

Bevacizumab Plus Irinotecan in Recurrent Glioblastoma Multiforme

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A B S T R A C T

Purpose

The prognosis for patients with recurrent glioblastoma multiforme is poor, with a median survival of 3 to 6 months. We performed a phase II trial of bevacizumab, a monoclonal antibody to vascular endothelial growth factor, in combination with irinotecan.

Patients and Methods

This phase II trial included two cohorts of patients. The initial cohort, comprising 23 patients, received bevacizumab at 10 mg/kg plus irinotecan every 2 weeks. The dose of irinotecan was based on the patient's anticonvulsant: Patients taking enzyme-inducing antiepileptic drugs (EIAEDs) received 340 mg/m², and patients not taking EIAEDs received 125 mg/m². After this regimen was deemed safe and effective, the irinotecan schedule was changed to an accepted brain tumor regimen of four doses in 6 weeks, in anticipation of a phase III randomized trial of irinotecan versus irinotecan and bevacizumab. The second cohort, comprising 12 patients, received bevacizumab 15 mg/kg every 21 days and irinotecan on days 1, 8, 22, and 29. Each cycle was 6 weeks long and concluded with patient evaluations, including magnetic resonance imaging.

Results

The 6-month progression-free survival among all 35 patients was 46% (95% CI, 32% to 66%). The 6-month overall survival was 77% (95% CI, 64% to 92%). Twenty of the 35 patients (57%; 95% CI, 39% to 74%) had at least a partial response. One patient developed a CNS hemorrhage, which occurred in his 10th cycle. Four patients developed thromboembolic complications (deep venous thrombosis and/or pulmonary emboli).

Conclusion

Bevacizumab and irinotecan is an effective treatment for recurrent glioblastoma multiforme and has moderate toxicity.

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INTRODUCTION

We performed a phase II trial for patients with recurrent glioblastoma multiforme (GBM), administering bevacizumab and irinotecan in combination therapy. A recent phase III randomized trial for newly diagnosed GBM demonstrated that radiation therapy with concurrent temozolomide, followed by 6 months of temozolomide was more efficacious than radiation therapy alone.¹ However, the subgroup of patients with methylated *MGMT* (O⁶-methylguanine-DNA methyltransferase) promoter demonstrated benefit from the combination therapy, as opposed to patients with unmethylated promoter who did not benefit from the addition of temozolomide.² Irinotecan is a topoisomerase 1 inhibitor, with a different mechanism of action than that of alkylating agents such as temozolo-

mid. Irinotecan has some activity in patients with recurrent GBM, with response rates of 0% to 17% reported for several trials.³⁻⁶ The activity of irinotecan is thus similar to that of other agents used for recurrent GBM.⁷

GBM has a high expression of vascular endothelial growth factor (VEGF),⁸ a protein that is produced by both tumor cells and stromal cells, including inflammatory cells.⁹ In human GBM specimens, the expression of VEGF is associated with a poor prognosis.¹⁰ Conversely, in a xenograft model, antibodies to VEGF have inhibited the growth of GBM.¹¹

Bevacizumab is a humanized immunoglobulin (Ig) G₁ monoclonal antibody that binds to and inhibits the activity of VEGF. Bevacizumab is synergistic with chemotherapy in colorectal, lung, and breast carcinomas.¹²⁻¹⁴ As a single agent, bevacizumab

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prolonged the time to progression for patients with metastatic renal cell carcinoma compared with that for patients receiving placebo.¹⁵

A preliminary report of the combination of bevacizumab and irinotecan for patients with malignant gliomas demonstrated an encouraging response rate of 43%.¹⁶ There were two treatment-related deaths, one caused by intracranial hemorrhage and one by intestinal perforation. Twenty-three of the patients included in this study were described in the initial report of the first 32 grade 3 or IV malignant glioma patients.¹⁷ We report the mature data for what is to our knowledge the first completed, prospectively designed phase II trial of bevacizumab and irinotecan for recurrent GBM.

