Published OnlineFirst April 29, 2011; DOI: 10.1158/1078-0432.CCR-11-0120

Cancer Therapy: Clinical

Clinical Cancer Research

The Addition of Bevacizumab to Standard Radiation Therapy and Temozolomide Followed by Bevacizumab, Temozolomide, and Irinotecan for Newly Diagnosed Glioblastoma

James J. Vredenburgh[4], Annick Desjardins[2], David A. Reardon[1,3], Katherine B. Peters[2], James E. Herndon II[6], Jennifer Marcello[6], John P. Kirkpatrick[5], John H. Sampson[1], Leighann Bailey[1], Stevie Threatt[1], Allan H. Friedman[1], Darell D. Bigner[4], and Henry S. Friedman[1,3]

Abstract

Purpose: To determine if the addition of bevacizumab to radiation therapy and temozolomide, followed by bevacizumab, temozolomide, and irinotecan, for newly diagnosed glioblastoma patients is safe and effective.

Experimental Design: A total of 75 patients with newly diagnosed glioblastoma were enrolled in the phase II trial that investigated the addition of bevacizumab to standard radiation therapy and daily temozolomide followed by the addition of bevacizumab and irinotecan to adjuvant temozolomide. The bevacizumab was given at 10 mg/kg every 14 days beginning a minimum of 4 weeks postcraniotomy. Two weeks after radiation therapy, the patients began 6 to 12 cycles of 5-day temozolomide with bevacizumab and irinotecan every 14 days. The primary endpoint was the proportion of patients alive 16 months after informed consent.

Results: The therapy had moderate toxicity. Three patients, one of whom had a grade 2 central nervous system hemorrhage, came off study during radiation therapy. Seventy patients started the postradiation therapy, and 16 (23%) terminated this adjuvant therapy early because of toxicity. The median overall survival was 21.2 months (95% CI: 17.2–25.4), and 65% of the patients were alive at 16 months (95% CI: 53.4–74.9). The median progression-free survival was 14.2 months (95% CI: 12–16).

Conclusion: The addition of bevacizumab to standard radiation therapy and temozolomide, followed by bevacizumab, irinotecan, and temozolomide, for the treatment of newly diagnosed glioblastoma has moderate toxicity and may improve efficacy compared with historical controls. The results from phase III trials are required before the role of bevacizumab for newly diagnosed glioblastoma is established. *Clin Cancer Res; 17(12); 4119–24. ©2011 AACR.*

Introduction

Glioblastoma is a devastating malignancy, with deleterious consequences on patients' quality of life and a poor survival rate. There are approximately 14,000 new cases of glioblastoma diagnosed in the United States annually (1). The prognosis remains poor, with a median survival of 12 to 18 months (2–4). The addition of temozolomide to radiation therapy has improved the survival and has become the standard of care for newly diagnosed glioblastoma (4). For patients who underwent a surgical resection, the median survival for patients treated with radiation therapy and daily temozolomide followed by 6 months of adjuvant temozolomide was 15.8 months (4). Importantly, the 5-year survival was improved with the addition of temozolomide, with 9.8% of patients alive in the combination chemoradiation therapy group compared 1.9% in the radiation therapy group (5).

Further advances in the survival of patients with glioblastoma must exploit tumor biology. The tumor microenvironment is quite aberrant in glioblastoma, with high interstitial pressure, low pH, and hypoxia, all of which favor tumor development, as well as resistance to chemotherapy and radiation therapy (6). One of the primary mediators of the tumor microenvironment is VEGF (7, 8). Glioblastomas have the highest levels of VEGF among malignancies (9). In addition, VEGF levels seem to be prognostic, with higher levels portending a poor prognosis (10).

