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Safety and maximum tolerated dose of superselective intraarterial cerebral infusion of bevacizumab after osmotic blood-brain barrier disruption for recurrent malignant glioma

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Abstract

Object—The authors assessed the safety and maximum tolerated dose of superselective intraarterial cerebral infusion (SIACI) of bevacizumab after osmotic disruption of the blood-brain barrier (BBB) with mannitol in patients with recurrent malignant glioma.

Methods—A total of 30 patients with recurrent malignant glioma were included in the current study.

Results—The authors report no dose-limiting toxicity from a single dose of SIACI of bevacizumab up to 15 mg/kg after osmotic BBB disruption with mannitol. Two groups of patients were studied; those without prior bevacizumab exposure (naïve patients; Group I) and those who had received previous intravenous bevacizumab (exposed patients; Group II). Radiographic changes demonstrated on MR imaging were assessed at 1 month postprocedure. In Group I

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patients, MR imaging at 1 month showed a median reduction in the area of tumor enhancement of 34.7%, a median reduction in the volume of tumor enhancement of 46.9%, a median MR perfusion (MRP) reduction of 32.14%, and a T2-weighted/FLAIR signal decrease in 9 (47.4%) of 19 patients. In Group II patients, MR imaging at 1 month showed a median reduction in the area of tumor enhancement of 15.2%, a median volume reduction of 8.3%, a median MRP reduction of 25.5%, and a T2-weighted FLAIR decrease in 0 (0%) of 11 patients.

Conclusions—The authors conclude that SIACI of mannitol followed by bevacizumab (up to 15 mg/kg) for recurrent malignant glioma is safe and well tolerated. Magnetic resonance imaging shows that SIACI treatment with bevacizumab can lead to reduction in tumor area, volume, perfusion, and T2-weighted/FLAIR signal.

Keywords

bevacizumab; glioma; brain neoplasm; intraarterial infusion; mannitol

Glioblastoma multiforme is the most aggressive human brain tumor. Until recently, there was no standard treatment for recurrent disease after combined chemotherapy and radiation treatment. Intravenously administered bevacizumab, a monoclonal antibody (IgG) to VEGF, has been used with safety and clinical success in recurrent GBM.^{1,7,32,33} Despite these recent successes with bevacizumab, all patients progress and require salvage therapy.³⁷

Intraarterial chemotherapy is a known strategy of dose intensification that results in a more concentrated and localized delivery of chemotherapy to brain tumors than in standard IV administration.^{2,30} Intracarotid mannitol has been shown to disrupt the BBB successfully in preclinical models, and it has a long history in the treatment of human CNS tumors.^{12,14,24} We therefore hypothesized that SIACI of bevacizumab was safe and well tolerated after BBB disruption with mannitol in humans. We informally studied 2 groups of patients—those without prior bevacizumab exposure (naïve patients; Group I) and those who had received previous intravenous bevacizumab (exposed patients; Group II). Toxicity from the treatment and radiographic changes revealed on MR imaging were assessed at 1 month postprocedure. We report no dose-limiting toxicity of SIACI of bevacizumab, up to a dose of 15 mg/kg, after BBB disruption with mannitol. Future studies will help determine if repeated SIACI therapy with mannitol/bevacizumab can lead to either a dose reduction for IV bevacizumab, a reduction in the number of cycles of IV bevacizumab, or its elimination altogether.

Methods

Patient Eligibility

Patients were recruited from August 2009 to June 2010. Adult patients (age > 18 years) who had recurrent or progressive malignant gliomas, in whom prior combined radiation treatment and chemotherapy with temozolamide failed, and who had a KPS score of > 60 were eligible. Patients in Group II (exposed to bevacizumab) were eligible for the study if they had received fewer than 12 doses (6 months) of previous IV bevacizumab treatment at 10 mg/kg. Noncircumscribed enhancing neoplasm, multifocal neoplasm, and/or leptomeningeal disease on MR imaging studies were not exclusion criteria.