PATIENTS AND METHODS

Patient Characteristics

Patients were at least 19 years of age and had histologically proven GBM for which they had received radiation therapy and temozolomide. All had experienced tumor progression, had measurable disease magnetic resonance imaging (MRI), and had recovered from their prior treatment. A minimum of 6 weeks was required from prior intracranial surgery, and a minimum of 4 weeks after radiation and other chemotherapeutic agents, unless there was evidence of tumor progression. The patients had to have an absolute neutrophil count more than 1,500 μL , a hematocrit more than 29%, and a platelet count more than 125,000 μL . The patients also had to have a serum creatinine less than 1.5 mg/dL, bilirubin less than 1.5 mg/dL, and serum AST less than 1.5 \times the upper limit of normal. A patient was excluded if there was evidence of hemorrhage on the baseline MRI; the patient had prior malignancy; the patient had previously been treated with bevacizumab; the patient was a female who was pregnant or nursing; or the patient had any other condition that would make the treatment unsafe. The protocol was reviewed and approved by the US Food and Drug Administration and the Duke University (Durham, NC) institutional review board. Each patient signed a written informed consent and met federal and institutional policies and regulations as a condition of registering for participation in this study.

Treatment

There were two cohorts of recurrent GBM patients. The first 23 patients received both bevacizumab and irinotecan every 14 days. The bevacizumab was administered at 10 mg/kg; the irinotecan was administered at 340 mg/m² for patients receiving enzyme-inducing antiepileptic drugs (EIAEDs) and 125 mg/m² for patients not receiving antiepileptic drugs or receiving non-EIAEDs. After the first cohort of patients was analyzed, and the regimen was determined to be active and safe, a second group, including 12 patients, was treated for two reasons: (1) to have an adequate number of GBM patients to make meaningful conclusions, and (2) to change the irinotecan schedule to an accepted GBM treatment of four doses in 6 weeks in anticipation of a randomized phase III trial. The second cohort received bevacizumab 15 mg/kg intravenously every 21 days, and the irinotecan was administered on days 1, 8, 22, and 29 of a 42-day cycle. The irinotecan was dosed at 350 mg/m² for patients receiving EIAEDs and 125 mg/m² for patients not receiving antiepileptic drugs or receiving non-EIAEDs. For those patients on dexamethasone, the dose had to be stable for at least 7 days before the first cycle, and efforts were made to maintain the same dose until the tumor assessment was done after the first cycle.

The irinotecan was administered over 90 minutes before the bevacizumab. The bevacizumab was administered over 90 minutes for the first dose, and if the patient had no adverse reactions, the second dose was administered over 60 minutes and all subsequent doses over 30 minutes. The patients had to have hematologic recovery as documented by an absolute neutrophil count more than 1,000 and platelets more than 100,000 before subsequent infusions. In addition, the AST enzyme level had to be less than 2.5 \times normal and creatinine less than 1.5 \times normal. In the first cohort of 23 patients, the protein-to-creatinine ratio in a spot urine specimen had to be less than 1.0

before re-treatment. In the second cohort of 12 patients, the spot urine protein-to-creatinine ratio had to be less than 3.5 before re-treatment.

Patients were allowed a one-time 25% dose reduction of irinotecan for grade 3 or 4 GI toxicity or a grade 4 hematologic toxicity. Patients were removed from protocol treatment for any of the following events: disease progression, patient withdrawal of consent, development of grade 2 or worse CNS hemorrhage or grade 4 nonhematologic toxicity, or determination by the investigators that the treatment regimen was unsafe.