Bevacizumab is a humanized monoclonal antibody to VEGF. It is an active treatment agent for recurrent glioblastoma (11–13). In a randomized phase II trial of bevacizumab or bevacizumab with irinotecan, both groups showed a higher response rate and 6-month

Authors' Affiliations: Departments of [1]Surgery, [2]Neurology, [3]Pediatrics, [4]Medicine, [5]Radiation Oncology, and [6]Cancer Center Biostatistics, Duke University Medical Center, Durham, North Carolina

Corresponding Author: James J. Vredenburgh, The Preston Robert Tisch Brain Tumor Center at Duke, Box 3624, Duke University Medical Center, Durham, NC 27710. Phone: 919-668-2993; Fax: 919-684-6673; E-mail: vrede001@mc.duke.edu

doi: 10.1158/1078-0432.CCR-11-0120

Published OnlineFirst April 29, 2011; DOI: 10.1158/1078-0432.CCR-11-0120

Translational Relevance

Bevacizumab and irinotecan are active against recurrent glioblastoma. This article reports on the addition of bevacizumab to standard radiation therapy and daily temozolomide, followed by temozolomide, bevacizumab, and irinotecan. The current trial is a logical next step in the investigation of inhibitors of vascular endothelial growth factor for the treatment of glioblastoma by moving the bevacizumab/irinotecan to the newly diagnosed setting. The current trial reports on important safety and efficacy results. Both the progression-free and overall survival rates are prolonged compared with historical controls. Given the limitations of single institution phase II trials, the ongoing phase III randomized, placebo-controlled bevacizumab trials are essential to understand the role of bevacizumab for newly diagnosed glioblastoma.

progression-free survival than historical controls (11). The original recurrent glioblastoma studies that investigated bevacizumab were in combination with irinotecan, so irinotecan was added to the adjuvant bevacizumab and temozolomide in this study to maximize efficacy. Also, the phase II randomized study of bevacizumab or bevacizumab and irinotecan in recurrent glioblastoma patients reported higher response rates and 6-month progression-free survivals with the combination (11). The current trial was designed to incorporate an anti-VEGF therapy into the treatment of newly diagnosed glioblastoma patients. In addition, irinotecan was added to adjuvant temozolomide with the goal of synergizing a topoisomerase I inhibitor with an alkylating agent.

Patients and Methods

Patients

Seventy-five newly diagnosed glioblastoma patients were enrolled in the trial and had received no therapy for their tumor besides surgical resection. Patients had a Karnofsky performance status (KPS) of 60% or greater and were 18 years or older. Patients enrolled for a minimum of 2 weeks but not more than 6 weeks from their last surgical procedure. Eligibility required adequate hematologic and organ function. Patients had uridine glucoronosyl transferase (UGT) genotyping. Patients with grade 2 or greater central nervous system (CNS) hemorrhage on their baseline MRI were excluded. All patients gave their informed consent, and the protocol was approved by the Duke Institutional Review Board.

Treatment

Surgery. The protocol did not mandate the type of surgery; however, patients who underwent only biopsy were enrolled in a separate trial for unresectable patients. Patients were evaluated following craniotomy and were required to have fully recovered from their last surgical procedure.

Radiation therapy. Patients received radiation therapy according to standard Radiation Therapy Oncology Group guidelines for a glioblastoma beginning 2 to 6 weeks after their craniotomy. The primary field was treated with a dose of 50.4 Gy in 1.8 Gy daily fractions, followed by a boost of 9 Gy also at 1.8 Gy daily fractions. The total dose was 59.4 Gy, delivered over 33 fractions. The details about the radiation and toxicity have been reported (14).

Temozolomide during radiation therapy. Patients took daily temozolomide at 75 mg/m^2/d throughout the course of radiation therapy. Temozolomide was taken 1 hour prior to the radiation therapy. Patients had a complete blood cell count weekly and serum chemistries every other week during radiation therapy. Temozolomide was held if the patient developed grade 3 or greater thrombocytopenia, grade 4 or greater neutropenia, or grade 4 or greater nonhematologic toxicity caused by temozolomide. Temozolomide was restarted at 50 mg/m^2/d when the absolute neutrophil count 1,500 or greater, platelet count 125,000 or greater, aspartate aminotransferase and total bilirubin levels less than 1.5 times the upper limits of normal, and the serum creatinine level of 1.5 mg/dL or less. If the patient had recurrent toxicity as specified above at 50 mg/m^2/d, temozolomide was held for the duration of radiation therapy.

