Overview

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Title: Bevacizumab in Combination With Radiotherapy and Temozolomide for Patients With Newly Diagnosed Glioblastoma Multiforme

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Author Summary: Abstract and Brief Discussion

Background

Patients with a newly diagnosed glioblastoma multiforme (GBM) have a high risk of recurrent disease with a dismal outcome despite intensive treatment of sequential surgery and chemoradiotherapy with temozolomide (TMZ), followed by TMZ as a single agent. Bevacizumab (BV) may increase response rates to chemotherapy in the recurrent treatment setting of GBM. We hypothesized that a neoadjuvant treatment strategy for patients with newly diagnosed GBM using chemoradiotherapy plus BV would improve resectability and thus survival. We performed a phase II trial of the treatment strategy of BV plus chemoradiation to determine the safety of this combination in patients who had already undergone primary surgery for their GBM.

Methods

After a biopsy (6 patients) or a resection (13 patients) of a newly diagnosed GBM, 19 patients received radiotherapy (30 fractions of 2 Gy) in combination with daily TMZ 75 mg/m^2 and BV 10 mg/kg on days 1, 14, and 28, followed by 6 monthly cycles of TMZ 150–200 mg/m^2 on days 1–5.

Results

The overall response rate was 26%. Three patients had a complete response after resection, and in two patients, a complete response after resection followed by chemoradiation plus BV was seen. No grade 3–4 toxicities were observed during combination treatment. The median progression-free survival was 9.6 months (95% confidence interval [CI]: 4.3–14.4 months). The median overall survival was 16 months (95% CI: 8.1–26.3 months), similar to a matched control group that received standard chemoradiotherapy from our institution.

Conclusion
Combination of bevacizumab with radiotherapy and TMZ is safe and feasible in patients with newly diagnosed GBM, but because of low response rates, this treatment strategy does not favor a neoadjuvant approach.

Discussion
We hypothesized that neoadjuvant treatment strategies for patients with a newly diagnosed GBM using chemo-radiotherapy plus bevacizumab may improve resectability and thus survival. However, neoadjuvant treatment is rarely applied for these patients because the most effective way to reduce intracranial pressure is still surgery. Tumor volume itself and the marked brain edema associated with GBM are responsible for elevated intracranial pressure with associated morbidity and mortality. Because of the risk of death through cerebral herniation and the fast growth of the tumor, most GBM patients are currently operated on within 1 or 2 weeks after initial diagnosis.

We hypothesized that BV treatment results in immediate and significant reduction of cerebral edema in patients with GBM and may provide the opportunity to postpone surgical resection while reducing tumor volume through a neoadjuvant strategy, eventually resulting in improved locoregional tumor control and improved survival.

The outcome of patients with GBM may benefit from this strategy with a more radical primary resection that will ultimately reduce the chance of residual disease. Tumor recurrence occurs in 90%–95% close to the resection margin. This is attributed to the findings of increased tumor cell density along the margin, with a sharp drop noted as the distance from the resection cavity increases. In view of this high locoregional tumor recurrence rate, it is worth increasing surgical efficiency to improve locoregional control. Neoadjuvant strategies have been successful at improving margin-free tumor resections and local control in patients with other solid tumors.

Because the addition of bevacizumab to treatment in the recurrent GBM setting leads to an immediate and significant reduction of cerebral edema and tissue hypoxia and normalization of the tumor vasculature, we hypothesized that neoadjuvant BV in combination with chemoradiation would improve the surgical outcome of GBM.

Because of the goal of our feasibility trial, BV administrations were not continued during adjuvant temozolomide cycles.

Analysis of toxicity data from our small group of 19 patients did not reveal any grade 3–4 toxicity during the experimental treatment phase of BV in combination with chemoradiotherapy (Table 2). The experimental treatment was well tolerated and was not complicated by known BV-related side effects. In comparison with the standard treatment for GBM in the European Organization for Research and Treatment of Cancer and National Cancer Institute of Canada (EORTC-NCIC) trial, we found slightly more grade 1–2 side effects but no grade 3–4 side effects (Table 3). Patient characteristics in our study are comparable to the standard patient characteristics in daily practice and, for example, in the EORTC-NCIC trial (Table 1). Our findings indicate that limiting the addition of BV to the concomitant treatment phase only is safe and feasible, but because of low response rates, this treatment strategy does not favor a neoadjuvant approach.