Patient Evaluations

Within 14 days of initiating therapy, a full medical history was taken for all patients, and the patients underwent full physical and neurologic examinations, vital sign exam, Karnofsky status determination, CBC with differential, prothrombin time and partial thromboplastin time determinations, serum chemistry profile, urine test for protein-to-creatinine ratio, and a pregnancy test for any woman of child-bearing potential. Within 7 days of starting treatment, the patient underwent a contrast and a noncontrast brain MRI, and this MRI examination was repeated every 6 weeks during treatment. A CBC with differential, serum chemistry profile, and urine protein-to-creatinine ratio analysis were repeated every 2 weeks for the first cohort; the CBC with differential and serum chemistry profile were also performed before each irinotecan infusion; and the urine protein-to-creatinine ratio analysis was performed before each bevacizumab infusion in the second cohort. A full medical history and physical examination, including a full neurologic examination, were completed every 6 weeks. The National Cancer Institute Common Terminology Criteria, version 3.0, was used to evaluate the toxicities.

Treatment Response Evaluation

The response to therapy was determined by two investigators who measured the tumors independently and agreed on any discrepancies. The response to therapy was determined by MRI and neurologic examination. The investigators utilized the Macdonald criteria to evaluate the MRI.¹⁸ The criteria use the largest cross-sectional area of the postcontrast images and also took into account the dexamethasone dose and clinical findings. The investigators also evaluated the noncontrast T1 images and the T2 and fluid-attenuated inversion recovery (FLAIR) images. A partial response was determined if the contrasted images showed a greater than 50% decrease in the area of enhancement and stable or decreased T2 and FLAIR signal, provided that the patient was on a stable or decreased dose of dexamethasone and also was stable or improved clinically. A complete response was determined by the resolution of all measurable abnormalities on the contrast images, as well as by stable or decreased disease on T2 and FLAIR images for any patient who was on a stable or decreased dexamethasone dose and also was stable and improved clinically. Disease progression was defined as a greater than 25% increase in the area of enhancement, appearance of a new lesion, or deterioration in the patient's clinical status that was thought to be related to tumor progression. The patient was deemed to be stable if the criteria for a partial or complete response or tumor progression were not met and if there was no disease progression.

Statistical Considerations

Yung et al¹⁹ reported that the treatment of GBM patients in first relapse with temozolomide produced a 6-month progression-free survival (PFS) rate of 21%, with 95% CI ranging between 13% and 29%. These data were used as the historical basis for the design of this phase II study. If the true 6-month PFS rate with bevacizumab and irinotecan was at least 20%, there would be interest in further investigation of this combination chemotherapy treatment. However, if the true 6-month PFS rate was less than 5%, there would be no interest in further studying this treatment. With a sample size of 35 patients, the study was designed to differentiate between 6-month PFS rates of 5% and 20% with type I and II error rates of 0.074 and 0.093, respectively. If five or more of the 35 patients lived at least 6 months without disease progression, the treatment regimen would be considered worthy of further study.

Early stopping rules for unacceptable toxicity were defined for the occurrence of a grade 2 or worse CNS hemorrhage or grade 4 or 5 nonhematologic toxicity caused by the treatment. An unacceptable toxicity rate of 15% or less would not be cause for stopping the trial, whereas a rate of 40% or greater would signal that the trial should be stopped. A statistical hypothesis

differentiating between a 15% and a 40% rate of unacceptable toxicity was tested with type I and II error rates of 0.053 and 0.053, respectively.

RESULTS

Patient Characteristics

Thirty-five patients with histologically documented GBM were enrolled onto the trial. There were 22 men and 13 women, and the median age was 48 (range, 18 to 66 years). Every patient had completed external-beam radiation therapy with concurrent temozolomide. Three of the patients had experienced disease progression less than 12 weeks after radiation therapy, and all three had progression outside the radiation field. If these three patients are excluded from the analysis, the response rate, PFS, and overall survival reported below remain unchanged. Table 1 lists the relevant patient characteristics. EIAEDs were used by 15 (43%) of the 35 patients. There were no differences between the results for the patients who used EIAEDs and those for the non-EIAEDs patients. Likewise, there were no statistical differences between the results for the 23 patients treated in cohort 1 with every-other-week irinotecan plus 10 mg/kg of bevacizumab and the results for the 12 patients treated in cohort 2 with four doses of irinotecan in a 6-week cycle and bevacizumab at 15 mg/kg every 3 weeks.