Study Design and Safety Oversight

The Weill Cornell Medical College Institutional Review Board and the FDA (Investigational New Drug 107, 402) approved this study, and each patient was provided with a written informed consent form to sign before entry into this study. Baseline evaluation included a complete physical and neurological examination and a contrast-enhanced MR imaging study

of the brain. A standardized MR brain imaging protocol was performed both before and after treatment. Patients then received SIACI of mannitol (25% 1.4 M mannitol, 10 ml/120 seconds) followed by SIACI of bevacizumab (dose escalation from 2 to 15 mg/kg) within 3 days of baseline MR imaging, as described previously (Fig. 1).^{26,27} After an approximately 28-day observation period for DLT, patients underwent repeat physical and neurological examination as well as brain MR imaging on the same magnet as their preprocedure MR imaging study. No additional therapy was started before the postinfusion MR imaging was completed. If no DLT occurred after 28 days, the patients began biweekly IV bevacizumab treatment (10 mg/kg) with or without irinotecan (CPT-11). Toxicity was evaluated using the National Cancer Institute's Common Toxicity Criteria software, version 4.2.

Response Evaluation

The radiographic response assessment of SIACI of bevacizumab was evaluated after 28 days by using brain MR imaging, according to criteria outlined by the recent Response Assessment in Neuro-Oncology Working Group's study.³⁶ Response assessments included the WHO-based criteria of Macdonald et al.¹³ that measure the area of the enhancing component of the tumor and the peritumoral T2-weighted/FLAIR signal changes (Fig. 2). Volumetric analyses of the enhancing component of the tumor and MRP were also routinely performed (Fig. 3). The T2-weighted/FLAIR signal changes were assessed independently by 2 board-certified neuroradiologists. Disagreements were resolved with a consensus read; however, this was not used because there were no interobserver discrepancies. The extent of the baseline T2-weighted/FLAIR MR imaging changes was compared directly to the follow-up 3- to 4-week MR imaging examination. Assessment was qualitative, and the criteria were as follows: 1) stable, 2) improved, and 3) progressed. No quantitative measurements were made, given the difficulty of accurately assessing the T2-weighted/FLAIR signal changes even with the use of segmentation software. The PET/CT imaging (Fig. 4) was performed in a small subset of patients before and after treatment. Volumetric tumor measurements were performed on a GE Advantage Workstation by using the Volume Analysis 3D option.

Statistical Considerations

This Phase I trial was designed to determine the MTD of SIACI of bevacizumab based on 10 escalating doses (2, 4, 6, 8, 10, 11, 12, 13, 14, and 15 mg/kg). If none of the initial 3 patients at a given dose level experienced DLT, the next dose level was studied in the following cohort of 3 patients. If 1 of the initial 3 patients at a given dose level experienced DLT, up to 3 additional patients would have been treated at that same dose level. Escalation would continue if only 1 of the 6 patients experienced DLT. If 2 or 3 of the first 3 patients experienced DLT, or if 2 or more of the 6 patients in both cohorts experienced DLT at a given dose level, the MTD would have been determined as the preceding dose level.

The DLT of this dose escalation regimen was Grade 3 or worse CNS hemorrhage, or Grade 4 hematological or nonhematological toxicity. Demographic, safety, and laboratory data, as well as MR imaging-based treatment response, were characterized by descriptive statistics (including medians and ranges). An informal comparison of the median reduction in the following parameters was performed using the nonparametric Wilcoxon rank-sum test: 1) the area of tumor enhancement; 2) the volume of tumor enhancement; and 3) MRP between patients without prior bevacizumab exposure (Group I) and patients with previous intravenous bevacizumab (Group II). The T2-weighted/FLAIR signal status between Groups I and II was assessed using the Fisher exact test. All analyses were performed using SPSS version 18.0 software (SPSS, Inc.).