Trial Information

Disease	Brain cancer - primary
Stage of disease / treatment	Primary
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	Safety
Secondary Endpoints	Progression Free Survival and Overall Response Rate
Investigator's Analysis	Active but results overtaken by other developments

Drug Information

Drug 1 **Generic/Working name**	Bevacizumab
Trade name	Avastin
Company name	Roche
Drug type	Antibody
Drug class	Angiogenesis - VEGF
Dose	10 mg intravenously every 2 weeks milligrams (mg) per kilogram (kg)
Route	IV
Schedule of Administration	10 mg intravenously every 2 weeks in combination with daily radiotherapy and temozolomide orally.
Drug 2 **Generic/Working name**	Temozolomide
Trade name	Temodal
Drug type	Chemotherapy
Drug class	Alkylating agent
Dose	75 mg (mg) per square meter (m^2)
Route	oral (po)
Schedule of Administration	Bevacizumab 10 mg intravenously every 2 weeks in combination with daily radiotherapy and temozolomide orally

Patient Characteristics

Number of patients, male	11
Number of patients, female	8
Stage	Histologically proven primary GBM
Age	Median (range): 48 (26–67) years
Number of prior systemic therapies	Median (range): 0
Performance Status:	KPS (Karnofsky performance score) ＞60 in all patients
Other	Not Collected
Cancer Types or Histologic Subtypes	• Glioblastoma multiforme

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients enrolled	19
Number of patients evaluable for toxicity	19
Number of patients evaluated for efficacy	19
Evaluation method	MR imaging of cerebrum
Response assessment CR	10.5%
Response assessment SD	89.5%
(Median) duration assessments PFS	9.6 months, CI: 4.3-14.4
(Median) duration assessments OS	16 months, CI: 8.1-26.3

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades
Fatigue (asthenia, lethargy, malaise)	63%	31%	5%	0%	0%	0%	36%
Anorexia	84%	15%	0%	0%	0%	0%	15%
Fever (in the absence of neutropenia, where neutropenia is defined as ANC ＜1.0 × 10e9/L)	94%	5%	0%	0%	0%	0%	5%
Weight loss	94%	5%	0%	0%	0%	0%	5%
Nausea	84%	15%	0%	0%	0%	0%	15%
Vomiting	94%	5%	0%	0%	0%	0%	5%
Gastrointestinal - pyrosis	94%	5%	0%	0%	0%	0%	5%
Infection - wound infection	89%	5%	5%	0%	0%	0%	10%
Leukocytes (total WBC)	84%	15%	0%	0%	0%	0%	15%
Platelets	78%	15%	5%	0%	0%	0%	21%
Mood alteration	94%	0%	5%	0%	0%	0%	5%

Adverse events at all dose levels, cycle 1: treatment-related toxicity in all 19 patients treated with chemoradiotherapy combined with bevacizumab, and adjuvant temozolomide.
*No Change from Baseline/No Adverse Event

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Not Collected
Investigator's Assessment	Active but results overtaken by other developments

Discussion

We hypothesized that neoadjuvant treatment strategies for patients with newly diagnosed glioblastoma multiforme (GBM) using chemoradiotherapy plus bevacizumab (BV) may improve resectability and thus survival. As far as we know, a neoadjuvant strategy in the first-line treatment of patients with a GBM has been tried only once, in 1976 [1]. In that study, 10 patients with high-grade astrocytoma were treated with preoperative radiotherapy and chemotherapy (VM26 and CCNU [also known as lomustine]). Survival was not improved, but preoperative treatment was considered of value to reduce tumor vascularization, making the operative procedure easier without compromising hemostasis or wound healing [1]. Another group showed a role for neoadjuvant chemotherapy (high-dose methotrexate and 5-fluorouracil) in 18 recurrent GBM patients (all initially not reoperable) in debulking tumor mass and improving patient performance status to create the conditions necessary to justify a second resection. The reoperated patients (27.7%) remained free of disease significantly longer than patients who were not reoperated [2]. One patient with an infiltrative 1p- and 19q-deleted anaplastic oligoastrocytoma of the right frontal lobe and genu of the corpus callosum, initially only partially resectable, was treated preoperatively with temozolomide (TMZ) for 24 months. After this treatment, a gross total resection was possible because of decreased tumor mass [3]. In 2006, Duffau and colleagues published another case of an adult patient operated for a supratentorial oligodendroglioma grade II with a complete resection made possible by preoperative chemotherapy (six cycles of TMZ) [4], Nevertheless, neoadjuvant treatment is rarely applied for patients with GBM because the most effective way to reduce intracranial pressure is still surgery. Tumor volume itself and the marked brain edema associated with GBM are responsible for elevated intracranial pressure with associated morbidity and mortality. Because of the risk of death through cerebral herniation and the fast growth of the tumor, most GBM patients are currently operated within 1 or 2 weeks after initial diagnosis.