PFS

The 6-month PFS was 46% (95% CI, 32% to 66%). The median PFS of the 35 GBM patients in the two cohorts was 24 weeks (95% CI, 18 to 36 weeks). There were no statistical differences between the two cohorts of patients. These PFS data are illustrated by the Kaplan-Meier curve in Figure 1.

Table 1. Patient Characteristics	
Characteristic	Value
No. of patients	35
Age, years	
Median	48
Range	18-66
Sex	
Male	22
Female	13
Karnofsky performance status, %	
< 70	3
70-80	19
90-100	13
Concomitant medications	
EIAED	15
Non-EIAED	14
No AEDs	6
Dexamethasone	22
No. of progressions	
Median	2
Range	1-5
Time from diagnosis, months	
Median	14
Range	3-56

Abbreviations: EIAED, enzyme-inducing antiepileptic drug; non-EIAED, non-enzyme-inducing antiepileptic drug; AED, antiepileptic drug.

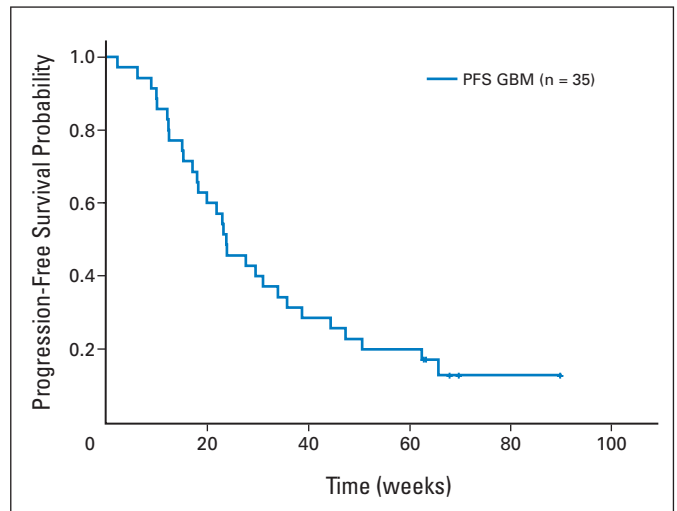


Fig 1. Kaplan-Meier progression-free survival (PFS). GBM, glioblastoma multiforme.

Overall Survival

The 6-month overall survival was 77% (95% CI, 64% to 92%). The median follow-up was 68 weeks (15.5 months). The median overall survival was 42 weeks (95% CI, 35 to 60 weeks). Overall survival is presented as a Kaplan-Meier curve in Figure 2.

Response

Twenty of the 35 patients (57%; 95% CI, 39% to 74%) had at least a partial response to the bevacizumab and irinotecan. Seven of the patients have completed a full year of therapy, and six of the seven had a hypometabolic 18-fluorodeoxyglucose (FDG) PET scan, or "cold" PET, suggesting no residual high-grade tumor after the year of therapy. Figures 3 and 4 are examples of the dramatic responses seen on this trial.

Toxicity

Eleven of the 35 patients had to stop receiving therapy secondary to toxicity. The reasons for which the patients discontinued therapy are listed in Table 2. Of the 11 patients, eight were in cohort 1 and three

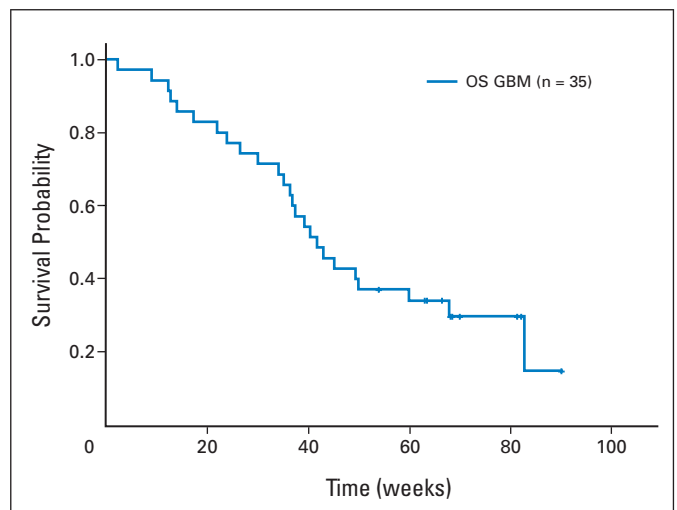


Fig 2. Kaplan-Meier overall survival (OS). GBM, glioblastoma multiforme.