Results

Patient Characteristics

Thirty patients (21 men, 9 women) with malignant glioma (GBM, anaplastic astrocytoma, oligodendroglioma, and pontine glioma) were enrolled in this trial (Table 1). The mean age was 53.1 years (range 29–68 years), and the mean KPS score was 79 (range 60–100). There were 19 patients in Group I (naïve to bevacizumab) and 11 in Group II (previously exposed to IV bevacizumab). The mean time since initial tumor diagnosis was 484 days (range 158–1328 days). There was no statistically significant difference between Groups I and II in age or KPS score, although for patients in Group II the diagnosis of their malignancy had been known for a significantly longer time compared with patients in Group I. Patients in Group II had received between 1 and 6 cycles of IV bevacizumab prior to enrolling in the study.

Safety of the Treatment

The safety and DLT of the treatment were evaluated for 28 days. After that time point, patients began their post-SIACI bevacizumab therapy. The MTD of SIACI of bevacizumab was not reached at 15 mg/kg, which is the highest FDA-approved dose for IV bevacizumab chemotherapy. There were no Grade 5 adverse events (death) from the treatment, and no Grade 3 or 4 adverse events were reported. There was no DLT associated with SIACI of mannitol followed by bevacizumab up to a dose of 15 mg/kg. There were no intratumoral or extratumoral CNS hemorrhages from intraarterial mannitol and bevacizumab.

There were 2 Grade 2 neurological adverse events; both were seizures in patients with known seizure disorders. One patient had a Grade 2 acneiform rash treated with oral and topical steroids. One patient with a known history of PE occurring 5 months earlier developed respiratory distress on intubation for the SIACI procedure, and was found to have had a “saddle” PE; this patient immediately underwent anticoagulation therapy. Another patient with a known history of lower-extremity PE returned to the emergency room with respiratory complaints 1 day after discharge. A CT scan of the chest revealed a segmental PE in the right upper lung. The patient recovered uneventfully after receiving anticoagulation therapy. One patient sustained a procedure-related stroke when inflation of an endovascular balloon in the distal anterior cerebral artery caused arterial rupture during the infusion of bevacizumab. To promote infusion to the orbitofrontal branch, and to prevent downstream runoff into the distal right anterior cerebral circulation, an endovascular balloon was inflated distal to the orbitofrontal branch and inflated during mannitol/chemotherapy infusion. The balloon was inflated and deflated at 3-minute intervals, and after approximately 80% of the drug had been infused, the balloon was reinflated, at which point contrast extravasation from the parent right anterior cerebral artery was noted. The balloon was then inflated to prevent further extravasation of contrast material. The balloon-induced vascular injury was immediately occluded endovascularly by using detachable coils and embolic glue. An intraoperative head CT scan demonstrated subarachnoid hemorrhage and intraventricular hemorrhage with ventriculomegaly, which was treated with a right frontal external ventricular drain. The patient awoke with a left hemiparesis.

Response to Treatment and Imaging Follow-Up

All patients were assessable for response to treatment and underwent standardized MR imaging prior to the SIACI treatment as well as repeat MR imaging prior to any additional therapy after SIACI treatment. Residual or recurrent enhancing tumor as well as T2-weighted/FLAIR signal on the immediate preprocedure MR imaging study was used as a baseline for evaluation.

We studied 2 groups of patients to perform an informal comparison: those without prior bevacizumab exposure (Group I, 19 patients) and those who had received previous intravenous bevacizumab (Group II, 11 patients). The radiographic results are summarized in Tables 2 and 3. In Group I patients, MR imaging at 1 month after a single treatment showed a median reduction of 34.7% in the area of tumor enhancement (vs a 15.2% reduction for Group II, $p = 0.02$), a median reduction of 46.9% in the volume of tumor enhancement (vs an 8.2% reduction for Group II, $p = 0.06$), a median MRP reduction of 32.1% (vs a 25.4% reduction for Group II, $p = 0.56$), and a T2-weighted FLAIR decrease in 9 (47.4%) of 19 patients (vs a 0% decrease [0 of 11 patients] for Group II, $p = 0.01$). The T2-weighted/FLAIR signal increased in 2 (10.5%) of 19 and in 3 (30%) of 10 patients in Groups I and II, respectively ($p = 0.31$), and the T2-weighted/FLAIR signal remained stable in 8 (42.1%) of 19 patients in Group I and in 7 (70%) of 10 Group II patients ($p = 0.25$); 1 patient did not undergo posttreatment T2-weighted/FLAIR imaging.

