceuticals, New York, New York; S. X. Jiang was supported by NIH Grant TL1 RR024126.

References

1. Weingart J, Grossman SA, Carson KA, Fisher JD, Delaney SM, Rosenblum ML, Olivi A, Judy K, Tatter SB, Dolan ME. Phase I trial of polifeprosan 20 with carmustine implant plus continuous infusion of intravenous O^6-benzylguanine in adults with recurrent malignant glioma: New approaches to Brain Tumor Therapy CNS Consortium trial. J Clin Oncol 2007;25:399–404.10.1200/JCO.2006.06.6290 [PubMed: 17264335]
2. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–996.10.1056/NEJMoa043330 [PubMed: 15758009]
3. Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, Brada M, Spence A, Hohl RJ, Shapiro W, Glantz M, Greenberg H, Selker RG, Vick NA, Rampling R, Friedman H, Phillips P, Bruner J, Yue N, Osoba D, Zaknoen S, Levin VA. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 2000;83:588–593.10.1054/bjoc.2000.1316 [PubMed: 10944597]
4. Yung WK, Prados MD, Yaya-Tur R, Rosenfeld SS, Brada M, Friedman HS, Albright R, Olson J, Chang SM, O'Neill AM, Friedman AH, Bruner J, Yue N, Dugan M, Zaknoen S, Levin VA. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. J Clin Oncol 1999;17:2762–2771. [PubMed: 10561351]
5. Batchelor TT, Gilbert MR, Supko JG, Carson KA, Nabors LB, Grossman SA, Lesser GJ, Mikkelsen T, Phuphanich S, NCNSC. Phase 2 study of weekly irinotecan in adults with recurrent malignant glioma: final report of NABTT 97-11. Neuro-oncology 2004;6:21–27.10.1215/S1152851703000218 [PubMed: 14769136]
6. Cloughesy TF, Filka E, Kuhn J, Nelson G, Kabbinavar F, Friedman H, Miller LL, Elfring GL. Two studies evaluating irinotecan treatment for recurrent malignant glioma using an every-3-week regimen. Cancer 2003;97:2381–2386.10.1002/cncr.11306 [PubMed: 12712460]
7. Friedman HS, Petros WP, Friedman AH, Schaaf LJ, Kerby T, Lawyer J, Parry M, Houghton PJ, Lovell S, Rasheed K, Cloughsey T, Stewart ES, Colvin OM, Provenzale JM, McLendon RE, Bigner DD, Cokgor I, Haglund M, Rich J, Ashley D, Malczyn J, Elfring GL, Miller LL. Irinotecan therapy in adults with recurrent or progressive malignant glioma. J Clin Oncol 1999;17:1516–1525. [PubMed: 10334539]
8. Raymond E, Fabbro M, Boige V, Rixe O, Frenay M, Vassal G, Faivre S, Sicard E, Germa C, Rodier JM, Vernillet L, Armand JP. Multicentre phase II study and pharmacokinetic analysis of irinotecan in chemotherapy-naive patients with glioblastoma. Ann Oncol 2003;14:603–614.10.1093/annonc/mdg159 [PubMed: 12649109]
9. Turner CD, Gururangan S, Eastwood J, Bottom K, Watral M, Beason R, McLendon RE, Friedman AH, Tourt-Uhlig S, Miller LL, Friedman HS. Phase II study of irinotecan (CPT-11) in children with high-risk malignant brain tumors: the Duke experience. Neuro-oncology 2002;4:102–108.10.1215/15228517-4-2-102 [PubMed: 11916501]
10. Gilbert MR, Supko JG, Batchelor T, Lesser G, Fisher JD, Piantadosi S, Grossman S. Phase I clinical and pharmacokinetic study of irinotecan in adults with recurrent malignant glioma. Clin Cancer Res 2003;9:2940–2949. [PubMed: 12912940]
11. Prados MD, Yung WK, Jaeckle KA, Robins HI, Mehta MP, Fine HA, Wen PY, Cloughesy TF, Chang SM, Nicholas MK, Schiff D, Greenberg HS, Junck L, Fink KL, Hess KR, Kuhn J. Phase 1 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American Brain Tumor Consortium study. Neuro-oncology 2004;6:44–54.10.1215/S1152851703000292 [PubMed: 14769140]
12. Newlands ES, Blackledge GR, Slack JA, Rustin GJ, Smith DB, Stuart NS, Quarterman CP, Hoffman R, Stevens MF, Brampton MH, et al. Phase I trial of temozolomide (CCRG 81045: M&B 39831: NSC 362856). Br J Cancer 1992;65:287–291. [PubMed: 1739631]
13. Houghton PJ, Stewart CF, Cheshire PJ, Richmond LB, Kirstein MN, Poquette CA, Tan M, Friedman HS, Brent TP. Antitumor activity of temozolomide combined with irinotecan is partly independent