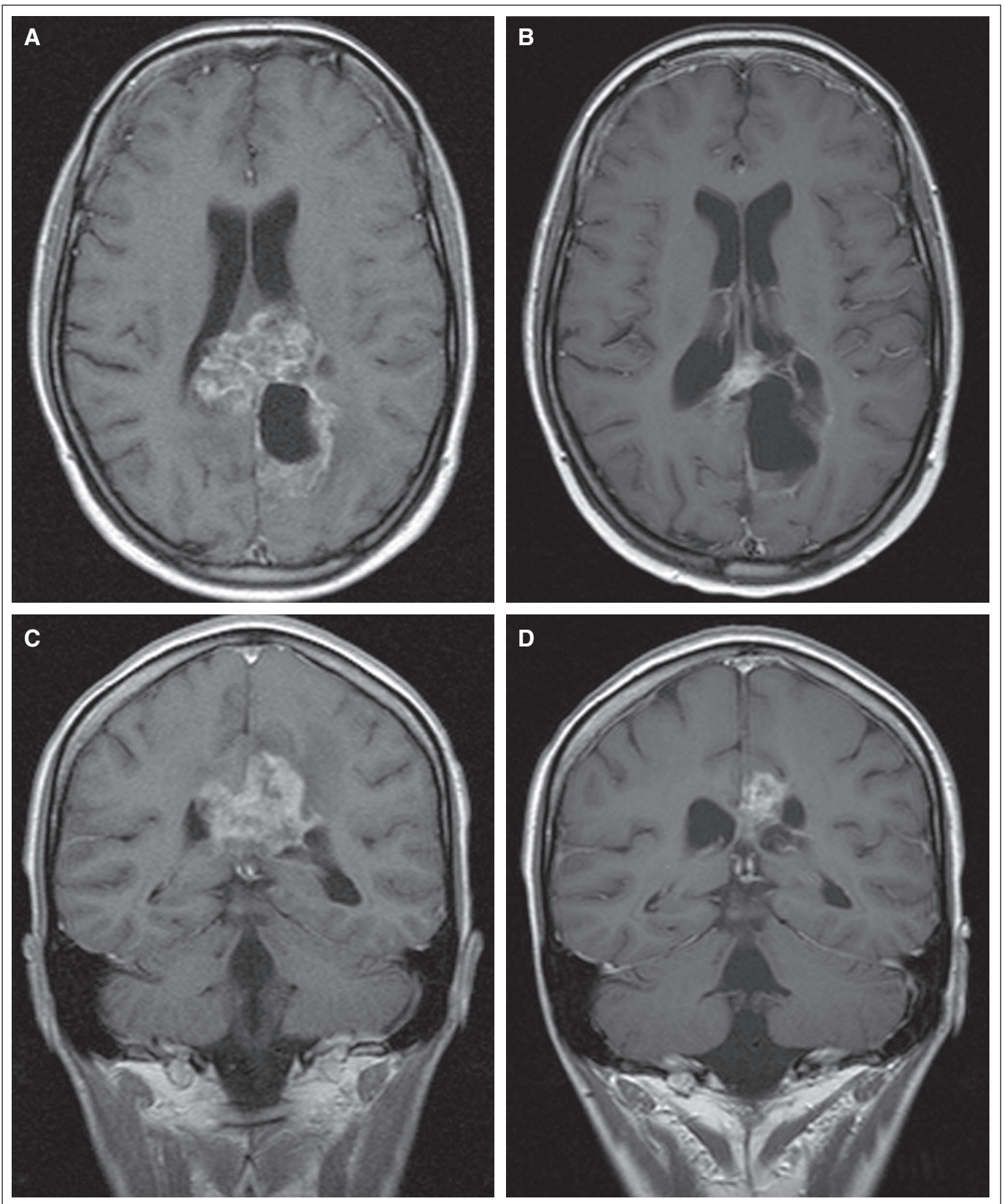


Fig 3. Baseline and post-treatment magnetic resonance imaging of patients treated with bevacizumab and irinotecan. Postcontrast axial and coronal T1-weighted magnetic resonance scans in a patient with glioblastoma multiforme at (A, B) baseline and (C, D) after four cycles of bevacizumab/irinotecan.