Bevacizumab. Bevacizumab was administered every 14 days at a dose of 10 mg/kg, beginning at a minimum of 28 days after the craniotomy and was given during the radiation therapy. Bevacizumab was held for any grade 3 or greater bevacizumab-related adverse events until the toxicity resolved to grade 1 or less. Bevacizumab was discontinued for grade 2 or greater pulmonary or CNS hemorrhage, or any grade 4 bevacizumab-related adverse event.

Adjuvant temozolomide, bevacizumab, and irinotecan. Two weeks following the completion of radiation therapy, the patient underwent reevaluation including an MRI of the brain. As long as there was no evidence of tumor progression and all treatment-related toxicities had resolved to grade 1 or less, the patient proceeded with 6 to 12 months of adjuvant temozolomide, bevacizumab, and irinotecan. Temozolomide was dosed at 200 mg/m^2/d, day 1 through 5 of each 28-day cycle. Bevacizumab was dosed at 10 mg/kg every 14 days. Irinotecan was dosed every 14 days at 125 mg/m^2 for patients not on an enzyme-inducing antiepileptic drug (EIAED). Irinotecan was dosed at 340 mg/m^2 for patients on an EIAED. Patients homozygous for the UGT 6/6 alleles or heterozygous for the 6/7 alleles received full-dose irinotecan. Patients homozygous for the UGT 7/7 alleles received reduced dose irinotecan, those not on EIAEDs received 75 mg/m^2, and patients on EIAEDs received 275 mg/m^2 every 2 weeks. Each cycle was of 28 days. Subsequent cycles were started when patients met re-treatment criteria including an absolute neutrophil count of 1,000 cells/μL or greater, platelet count more than 100,000/μL, aspartate aminotransferase and bilirubin levels less than 1.5 times the upper limits of normal and a

Published OnlineFirst April 29, 2011; DOI: 10.1158/1078-0432.CCR-11-0120

serum creatinine level of 1.5 mg/dL or less, and resolution of all treatment-related toxicities to less than grade 1.

Evaluation procedures

Patients had a complete blood cell count with differential weekly, complete metabolic panel and blood pressure check every 2 weeks, and a urinalysis with a protein-to-creatinine ratio every 4 weeks. Every 8 weeks, they also underwent a physical examination, MRI of the brain, and toxicity assessment. MRI scans were evaluated using standard response assessment in neuro-oncology (RANO) criteria (15), such that every image in each series was evaluated. In addition to MRI assessments, clinical status, corticosteroid dose, and KPS were determined at each evaluation. Study investigators used the constellation of clinical findings and MRIs to determine progression. The RANO criteria define progression as clinical deterioration not attributable to concurrent medications or conditions, as well as increase in the postcontrast or T2/FLAIR nonenhancing lesions.

Treatment duration

The protocol was originally written for six 28-day cycles of adjuvant therapy. After the protocol was begun, some patients requested continuing for a total of 12 cycles. The protocol was amended so that the patients had the choice of continuing their adjuvant therapy to complete a full 12 cycles or to stop at 6 cycles.

Statistics

Efficacy assessments for the study regimen were based on assessment from the time of consent to participate on the trial, and the analysis was intent to treat. The primary endpoint and basis for sample size calculation were the proportion of patients alive 16 months after protocol enrollment based on a median survival of 15.8 months for resected patients treated with standard treatment (4). If the true proportion of survivors was 45% or less, then the study treatment regimen would not be considered worthy of further development without modification. However, if the true proportion of survivors was 60% or greater, then there would be interest in further evaluating the study regimen. The Kaplan–Meier estimator was used to describe the overall and progression-free survival of patients treated with the combination chemotherapy treatment.