Three patients had a pre- and postprocedure FDGPET brain scan to assess the effect of SIACI of mannitol/bevacizumab on tumor metabolism. All 3 of the 30-day follow-up FDGPET brain scans demonstrated a qualitative diminution of metabolic activity in the tumor regions treated by SIACI (Fig. 4). The PET images were acquired at a 3-hour delay after radiotracer administration to increase tumor-to-background conspicuity. In 2 patients we were also able to perform quantitative assessments of PET SUVs and to compare pre- and postinfusion FDG-PET uptake values done at our institution on the same scanner. In those 2 patients, a single-dose SIACI of bevacizumab at 30 days showed a reduction of SUV_{max} of 30% in one and 36% in the other, and a reduction of the SUV average of -27% and -57%, respectively.

Discussion

Chemotherapy administration via the IA route in conjunction with BBB disruption is an approach that can potentiate chemotherapy delivery to brain tumors while avoiding systemic toxicities.⁶ The substantial pharmacological advantage of IA cerebral delivery compared with IV cerebral chemotherapy has been proven in animal models of glioma as well as in clinical studies.¹⁵ Intraarterial injection can yield local concentrations of chemotherapy to the brain tumor that are up to 389 times (mean 48.9 times) that of IV delivery.^{9,10,14,29} No studies to date have evaluated the safety or efficacy of SIACI of bevacizumab to human brain tumors following osmotic BBB disruption. The large size of bevacizumab molecules (160,000 D, 15 nm) may limit their exposure to brain tumor tissue because the disruption of the BBB in malignant brain tumors is quite heterogeneous and often incomplete, and maximum interendothelial cell pore size has been shown to be only 12 nm.^{12,16,25} For these reasons, a transient BBB opening caused by IA infusion of a high-osmotic-pressure solution such as mannitol may further enhance the CNS permeability to these drugs.^{1,16-23} In fact, osmotic BBB disruption has been shown to intensify drug delivery to the tumor and surrounding brain, particularly when using higher-molecular-weight therapeutic agents like bevacizumab.⁶ It is now known that VEGF protein is produced by tumor cells, stromal cells, recruited circulating endothelial progenitor cells, and brain tumor stem cells.¹² Recent work has shown that human glioblastoma cells endogeneously express 3 different VEGF variants or isoforms (VEGF₁₂₁, VEGF₁₆₅, and VEGF₁₈₉), and that circulating endothelial progenitor cells are recruited to the angiogenic vascular system of malignant gliomas via VEGF receptor-2 expression.³¹ It is for these reasons that we decided to augment our delivery of bevacizumab with osmotic BBB disruption with mannitol to target the extravascular VEGF ligand. We have stained multiple brain tumor specimens with VEGF antibody and found immunohistochemical methods to label VEGF throughout the tumor, in tumor vessels and on all types of tumor cells and stroma (data not shown).

It is suggested that osmotic BBB opening is mediated by cerebrovascular dilation. In rats, transient BBB disruption is achieved with 1.4 M mannitol at a rate of 0.01–0.1 ml/second for 30 seconds.³ Optimum BBB disruption as measured by Evans blue dye was achieved in these animals infused with mannitol at 0.026 ml/second for at least 30 seconds.³ Therefore, all patients in our study received an infusion of 0.083 ml/second for 60 seconds, with no associated morbidity or death.^{9,10} We documented cerebrovascular dilation after IA mannitol by noting an increase in “tumor blush” on a post-IA mannitol delivery contrast run during the angiogram obtained prior to the bevacizumab infusion. This suggested that our dose of mannitol was sufficient to open the BBB transiently.