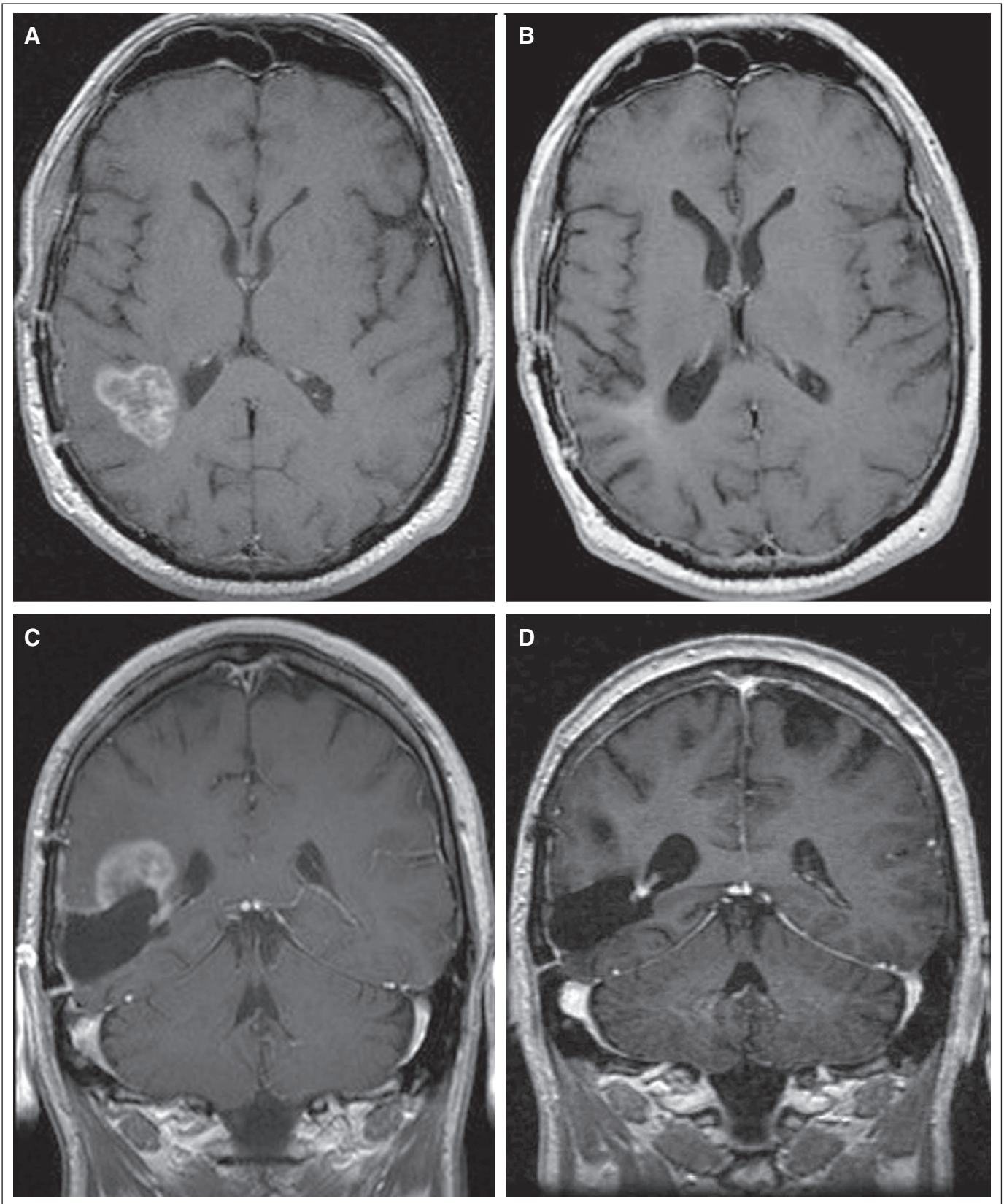


Fig 4. Baseline and post-treatment magnetic resonance imaging of a second patient treated with bevacizumab and irinotecan. Postcontrast axial and coronal T1-weighted magnetic resonance scans in a patient with a glioblastoma multiforme at (A, B) baseline and (C, D) after four cycles of bevacizumab/and irinotecan.

Table 2. Reasons for Patient Discontinuation From the Study and Duration of Patients on Study

Reason for Treatment Discontinuation	No. of Patients			Duration on Study (weeks)
	Cohort 1	Cohort 2	Total	
Disease progression	10	3	13	6-36
Thromboembolic complications	3	1	4	6-12
Required surgery for unrelated conditions	2	1	3	6-14
Grade 2 proteinuria	2	0	2	6, 8
Grade 2 fatigue and withdrew consent	1	3	4	6, 8
Sepsis	1	0	1	8
CNS hemorrhage	1	0	1	60
Leg ulcers	0	1	1	8

NOTE: Six of the 35 patients completed 54 weeks after treatment initiation, had a hypometabolic positron emission tomography scan that suggested no residual high-grade tumor, and stopped therapy. Cohort 1 received irinotecan and bevacizumab every 2 weeks, and cohort 2 received irinotecan on days 1, 8, 22, and 29 and bevacizumab on days 1 and 22.

were in cohort 2. Two of the patients in cohort 1 had grade 2 proteinuria, which required that the patients discontinue the study, but the protocol was amended for cohort 2 to allow up to grade 3 proteinuria before the patient had to come off study. There may be an increased risk of venous thromboembolic disease with this therapy; four patients had to stop therapy because of thromboembolic complications (deep venous thromboses and/or pulmonary emboli). In addition, three patients in cohort 2 and one patient in cohort 1 elected to stop the treatment, and all four cited fatigue as the reason. There were no patients in cohort 1 who required a dose reduction for GI toxicity, but four of the 12 in cohort 2 required a dose reduction for grade 3 or worse GI toxicity.