The effect of various patient-specific prognostic factors on overall and progression-free survival was examined using a series of Cox models each with a single predictor. HRs and associated Wald χ^2 test results are reported. One of the patient-specific prognostic factors was the recursive partitioning analysis (RPA) class, developed and verified by the RTOG (16).

A landmark analysis was conducted to compare survival outcomes between study patients who received 6 cycles of temozolomide/bevacizumab/irinotecan and those who received more than 6 cycles. For this analysis, overall and progression free survival was computed from the time of the sixth cycle for all patients who completed at least 6 cycles without evidence of progression.

Table 1. Patient characteristics

Characteristic	Total (*n*)
Total	75 patients
Male/female	45/30
Median age	55.6 (range: 19–78)
Gross total resection/subtotal resection	40/35
KPS	
70–80	22
90–100	53
Corticosteroid use	
Yes	53
No	22
Median dose of dexamethasone	4 mg (range: 0–40 mg)
Antiepileptic drug	
Yes	63
No	12
EIAED vs. non-EIAED	23/40
Median number of days from craniotomy to initiation of radiation therapy	28 (range: 17–55)

Abbreviations: KPS, Karnofsky performance status; EIAED, enzyme-inducing antiepileptic drug.

Results

Patient characteristics

The initial 75 patients enrolled in the trial are included in this survival analysis, with the data cutoff May 13, 2010. All patients had a minimum follow-up of 18 months. Patients enrolled between April 15, 2007, and September 4, 2008. Patient characteristics are listed in Table 1.

Overall survival

The primary endpoint of the trial was the proportion of patients alive 16 months after consenting to the clinical trial for their newly diagnosed glioblastoma. The median follow-up was 23.1 months (95% CI: 21.7–26.1). The median time from signing consent to starting therapy was 7 days. Sixty-five percent (95% CI: 53.4–74.9) of the patients were alive 16 months after signing informed consent. The median overall survival was 21.2 months (95% CI: 17.2–25.4). The 1-year survival rate was 78.7% (95% CI: 67.6–86.3), and the 2-year survival rate was 44.9% (95% CI: 32.7–56.5). Figure 1 shows the Kaplan-Meier overall and progression-free survival curves.

Progression-free survival

The median progression-free survival was 14.2 months (95% CI: 12–16). The 1-year progression-free survival rate was 62.7% (95% CI: 50.7–72.5), and the 2-year progression-free survival rate was 13.3% (95% CI: 6.1–23.3).

Published OnlineFirst April 29, 2011; DOI: 10.1158/1078-0432.CCR-11-0120

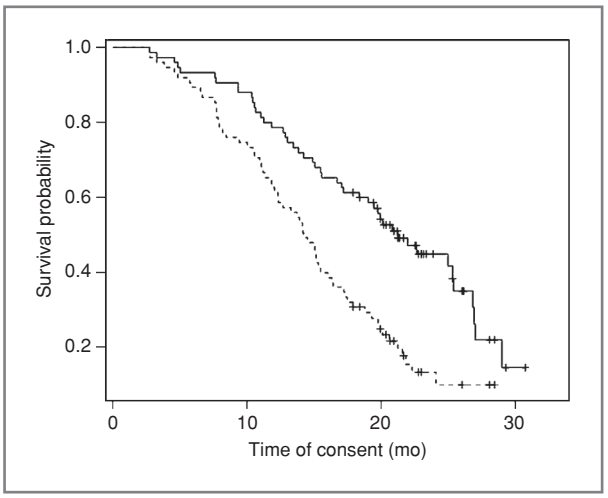

Figure 1. Progression-free survival and overall survival from time of consent.

Table 2. Toxicity during temozolomide, bevacizumab, and irinotecan

Reasons patients were removed from protocol treatment	*n* (%)
Recurrent grade 4 thrombocytopenia	2 (2.9)
Deep vein thrombosis/pulmonary embolism	4 (5.7)
Gastrointestinal toxicity	
Bowel perforation	1 (1.4)
Rectal abscess	1 (1.4)
Sepsis	1 (1.4)
Fatigue with decreased KPS	5 (7.1)
Pneumocystis carinii pneumonia	1 (1.4)
Optic neuritis	1 (1.4)

Abbreviation: KPS, Karnofsky performance status.