We hypothesized that BV treatment results in immediate and significant reduction of cerebral edema and may provide the opportunity to postpone surgical resection while reducing tumor volume through a neoadjuvant strategy, eventually resulting in improved locoregional tumor control and improved survival.

We hypothesized that adding bevacizumab during the treatment phase with chemoradiation would improve response rate. The outcome of patients with GBM may benefit from this strategy with a more radical primary resection that will ultimately reduce the chance of residual disease. Tumor recurrence occurs in 90%–95% close to the resection margin. This is attributed to the findings of increased tumor cell density along the margin, with a sharp drop noted as the distance from the resection

cavity increases [5, 6]. In view of this high locoregional tumor recurrence rate, it is worth increasing surgical efficiency to improve locoregional control [7]. Neoadjuvant strategies have been successful in improving margin-free tumor resections and local control in patients with other solid tumors.

Because the addition of bevacizumab to treatment in the recurrent GBM setting leads to an immediate and significant reduction of cerebral edema and tissue hypoxia and normalization of the tumor vasculature, we hypothesized that neoadjuvant BV in combination with chemoradiation could improve the surgical outcome of GBM [8–10].

Because of the goal of our feasibility trial, BV administration was not continued during adjuvant temozolomide cycles. Our approach was different from those of reported studies in the literature, in which bevacizumab was continued during the adjuvant temozolomide cycles [11–16].

Promising radiological response rates, ranging from 26% to 61%, and 6-month progression-free survival (PFS) rates, ranging from 29% to 46%, have been shown in nonrandomized phase II studies using bevacizumab alone or in combination with irinotecan, in patients with recurrent GBM [17–20]. Recently, an improvement in 9-month overall survival (OS) in patients with recurrent GBM was shown in a three-arm phase II study (BELOB) using BV versus lomustine versus the combination of lomustine and bevacizumab [21].

Based on these phase II results in the treatment of recurrent GBM, the use of BV was translated to the treatment of newly diagnosed GBM patients but is still a matter of intensive debate.

At the 2013 meeting of the American Society of Clinical Oncology, the results of the AVAGLIO and RTOG0825 studies were presented, and these results were recently published [22, 23]. In these two double-blind, placebo-controlled, multicenter, phase III trials in patients with newly diagnosed GBM comparing BV versus placebo during the two treatment phases of chemoradiation and adjuvant chemotherapy, increased PFS but no improvement in OS was observed. Consequently, BV has not been approved for standard first-line combination treatment [22, 23].

Analysis of toxicity data from our small group of 19 patients did not reveal any grade 3–4 toxicity during the experimental treatment phase of BV in combination with chemoradiotherapy. The experimental treatment was well tolerated and was not complicated by known BV-related side effects, such as hypertension, thromboembolism, or intracranial bleeding. Our toxicity is shown in Table 2. In comparison with the standard treatment for GBMs in the European Organization for Research and Treatment of Cancer and National Cancer Institute of Canada (EORTC-NCIC) trial, we found slightly more grade 1–2 side effects but no grade 3–4 side effects. Patient characteristics in our study are comparable to the standard patient characteristics in daily practice and, for example, in the EORTC-NCIC trial [24]. A comparison of these patient characteristics is presented in Table 1, and a comparison of the toxicity in both studies is presented in Table 3.

The safety and feasibility of using BV in combination with radiotherapy and TMZ in patients with a newly diagnosed GBM has been reported by two other groups [11–14]. Table 1 includes the patient characteristics of the studies of Lai et al. [11, 12] and Narayana et al. [13, 14]. A comparison of the toxicity data of our study with these studies is presented in Table 3.

The overall toxicity in our patient group during concomitant chemoradiotherapy with bevacizumab was slightly lower compared with the toxicity reported by Lai et al. [11, 12] and Narayana et al. [13, 14], and the overall toxicity in our patient group during the adjuvant cycles TMZ was comparable with the reported toxicity by Stupp and colleagues in the EORTC-NCIC trial [24].