DISCUSSION

We report what is to our knowledge the first phase II trial of irinotecan and bevacizumab for the treatment of recurrent GBM.¹⁷ The study produced some notable results, including a striking improvement in the 6-month PFS compared with that of historical controls, as well as a high response rate. Importantly, there were no early CNS hemorrhages, but there was a suggestion of an increased risk of thromboembolic complications. Given the similar efficacy and increased toxicity with the schedules for cohorts 1 and 2, the schedule for cohort 1, with irinotecan and bevacizumab administered every other week, will be utilized in subsequent studies.

This study was conducted to improve the prognosis for recurrent GBM, for which response to therapy has generally been less than 20% and 6-month PFS less than 30%.¹⁹⁻²² Although temozolomide in combination with radiation therapy followed by 6 months of temozolomide has become the standard of care for newly diagnosed GBM,¹ temozolomide has shown only minimal activity for recurrent GBM in patients who have received no chemotherapy or a nitrosourea-based regimen. In the trial reported by Yung et al,¹⁹ the response rate was 8% and the 6-month PFS 21%. In addition, the 6-month overall survival with bevacizumab and irinotecan was improved compared with temozolomide: 77% versus 60% respectively. Our trial of bevacizumab and irinotecan also compares favorably with the results detailed by Wong et al,⁷ which represents patients with recurrent GBM, who were treated on one of eight different chemotherapy trials. Comparison of the current