Overall survival from the time of progression

Following documented tumor progression, the median overall survival was 5 months (95% CI: 2.1–7.8), with a range of 1 month to 27+ months. Patients were treated with a number of different regimens at the time of progression, the majority included bevacizumab.

Toxicity during combined radiation therapy and daily temozolomide and bevacizumab

The addition of bevacizumab to radiation therapy and daily temozolomide had minimal toxicity. Seventy-two of the 75 patients (96%) completed the radiation therapy, whereas 3 patients terminated protocol-prescribed radiation treatment early for different reasons—first patient had a grade 2 CNS hemorrhage; second patient had pancytopenia; and the third patient had a symptomatic pulmonary embolus. All 3 patients subsequently completed their radiation therapy off protocol. In addition to the 3 patients who came off study during their radiation therapy, 3 patients, including 2 patients with grade 4 thrombocytopenia and 1 patient with grade 4 neutropenia, had their daily temozolomide held for hematologic toxicity. Temozolomide was restarted at a reduced dose for these patients and they were able to complete planned radiation therapy including co-administration of temozolomide for more than 75% of planned days. The mean number of doses of bevacizumab during radiation therapy was 3, with a range of 1 to 4. In addition to the 3 patients who came off of study during the radiation therapy, the 2 patients with grade 4 thrombocytopenia had their bevacizumab held and another patient had a dose of bevacizumab held to repair a stitch abscess. Two patients had tumor progression following radiation therapy, so they never started the adjuvant chemotherapy and bevacizumab.

Toxicity during adjuvant temozolomide, bevacizumab, and irinotecan therapy

Patients received between 6 and 12 cycles of temozolomide, bevacizumab, and irinotecan on study. Six patients (8%) developed grade 4 thrombocytopenia, and an additional 4 patients (5%) developed grade 4 neutropenia. There were 2 toxic deaths, 1 from neutropenic sepsis and 1 from a pulmonary embolism. In addition, 16 of the 70 patients (23%) who started adjuvant temozolomide, bevacizumab, and irinotecan terminated protocol treatment of toxicity, including 1 bowel perforation, likely attributable to the bevacizumab. The grade 4 hematologic toxicities and reasons the patients came off study during the adjuvant chemotherapy are listed in Table 2.

Prognostic factors

We investigated a number of patient-specific prognostic factors to determine whether they predicted progression-free or overall survival. An analysis of tumor-specific prognostic factors, such as O^6-Methylguanine-DNA methyltransferase promoter methylation status, is underway and the results will be reported separately. The list of prognostic factors examined in the analysis included age (as a continuous variable), age group ($\geq$50 vs. <50), antiepileptic drug (EIAED vs. non-EIAED; EIAED vs. none; non-EIAED vs. none; and EIAED vs. non-EIAED/none), steroid (dexamethasone vs. none), steroid dose (daily total), UGT1A1 genotype (homozygous 7/7 vs. homozygous 6/6 or heterozygous 6/7), KPS (continuous), KPS group (<90 vs. $\geq$90) RPA class (4 vs. 3), resection type (subtotal vs. gross total), time from surgery to XRT (weeks), and time from surgery to XRT (<4 vs. $\geq$ 4 weeks). Greater age, subtotal resection, and RPA class 4 were significant predictors of poorer overall survival. Dexamethasone usage was a significant predictor of poorer progression-free survival, with the effect of uncategorized age, poorer KPS, and subtotal resection trending toward statistical significance. Table 3 provides a list of the clinical characteristics associated with overall and progression-free survival.