of O^6-methylguanine-DNA methyltransferase and mismatch repair phenotypes in xenograft models. Clin Cancer Res 2000;6:4110–4118. [PubMed: 11051264]

14. Patel VJ, Elion GB, Houghton PJ, Keir S, Pegg AE, Johnson SP, Dolan ME, Bigner DD, Friedman HS. Schedule-dependent activity of temozolomide plus CPT-11 against a human central nervous system tumor-derived xenograft. Clin Cancer Res 2000;6:4154–4157. [PubMed: 11051270]
15. Pourquier P, Waltman JL, Urasaki Y, Loktionova NA, Pegg AE, Nitiss JL, Pommier Y. Topoisomerase I-mediated cytotoxicity of N-methyl-N′-nitro-N-nitrosoguanidine: trapping of topoisomerase I by the O^6-methylguanine. Cancer Res 2001;61:53–58. [PubMed: 11196197]
16. Reardon DA, Quinn JA, Rich JN, Desjardins A, Vredenburgh J, Gururangan S, Sathornsumetee S, Badruddoja M, McLendon R, Provenzale J, Herndon JE II, Dowell JM, Burkart JL, Newton HB, Friedman AH, Friedman HS. Phase I trial of irinotecan plus temozolomide in adults with recurrent malignant glioma. Cancer 2005;104:1478–1486.10.1002/cncr.21316 [PubMed: 16088964]
17. Loghin ME, Prados MD, Wen P, Junck L, Lieberman F, Fine H, Fink KL, Metha M, Kuhn J, Lamborn K, Chang SM, Cloughesy T, DeAngelis LM, Robins IH, Aldape KD, Yung WK. Phase I study of temozolomide and irinotecan for recurrent malignant gliomas in patients receiving enzyme-inducing anti-epileptic drugs: a North American Brain Tumor Consortium study. Clin Cancer Res 2007;13:7133–7138.10.1158/1078-0432.CCR-07-0874 [PubMed: 18056194]
18. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990;8:1277–1280. [PubMed: 2358840]
19. McLendon RE, Cleveland L, Pegram C, Bigner SH, Bigner DD, Friedman HS. Immunohistochemical detection of the DNA repair enzyme O^6-methylguanine-DNA methyltransferase in formalin-fixed, paraffin-embedded astrocytomas. Lab Investig 1998;78:643–644. [PubMed: 9605190]
20. Gilbert MR, Friedman HS, Kuttesch JF, Prados MD, Olson JJ, Reaman GH, Zaknoen SL. A phase II study of temozolomide in patients with newly diagnosed supratentorial malignant glioma before radiation therapy. Neuro-oncology 2002;4:261–267.10.1215/15228517-4-4-261 [PubMed: 12356356]
21. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:29–41.10.2307/2281868
22. Brada M, Ashley S, Dowe A, Gonsalves A, Huchet A, Pesce G, Reni M, Saran F, Wharram B, Wilkins M, Wilkins P. Neoadjuvant phase II multicentre study of new agents in patients with malignant glioma after minimal surgery. Report of a cohort of 187 patients treated with temozolomide. Ann Oncol 2005;16:942–949.10.1093/annonc/mdi183 [PubMed: 15870090]
23. Friedman HS, McLendon RE, Kerby T, Dugan M, Bigner SH, Henry AJ, Ashley DM, Krischer J, Lovell S, Rasheed K, Marchev F, Seman AJ, Cokgor I, Rich J, Stewart E, Colvin OM, Provenzale JM, Bigner DD, Haglund MM, Friedman AH, Modrich PL. DNA mismatch repair and O^6-alkylguanine-DNA alkyl-transferase analysis and response to temodal in newly diagnosed malignant glioma. J Clin Oncol 1998;16:3851–3857. [PubMed: 9850030]
24. Stupp R, Dietrich PY, Ostermann Kraljevic S, Pica A, Maillard I, Maeder P, Meuli R, Janzer R, Pizzolato G, Miralbell R, Porchet F, Regli L, de Tribolet N, Mirimanoff RO, Leyvraz S. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol 2002;20:1375–1382.10.1200/JCO.20.5.1375 [PubMed: 11870182]
25. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JEC, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC, Stupp R. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997–1003.10.1056/NEJMoa043331 [PubMed: 15758010]
26. Tolcher AW, Gerson SL, Denis L, Geyer C, Hammond LA, Patnaik A, Goetz AD, Schwartz G, Edwards T, Reyderman L, Statkevich P, Cutler DL, Rowinsky EK. Marked inactivation of O^6-alkylguanine-DNA alkyltransferase activity with protracted temozolomide schedules. Br J Cancer 2003;88:1004–1011.10.1038/sj.bjc.6600827 [PubMed: 12671695]
27. Paz MF, Yaya-Tur R, Rojas-Marcos I, Reynes G, Pollan M, Aguirre-Cruz L, Garcia-Lopez JL, Piquer J, Safont MJ, Balana C, Sanchez-Cespedes M, Garcia-Villanueva M, Arribas L, Esteller M. CpG island hypermethylation of the DNA repair enzyme methyltransferase predicts response to temozolomide in primary gliomas. Clin Cancer Res 2004;10:4933–4938.10.1158/1078-0432.CCR-04-0392 [PubMed: 15297393]