This prospective trial was performed primarily to evaluate toxicity and to estimate the MTD of SIACI of bevacizumab administered in conjunction with osmotic BBB disruption. Bevacizumab administered using SIACI after osmotic BBB disruption with mannitol in malignant glioma recurrences was safe and effective in this pilot study. Overall toxicity in our study was equal to other reports of IV bevacizumab use in patients with malignant glioma.^{33,35} No significant adverse reactions were attributable to the interaction of SIACI of bevacizumab with osmotic BBB disruption. We did not see DLT in this study and did not reach an MTD, although we stopped the dose escalation at 15 mg/kg, which is the highest FDA-approved IV dose for the drug. Most importantly, we had no cases of intratumoral hemorrhage in any of our patients as a result of the drug’s interaction with tumor tissue. Our most significant complication was the 1 patient who suffered a stroke after balloon insufflation ruptured a distal anterior cerebral vessel. Because of this complication we have modified our technique, and will only use balloon assistance in deep thalamic tumors or brainstem tumors in which the parent vessels are larger and can withstand insufflation and deflation.

Secondarily, this pilot study demonstrated that a single- dose SIACI treatment with bevacizumab after BBB disruption was followed by a meaningful reduction in tumor size according to the Response Assessment in Neuro- Oncology Working Group’s criteria³⁶ in the majority of patients with recurrent malignant glioma. This finding was more pronounced in patients who were not previously exposed to IV bevacizumab (Group I patients). All 17 patients in Group I with measurable disease, compared with 6 (67%) of 9 patients in Group II with measurable disease, had a reduction in either the area or volume of contrast enhancement of the tumor after a single-dose SIACI of bevacizumab. Our findings compare favorably to recent data with IV bevacizumab (10 mg/kg) that showed an objective radiographic response rate in 50% of patients.³³ Our data compare very favorably to historical data from 375 patients with recurrent malignant gliomas enrolled in Phase II clinical trials, in which the radiographic response rate was 14% and the radiographic disease control rate was 39%.²⁶ Although precise quantification of the changes in T2-weighted/FLAIR signal can be difficult and must be differentiated from other causes of increased or decreased signal, we quantified a change as either increased, decreased, or unchanged 28 days after SIACI. We found that 47% of Group I patients had a reduction in T2-weighted/FLAIR signal compared with 0% of Group II patients, and this was statistically significant ($p = 0.01$). In addition, Group I had a significantly greater reduction in the area of tumor enhancement compared with Group II ($p = 0.02$), and similarly trended toward a greater reduction in the volume of tumor enhancement compared with Group II ($p = 0.06$).

Three patients who underwent an FDG-PET brain scan after the 1-month follow-up imaging session showed a robust diminution of metabolic activity in the tumor, suggesting the SIACI treatment may be having a genuine effect on tumor metabolism, and is not just “normalizing” the BBB and preventing the entrance of contrast agent into the tumor. In 2 patients we saw a reduction in the average SUV of the tumor (27% in one and 57% in the other).¹¹ Given that the reported doubling time of malignant glioma ranges from 2 days to 1

month, with a median of 17 days, the fact that we only saw 3 (10%) of 30 patients with increases in the area and volume of the enhancing tumor 1 month after SIACI of bevacizumab suggests that the drug is effective in controlling growth in this disease.³⁴

From a technical perspective this study highlights recent advances and risks of microcatheter and balloon-assisted endovascular devices. There was 1 stroke attributed to our use of these additional novel microcatheter techniques. Endovascular balloons are commonly and safely used in the treatment of neurovascular diseases such as vasospasm and in aneurysm remodeling. The indication for balloon assistance in SIACI of mannitol and bevacizumab depends on the size and location of the particular arteries being catheterized. For small, proximal vasculature that are both too numerous and too small for safe individual catheterization (that is, basilar perforating vessels, lenticulostriate perforating vessels), an occlusive single-lumen balloon can be inflated distal to the perforating vessels in the parent artery during infusion to prevent runoff into nontargeted downstream circulation. This helps concentrate the infusion to a particular proximal region of arterial branches.²⁸ However, particular care must be used when the balloon is inflated and deflated in smaller vessels near the tumor, because these vessels have also been irradiated and may be more prone to rupture, as was seen in one of our cases.