Six cycles versus 12 cycles

A landmark analysis was done to determine whether there were any differences in overall survival or progres-

Published OnlineFirst April 29, 2011; DOI: 10.1158/1078-0432.CCR-11-0120

Table 3. Cox models predicting overall and progression-free survival

Covariate	Overall survival		Progression-free survival	
	HR (95% CI)	Wald χ^2 *P*	HR (95% CI)	Wald χ^2 *P*
Age at consent (continuous)	1.05 (1.02–1.08)	0.01	1.02 (1–1.04)	0.09
Age group (≥50 vs. <50)	2.06 (0.99–4.29)	0.05	1.52 (0.84–2.72)	0.16
Steroid (dexamethasone vs. none)	1.63 (0.81–3.3)	0.17	1.94 (1.08–3.49)	0.02
KPS (continuous)	0.96 (0.93–1)	0.05	0.97 (0.94–1)	0.06
RPA class (4 vs. 3)	2.37 (1.06–5.33)	0.04	1.73 (0.92–3.27)	0.09
Resection type (subtotal vs. gross total)	2.02 (1.09–3.72)	0.02	1.63 (0.98–2.7)	0.06

Abbreviations: KPS, Karnofsky performance status; RPA, recursive partitioning analysis.

sion-free survival between patients who completed 6 cycles versus those patients who received more than 6 cycles. There were no differences between the 2 groups.

Discussion

The prognosis for newly diagnosed glioblastoma remains poor with median overall survival in the 12 to 18 months range (2–4). The phase III EORTC/NCIC study showed that the addition of temozolomide to standard radiation therapy, followed by adjuvant temozolomide, improved median overall survival of newly diagnosed glioblastoma patients by 2.5 to 14.6 months, compared with 12.1 months with radiation therapy alone (4). This phase III trial established a new standard of care for newly diagnosed glioblastoma patients by using radiation therapy plus concomitant and adjuvant temozolomide. However, the prognosis remains relatively poor, with less than 10% of patients alive at 5 years with the combination therapy (5). VEGF is a critical determinant of glioblastoma biology (6, 15). Glioblastoma tumors have the highest levels of VEGF compared with other tumor types, and the more VEGF, the worse the prognosis (9, 10). Bevacizumab, a humanized monoclonal antibody to VEGF, has shown activity in recurrent glioblastoma (11–13). The current phase II trial reports the addition of bevacizumab to standard radiation therapy and temozolomide, followed by adjuvant temozolomide, bevacizumab, and irinotecan, for newly diagnosed glioblastoma. Overall, the regimen was tolerable with moderate toxicity, and there is a suggestion of an improvement in both progression-free survival and overall survival compared with historical controls.

At the time the current trial was designed, the most robust data were from the EORTC/NCIC phase III study. The current trial was developed to compare with the temozolomide plus radiation therapy arm, and only included those patients who underwent surgical resection because every patient in the current trial underwent surgical resection. The goal of the trial was to provide safety and efficacy data to justify a phase III trial. The primary endpoint was the percentage of patients alive 16 months from the time of study enrollment, with a goal of 60% overall survival. The current trial resulted in 65% overall survival at 16 months, compared with 50% among patients treated on the EORTC/NCIC study with concurrent temozolomide and radiotherapy after resection (4). Furthermore, median overall survival on our study was 21.2 months. Our survival data are similar to those reported in a phase II study from UCLA that added bevacizumab to standard radiation therapy and temozolomide followed by temozolomide and bevacizumab (17).

The UCLA trial reported a median overall survival of 19.6 months. The authors compared the data with a nonrandomized, concurrently treated group that did not receive bevacizumab as part of their initial therapy. Selection bias and treatment at the time of progression make the comparison difficult to interpret. In addition, the UCLA study reported survival from the date of diagnosis and not the date of enrollment. Both the EORTC/NCIC and our study reported survival from the date of enrollment, which was a median 1 month after diagnosis. The rationale for including irinotecan in the adjuvant therapy was to synergize a topoisomerase I inhibitor with an alkylating agent and to inhibit hypoxia-inducing factor-1 alpha (HIF-1α). There are some data that topoisomerase I inhibitors inhibit HIF-1α (18, 19). It is impossible to determine the role of irinotecan in the results if selection bias or irinotecan contributed to the approximate 2.5 months' improvement in overall survival in our study versus the UCLA study.