28. Chinot OL, Barrie M, Fuentes S, Eudes N, Lancelot S, Metellus P, Muracciole X, Braguer D, Ouafik L, Martin PM, Dufour H, Figarella-Branger D. Correlation between O^6-methylguanine-DNA methyltransferase and survival in inoperable newly diagnosed glioblastoma patients treated with neoadjuvant temozolomide. J Clin Oncol 2007;25:1470–1475.10.1200/JCO.2006.07.4807 [PubMed: 17442989]

29. Brandes AA, Tosoni A, Cavallo G, Bertorelle R, Gioia V, Franceschi E, Biscuola M, Blatt V, Crino L, Ermani M. Temozolomide 3 weeks on and 1 week off as first-line therapy for recurrent glioblastoma: phase II study from gruppo italiano cooperativo di neuro-oncologia (GICNO). Br J Cancer 2006;95:1155–1160.10.1038/sj.bjc.6603376 [PubMed: 17024124]

30. Quinn JA, Jiang SX, Reardon DA, Desjardins A, Vredenburgh JJ, Gururangan S, Sampson JH, McLendon RE, Herndon IJ, Friedman HS. Phase I trial of temozolomide (TMZ) plus irinotecan (CPT-11) plus O^6-benzylguanine (O6-BG) in adults with recurrent malignant glioma. Cancer. 2008 in press.