It is important to emphasize that the results reported here come from the completed Phase I portion of a Phase I/II study design. Although important information can be drawn concerning safety and toxicity of SIACI combined with BBB disruption therapy for malignant glioma, inherent limitations in response assessment attributable to small numbers of patients and incomplete Phase II data should be noted. In addition, challenges remain in determining the correct radiological response criteria to be used to evaluate efficacy in patients using antiangiogenic agents.³⁶ The safety reported here regarding SIACI of bevacizumab and osmotic BBB disruption supports the further examination of this treatment modality for patients with recurrent malignant glioma.⁸

Conclusions

The SIACI therapy of a targeted antibody such as bevacizumab is at its greatest advantage during its first pass through the vessels feeding the tumor.^{4,5} The combination of SIACI of bevacizumab and osmotic BBB disruption with mannitol was well tolerated in our patients, with promising signs of efficacy in patients with recurrent malignant glioma. These results suggest that it is reasonable to increase the number of patients with recurrent malignant gliomas who are treated with this regimen, and also to export this approach to other targeted agents. A larger Phase II trial using multiple SIACI treatments in the setting of recurrent disease will be used to assess progression-free survival and overall survival after patients receive this treatment modality. Further work is underway to label bevacizumab with tracers such as copper-64 to understand the biodistribution, clearance, and dosimetry of bevacizumab after SIACI.

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Abbreviations used in this paper

BBB blood-brain barrier

DLT	dose-limiting toxicity
FDG	[¹⁸ F]fluorodeoxyglucose
GBM	glioblastoma multiforme
IA	intraarterial
IV	intravenous
KPS	Karnofsky Performance Scale
MRP	MR perfusion
MTD	maximum tolerated dose
PE	pulmonary embolism
SIACI	superselective intraarterial cerebral infusion
SUV	standard uptake value
VEGF	vascular endothelial growth factor

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Fig. 1.

A: Sagittal Gd-enhanced T1-weighted MR image showing a large right posterior temporal GBM (*arrow*). **B:** The microcatheter tip (*arrow*) adjacent to the craniotomy site on an unsubtracted digital subtraction angiography study delineates the point of chemotherapy injection. **C:** Digital subtraction angiogram showing contrast infusion into the distal branch of the right middle cerebral artery (*arrowhead*) supplying the neoplasm demonstrates the distribution of IA infusion of mannitol and bevacizumab.

Fig. 2. Contiguous Gd-enhanced T1-weighted MR images demonstrating a marked interval decrease in the size of the enhancing component (**A and B**) and the associated T2-weighted/FLAIR images (**C and D**) of the patient's recurrent posterior right temporal GBM before (panels **A and C**) and 1 month after (panels **B and D**) IA bevacizumab treatment.

Fig. 3.

Gadolinium-enhanced T1-weighted images (**A and B**) obtained pre- and post-IA bevacizumab infusion demonstrating a 29.6% interval decrease in the area of the targeted enhancing component of a recurrent left frontal GBM. The 3D volumetric measurements (**C and D**) of the targeted left frontal component (*arrows*) demonstrate an interval decrease of 66.8% in the volume of the neoplasm. The patient had marked clinical improvement in speech and comprehension 4 days after the procedure. Functional regional cerebral blood volume maps (**E and F**) on the corresponding MRP image, with regions of interest placed within the enhancing component, showing a 43% decrease in the regional cerebral blood volume values from 3.58 to 2.04 ml/100 g of brain tissue.

Fig. 4. Selected axial and coronal FDG-PET brain images obtained in a patient immediately before (**A**) and approximately 1 month after (**B**) SIACI therapy demonstrate a qualitative diminution of metabolic activity in the left frontal and deep thalamic lesions. The images were acquired at a 3-hour delay after radiotracer administration to increase tumor-to-background conspicuity.