However, our study results should be interpreted with caution for several reasons. First, the care for glioblastoma patients has evolved over the past decade, with a steady improvement in the overall survival, compared with historical controls (20). Three recent single-agent phase II studies from the New Approaches to Brain Tumor Therapy CNS consortium (NABTT) reported a median overall survival of approximately 18 to 20 months (20, 21). Importantly, these 3 studies also measured overall survival from the date of diagnosis rather than the date of study enrollment. Second, results of single-institution studies frequently report encouraging results that are not confirmed in phase III trials because of several factors, including selection bias. Finally, further follow-up is required for maturation of our study data.

There is a theoretical risk of including anti-VEGF therapy in the treatment of newly diagnosed glioblastoma patients. In the absence of VEGF, tumors may co-opt normal vessels,

Published OnlineFirst April 29, 2011; DOI: 10.1158/1078-0432.CCR-11-0120

which may result in a more invasive phenotype and less concentrated mass of tumors (22–24). There are preclinical reports that the inclusion of anti-VEGF therapy into the therapy of malignant gliomas may produce a more invasive phenotype (23). This raises the concern that the inclusion of bevacizumab in the therapy for newly diagnosed patients will result in an improvement in the progression-free survival but no improvement in the overall survival. However, the 2 phase II trials to date that included bevacizumab in the treatment of newly diagnosed glioblastoma patients (our study and that cited in ref. 17) suggest that overall survival may be improved.

The current trial of the addition of bevacizumab to radiation therapy and temozolomide, followed by temozolomide, bevacizumab, and irinotecan, reports important safety data about the inclusion of bevacizumab in the treatment of newly diagnosed glioblastoma and also reports a suggestion of improvement in the progression-free survival. It is critical to complete the 2 large phase III placebo-controlled trials investigating the inclusion of bevacizumab in the treatment of newly diagnosed glioblastoma patients, as well as understanding VEGF resistance to further improve the survival in glioblastoma.

Disclosure of Potential Conflicts of Interest

J.J. Vredenburgh, D.A. Reardon, H.S. Friedman have honoraria from Speakers Bureau and are consultants/advisory board members for Genentech/Roche.

Grant Support

This work was supported by NIH grants 5P50-NS-20023 and 5 R37 CA11898; NIH grant MO1 RR 30, GCRC Program, NCRR; and NCI SPORE 1 P20 CA096890; and a grant from Genentech Pharmaceuticals.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received January 16, 2011; revised March 18, 2011; accepted April 6, 2011; published OnlineFirst April 29, 2011.