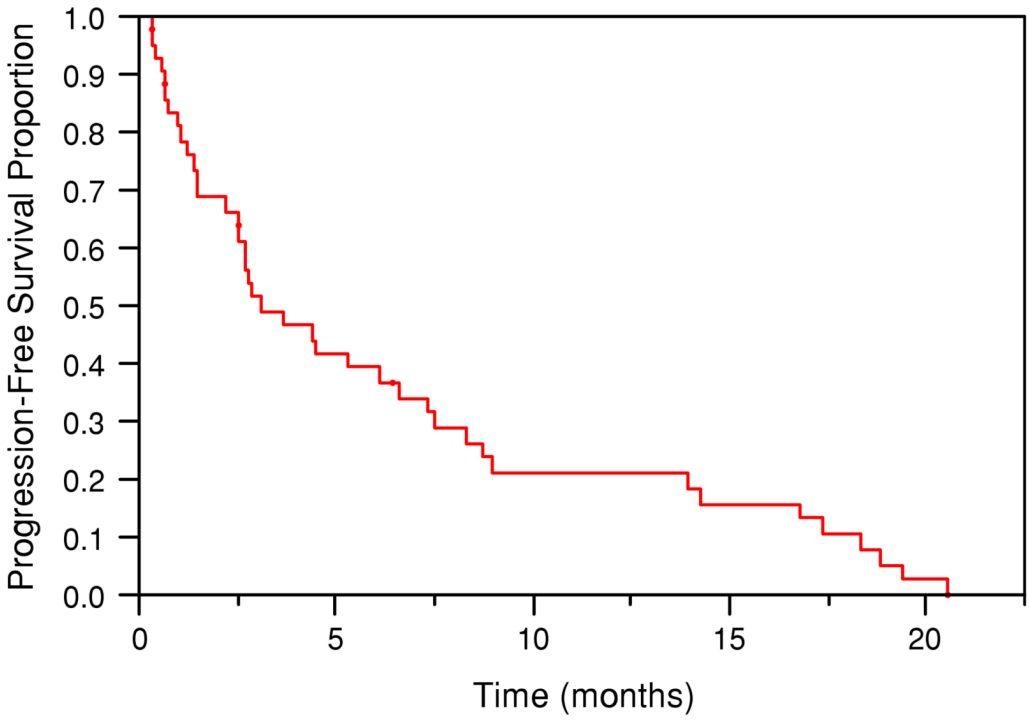

Fig. 1.
Progression-free survival

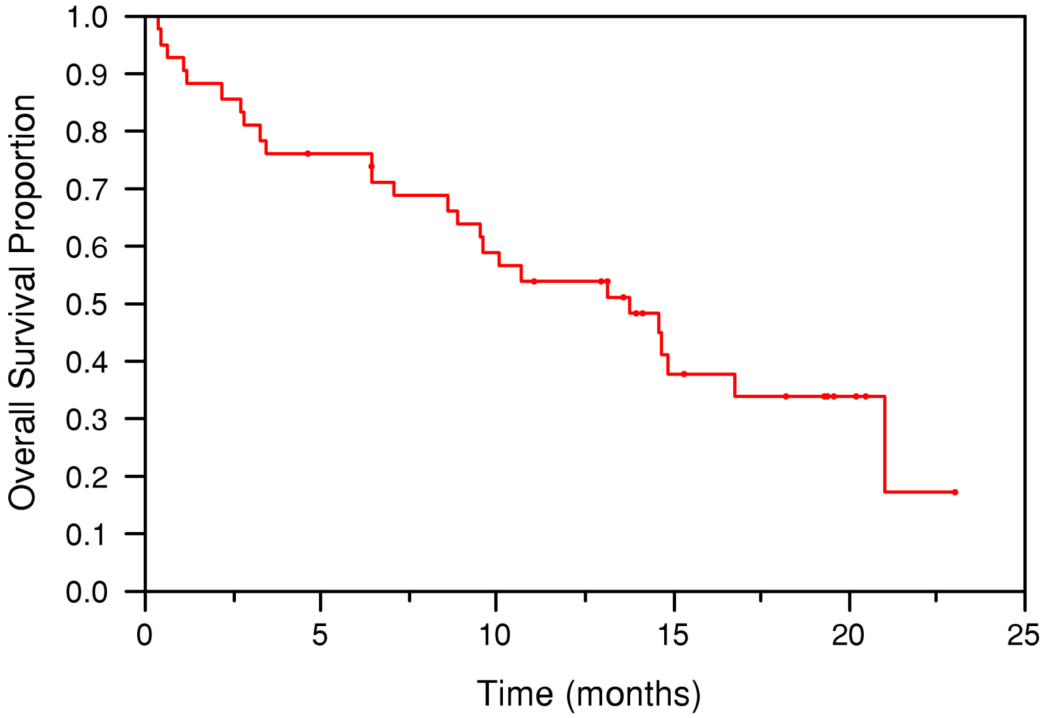

Fig. 2.
Overall survival

Table 1

Patient characteristics

Characteristics	Number of patients
Total number of patients	42
Median age in years, 57 (range, 37–71)	
Sex, *n* (%)	
Male	28 (66.7)
Female	14 (33.3)
KPS, *n* (%)	
70	11 (26%)
80	11 (26%)
90	14 (34%)
100	6 (14%)
Median time from diagnosis	
Months, .48 (range, .03–1.8 months)	
Days, 14.5 (range, 1–56 days)	
Surgery, *n* (%)	
Biopsy	34 (81%)
Subtotal resection	8 (19%)
EIAED, *n* (%)	
Yes	13 (31%)
No	29 (69%)

EIAED enzyme-inducing antiepileptic drugs

Table 2

Toxicities[a]

Adverse event	Grade 3		Grade 4		Grade 5		Grade 3 or 4	
	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%
Total toxicities	6	14	7	17	2	5	15	36
Hematologic	6	14	6	14			12	29
Anemia	1	2	–	–			1	2
Neutropenia	5	12	6	14			11	26
Leukopenia	3	7	4	10			7	17
Thrombocytopenia	4	10	4	10			8	19
Non-Hematologic	4	10	4	10	2	5	10	24
Gastrointestinal	4	10	3	7			7	17
Diarrhea	4	10	–	–			4	10
Dehydration	1	2	1	2			2	5
Colitis/typhlitis	–	–	2	5			2	5
Infection	1	2	3	7			4	10