Our findings indicate that limiting the addition of BV to the concomitant treatment phase only is safe and feasible.

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Figures and Tables

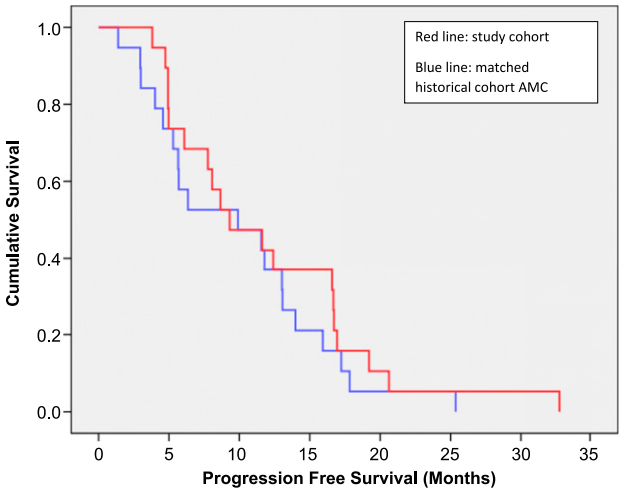

Figure 1. Progression-free survival (months): study cohort (red line) treated with radiotherapy, temozolomide and bevacizumab versus matched historical cohort (blue line) treated with radiotherapy and temozolomide. Median progression-free survival was 9.6 months for experimental cohort versus 9.9 months for historical controls.

Abbreviation: AMC, Academic Medical Center.

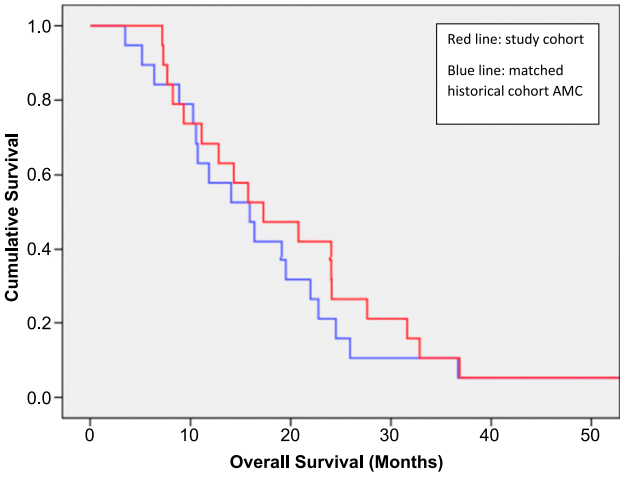

Figure 2. Overall survival (months): study cohort (red line) treated with radiotherapy, temozolomide and bevacizumab versus matched historical cohort (blue line) treated with radiotherapy and temozolomide. Median overall survival rate was 16.0 months for experimental cohort versus 15.8 months for historical controls.

Abbreviation: AMC, Academic Medical Center.

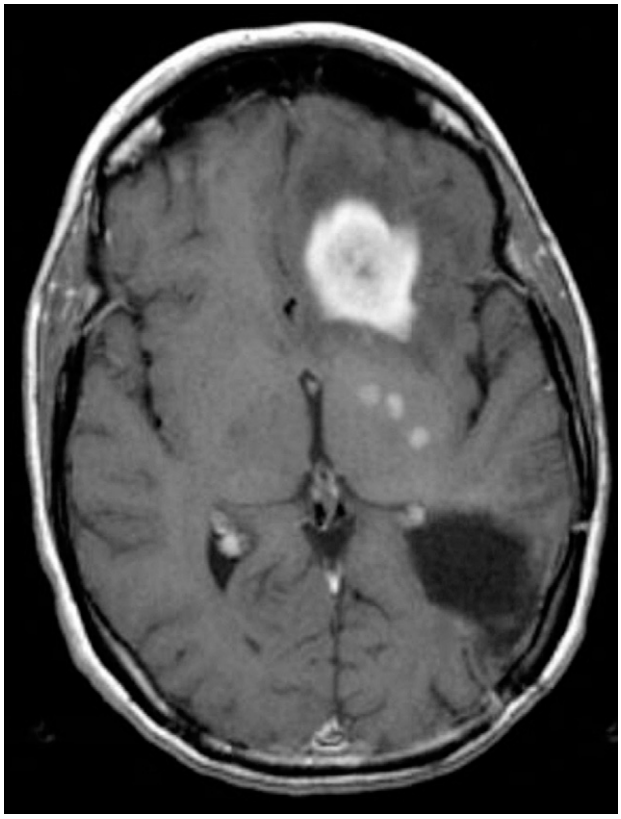

Figure 3. Typical recurrence pattern on contrast-enhanced T1 magnetic resonance imaging of a glioblastoma patient treated with concurrent radiotherapy, temozolomide, and bevacizumab. Primary tumor (resection cavity) responded well to adjuvant treatment, but infiltrating tumor components gave rise to some small and one larger outfield recurrence, leading to clinical symptoms.