References

1. Cancer Facts & Figures 2009. Atlanta: American Cancer Society; 2009.
2. Jeon HJ, Kong DS, Park KB, Lee JI, Park K, Kim JH, et al. Clinical outcome of concomitant chemoradiotherapy followed by adjuvant temozolomide therapy for glioblastomas: single-center experience. Clin Neurol Neurosurg 2009;111:679–82.
3. Prados MD, Chang SM, Butowski N, DeBoer R, Parvataneni R, Carliner H, et al. Phase II study of erlotinib plus temozolomide during and after radiation therapy in patients with newly diagnosed glioblastoma multiforme or gliosarcoma. J Clin Oncol 2009;27:579–84.
4. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.
5. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459–66.
6. Jain RK, di Tomaso E, Duda DG, Loeffler JS, Sorensen AG, Batchelor TT. Angiogenesis in brain tumours. Nat Rev Neurosci 2007;8:610–22.
7. Lamszus K, Ulbricht U, Matschke J, Brockmann MA, Fillbrandt R, Westphal M. Levels of soluble vascular endothelial growth factor (VEGF) receptor 1 in astrocytic tumors and its relation to malignancy, vascularity, and VEGF-A. Clin Cancer Res 2003;9:1399–405.
8. Salmaggi A, Eoli M, Frigerio S, Silvani A, Gelati M, Corsini E, et al. Intracavitary VEGF, bFGF, IL-8, IL-12 levels in primary and recurrent malignant glioma. J Neurooncol 2003;62:297–303.
9. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol 2002;20:4368–80.
10. Birner P, Piribauer M, Fischer I, Gatterbauer B, Marosi C, Ambros PF, et al. Vascular patterns in glioblastoma influence clinical outcome and associate with variable expression of angiogenic proteins: evidence for distinct angiogenic subtypes. Brain Pathol 2003;13:133–43.
11. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009;27:4733–40.
12. Vredenburgh JJ, Desjardins A, Herndon JE, Dowell JM, Reardon DA, Quinn JA, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 2007;13:1253–9.
13. Vredenburgh JJ, Desjardins A, Herndon JE, Marcello J, Reardon DA, Quinn JA, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 2007;25:4722–9.
14. Vredenburgh JJ, Desjardins A, Kirkpatrick JP, Reardon DA, Peters KB, Herndon JE II, et al. Addition of bevacizumab to standard radiation therapy and daily temozolomide is associated with minimal toxicity in newly diagnosed glioblastoma multiforme. Int J Radiat Oncol Biol Phys 2010 Oct 30. [Epub ahead of print].
15. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010;28:1963–72.
16. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 1993;85:704–10.
17. Lai A, Tran A, Nghiemphu PL, Pope WB, Solis OE, Selch M, et al. Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. J Clin Oncol 2011;29:142–8.
18. Rapisarda A, Hollingshead M, Uranchimeg B, Bonomi CA, Borgel SD, Carter JP, et al. Increased antitumor activity of bevacizumab in combination with hypoxia inducible factor-1 inhibition. Mol Cancer Ther 2009;8:1867–77.
19. Baranello L, Bertozzi D, Fogli MV, Pommier Y, Capranico G. DNA topoisomerase I inhibition by camptothecin induces escape of RNA polymerase II from promoter-proximal pause site, antisense transcription and histone acetylation at the human HIF-1alpha gene locus. Nucleic Acids Res 2010;38:159–71.
20. Grossman SA, Ye X, Piantadosi S, Desideri S, Nabors LB, Rosenfeld M, et al. Survival of patients with newly diagnosed glioblastoma treated with radiation and temozolomide in research studies in the United States. Clin Cancer Res 2010;16;2443–9.
21. Grossman SA, Ye X, Chamberlain M, Mikkelsen T, Batchelor T, Desideri S, et al. Talampanel with standard radiation and temozolomide in patients with newly diagnosed glioblastoma: a multicenter phase II trial. J Clin Oncol 2009;27:4155–61.
22. de Groot JF, Fuller G, Kumar AJ, Piao Y, Eterovic K, Ji Y, et al. Tumor invasion after treatment of glioblastoma with bevacizumab: radiographic and pathologic correlation in humans and mice. Neuro Oncol 2010;12;233–42.
23. Holash J, Maisonpierre PC, Compton D, Boland P, Alexander CR, Zagzag D, et al. Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. Science 1999;284:1994–8.
24. Leenders WP, Küsters B, Verrijp K, Maass C, Wesseling P, Heerschap A, et al. Antiangiogenic therapy of cerebral melanoma metastases results in sustained tumor progression via vessel co-option. Clin Cancer Res 2004;10:6222–30.

AACR American Association for Cancer Research

Clinical Cancer Research

The Addition of Bevacizumab to Standard Radiation Therapy and Temozolomide Followed by Bevacizumab, Temozolomide, and Irinotecan for Newly Diagnosed Glioblastoma

James J. Vredenburgh, Annick Desjardins, David A. Reardon, et al.

Clin Cancer Res 2011;17:4119-4124. Published OnlineFirst April 29, 2011.