Pulmonary	–	–	2	5			2	5
Pneumonitis/pulm. inf.	–	–	1	2			1	2
ARDS	–	–	1	2			1	2
Thrombosis	1	2	2	5			3	7
Hypotension	1	2	1	2			2	5
ALT	1	2	–	–			1	2
Renal failure	–	–	–	–	1	2	–	–
Cerebral CNS hemorrhage	–	–	–	–	1	2	–	–

ALT alanine transaminase, *ARDS* acute respiratory distress syndrome, *CNS* central nervous system, *pulm. Inf.*, pulmonary infiltrates

[a]Some patients had more than one type of toxicity, and totals therefore may exceed 42

Table 3

Grade 3, 4, or 5 AE requiring discontinuation of therapy

	Patient (grade of AE)						
	1	**2**	**3**	**4**	**5**	**6**	**7**
Hematologic							
Neutropenia	4	4		4	4	4	4
Thrombocytopenia		4		4	4	3	4
Non-Hematologic							
Gastrointestinal							
Diarrhea				3	3		3
Dehydration					3		4
Colitis/typhlitis				4		4	
Infection				4		4	
Thrombosis				4		4	
Hypotension					3		4
Renal failure							5
CNS hemorrhage			5				

Table 4

Percent of patients with grade 3 and 4 hematologic toxicity by study

Study	Agents	Thrombocytopenia		Neutropenia	
		Grade 3	Grade 4	Grade 3	Grade 4
Friedman et al. 1998 [23]	TMZ	3	5	3	0
Gilbert et al. 2002 [20]	TMZ	4	5	0	2
Quinn [30]	TMZ + CPT-11	10	10	12	14