Table 1. Comparison of patient characteristics

Characteristics	This study	Matched control group	EORTC-NCIC RT/TMZ [1][a]	Lai et al. [11, 12]	Narayana et al. [13, 14]
Patients, *n*	19	19	287	70	15
Men, %	60	58	64	56	73
Women, %	40	42	36	44	27
Age, years, median (range)	48 (26–67)	—	56 (19–70)	57 (31–76)	(19–66)
Mean age, years	50	48	—	—	—
WHO grade III, %	0	0	3	0	20
WHO grade IV, %	100	100	92	100	80
Biopsy, %	21	21	17	3	33
Resection, %	79	79	83	97	67

[a]EORTC-NCIC study 1 (standard treatment).

Abbreviations: —, no data; EORTC, European Organization for Research and Treatment of Cancer; NCIC, National Cancer Institute of Canada; TMZ, temozolomide; WHO, World Health Organization.

Table 2. Treatment-related toxicity in all 19 patients treated with chemoradiotherapy combined with bevacizumab and adjuvant temozolomide

	RT-TMZ-BV, *n* (%)		TMZ, *n* (%)	
Toxicities	**Grades 1–2**	**Grades 3–4**	**Grades 1–2**	**Grades 3–4**
Nonhematological				
Fatigue	11 (58)	—	10 (53)	3 (16)
Depression	1 (5)	—	2 (11)	1 (5)
Hypertension	—	—	1 (5)	—
Anorexia	5 (26)	—	8 (42)	—
Taste alteration	1 (5)	—	5 (26)	—
Weight loss	1 (5)	—	1 (5)	—
Nausea	6 (32)	—	8 (42)	—
Vomiting	2 (11)	—	—	—
Pyrosis	1 (5)	—	1 (5)	—
Allergy	—	—	1 (5)	—
Wound infection	2 (11)		—	1 (5)
Memory impairment	—	—	4 (21)	—
Dizziness	—	—	1 (5)	—
Fever	—	—	1 (5)	—
Hematological				
Anemia	—	—	1 (5)	—
Leucopenia	5 (26)	—	6 (32)	—
Thrombocytopenia	4 (21)	—	12 (63)	—

Abbreviations: —, no data; BV, bevacizumab; RT, radiotherapy; TMZ, temozolomide.

Table 3. Comparison of toxicity

Toxicity	**This study, RT/TMZ/BV (*n* = 19), %**		**EORTC-NCIC study [1],[a] RT/TMZ (*n* = 287), %**		**Lai et al. [11, 12], RT/TMZ/BV (*n* = 70), %**		**Narayana et al. [13, 14], RT/TMZ/BV (*n* = 15), %**	
	Grades 1–2	**Grades 3–4**	**Grade 2**	**Grades 3–4**	**Grades 1–2**	**Grades 3–4**	**Grade 2**	**Grades 3–4**
Nonhematological								
Fatigue	58	0	26	7		20	20	0
Hypertension	0	0				11		7
Nausea/vomiting	43	0	13	<1		10		
Wound infection	11	0				6		
Dizziness	0	0		1		7		
Infection	0	0	1	3		7		
Venous thrombosis/ pulmonary embolism	0	0				19		13
GI bleed/perforation	0	0				6		
Proteinuria	0	0				11		
CNS-CVA/hemorrhage	0	0				12		

Hematological					
Anemia	0	0	<1	1	
Leucopenia	26	0	2	4	
Neutropenia			4	7	7

[a]EORTC-NCIC study 1 (standard treatment).
Abbreviations: BV, bevacizumab; CNS, central nervous system; CVA, cerebrovascular accident; EORTC, European Organization for Research and Treatment of Cancer; GI, gastrointestinal; NCIC, National Cancer Institute of Canada; RT, radiotherapy; TMZ, temozolomide; WHO, World Health Organization.