TABLE 1

Demographic characteristics of the 30 patients in the current series *

Characteristic	Total (%)	Group I (%)	Group II (%)	p Value [†]
all patients	30	19	11	
mean age (yrs)	53.1 ± 10.3	52.4 ± 9.8	54.4 ± 11.5	NS
sex				
M	21 (70.0)	13 (68.4)	8 (72.7)	NS
F	9 (30.0)	6 (31.6)	3 (27.3)	
mean KPS score	78.7 ± 12.5	79.0 ± 13.7	78.2 ± 10.8	NS
pathological findings				
GBM	26 (86.7)	17 (89.5)	9 (81.8)	NA
WHO Grade III	2 (6.7)	1 (5.3)	1 (9.1)	
oligo	1 (3.3)	1 (5.3)	0 (0.0)	
brainstem glioma	1 (3.3)	0 (0.0)	1 (9.1)	
mean time since dx (days)	483.8 ± 257.6	393.7 ± 174.8	639.4 ± 308.8	0.01
no. of previous resections				
0	3 (10.0)	1 (5.3)	2 (18.2) [‡]	NA
1	15 (50.0)	9 (47.4)	6 (54.5)	
2	11 (36.7)	8 (42.1)	3 (27.3)	
>2	1 (3.3)	1 (5.3)	0 (0.0)	
no. of previous txs w/IV bevacizumab				
1	3 (10)	NA	3 (27.3)	NA
3	2 (6.7)		2 (18.2)	
4	4 (13.3)		4 (36.4)	
6	2 (6.7)		2 (18.2)	

* Mean values are expressed ± SDs.

Abbreviations: NA = not applicable; NS = not statistically significant; oligo = oligodendroglioma.

[†]The Mann-Whitney U-test was used for all comparisons.[‡]Denotes a diagnostic biopsy.

TABLE 2
Individual results for area, volume, MRP, and FLAIR imaging in 30 patients in Groups I and II*

Group I (19 patients)					Group II (11 patients)				
Case No.	Area (%)	Vol (%)	MRP (%)	FLAIR	Case No.	Area (%)	Vol (%)	MRP (%)	FLAIR
1	1.59	-29.22	NA	NC	1	NMD	NMD	-2.94	NC
2	-71.43	-79.05	NA	+	2	-32.40	1.44	-46.96	NC
3	-41.71	1.41	NA	-	3	-15.20	-84.37	-38.38	+
4	-15.15	44.00	NA	-	4	39.50	50.65	NA	NC
5	-54.00	-60.12	NA	NC	5	-21.40	-8.26	-8.76	+
6	-28.00	25.00	-39.31	-	6	NMD	NMD	-57.73	NC
7	-12.50	1.99	38.93	NC	7	-6.25	-16.31	-3.64	NC
8	-29.60	-66.76	-43.02	NC	8	-39.18	-37.01	NA	NA
9	-92.22	-26.92	NA	NC	9	-37.33	-41.30	NA	NC
10	NMD	NMD	NA	-	10	-28.95	-5.31	-66.67	+
11	NMD	NMD	-18.19	NC	11	26.12	43.18	-12.57	NC
12	-37.50	-41.90	-31.58	-					
13	-33.80	-59.90	-59.26	-					
14	-53.00	-67.71	-58.97	NC					
15	-41.00	-40.71	NA	-					
16	-27.80	-54.72	-65.22	NC					
17	-50.00	-66.09	-32.14	-					
18	-34.70	-46.91	-32.14	+					
19	-28.00	-69.95	-28.00	-					

* NC = no change; NMD = no measurable disease; + = increase; - = decrease.

TABLE 3

Summary of results for area, volume, MRP, and FLAIR imaging in 30 patients in Groups I and II

% Reduction *	Group I		Group II		p Value [†]
	Median ± SD	Range	Median ± SD	Range	
area	-34.70 ± 22.15	1.59 to -92.2	-15.20 ± 30.63	39.50 to -39.18	0.02
vol	-46.91 ± 32.31	44.0 to -79.05	-8.26 ± 41.74	50.65 to -84.37	0.06
MRP	-32.14 ± 28.22	38.93 to -65.22	-25.47 ± 25.78	-2.94 to -66.67	0.56

* Comparison of reduction on T2-weighted/FLAIR images between groups was significant (p = 0.01, Fisher exact test).

[†] Informal comparisons performed using the nonparametric Wilcoxon rank-sum test.