results show a 6-month PFS and median PFS in patients with GBM of 43% and 24 weeks, compared with the Wong et al results of 15% and 9 weeks, respectively, in patients with GBM. The 1-year overall survival is improved in our trial of bevacizumab and irinotecan compared with the Wong et al results: 37% versus 21%, respectively. Temozolomide in combination with other agents such as irinotecan, etoposide, or erlotinib has produced modest improvements in the response rates and survival compared with historical controls of temozolomide alone,²³⁻²⁵ but not as dramatic as bevacizumab and irinotecan.

Because the majority of patients fail to respond to temozolomide in the up-front or recurrent disease setting, clearly, new regimens are needed for the more formidable recurrent GBM. One approach has been to administer nitrosoureas, which are also alkylating agents, and for which the mechanisms of resistance are similar to those encountered with temozolomide therapy, particularly, the resistance enzyme MGMT. As with single-agent temozolomide, nitrosoureas alone produce response rates of less than 10%, 6-month PFS rates of less than 20%, and median survivals of 6 to 12 weeks.²⁶ However, nitrosoureas in combination with procarbazine and vincristine have resulted in small improvements in response rates and survival.²¹ Nitrosoureas in combination with irinotecan have also produced similar, small increments in response rates and survival.²⁷

Topoisomerase 1 inhibitors, such as irinotecan and topotecan, have a different mechanism of cytotoxicity from that of alkylating agents. In addition, topoisomerase 1 inhibitors are not affected by the resistance enzyme MGMT. Therefore, topoisomerase 1 inhibitors are reasonable therapeutic options for recurrent GBM after failure of alkylating agents. Topoisomerase 1 inhibitors have excellent penetration through the blood-brain barrier, but the treatment results for glioblastomas have been disappointing. For example, the rates of response to single-agent irinotecan range from 0% to 17%, the 6-month PFS rates are consistently less than 20%, and median survival is less than 12 weeks.³⁻⁶ The reasons for the improved efficacy with the combination of irinotecan and bevacizumab are unclear. There are a number of potential mechanisms to explain the results, two of which may be particularly important. GBM is similar to other tumors, with a stem-like cell compartment as well as more differentiated tumor cells. Chemotherapy may be active against more differentiated cells but may not

affect the tumor stem cells.²⁸ Recently, Bao et al²⁹ demonstrated that bevacizumab suppresses the proangiogenic effect of glioma stem cells derived from human glioblastoma tumors and xenografts. Therefore, the combination of bevacizumab and irinotecan would treat both cellular compartments, the glioma stem cells and the more differentiated cells.

Another potential mechanism is normalization of the tumor vasculature as proposed by Jain et al.³⁰⁻³² Tumor angiogenesis produces abnormal vessels with increased tortuosity. The resultant high interstitial pressure produces hypoxia and a growth advantage for tumor cells.³⁰ In addition, the elevated interstitial pressure limits perfusion of chemotherapeutic agents to the tumor cells.³¹ Also, chemotherapeutic agents and radiation therapy are not as effective in areas of hypoxia.³² In summary, the efficacy seen with the combination of bevacizumab and irinotecan could be explained by an antitumor stem-cell effect by bevacizumab and an anti-differentiated glioma tumor cell effect by irinotecan, as well as normalization of tumor vasculature, resulting in decreased interstitial pressure, less hypoxia, and increased delivery of irinotecan to the tumor.

In conclusion, the combination of bevacizumab and irinotecan was strikingly active against recurrent GBM. The toxicity was significant but acceptable, given the extremely poor prognosis of recurrent GBM. Further studies are needed to optimize the use of bevacizumab in glioblastoma patients and further improve their survival. A phase II randomized trial of bevacizumab alone versus bevacizumab and irinotecan in recurrent GBM is ongoing. The addition of bevacizumab to the initial treatment of GBM patients may have the greatest impact on improving survival.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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