MRI in patients with high-grade gliomas treated with bevacizumab and chemotherapy

Abstract—Patients with recurrent gliomas (n = 14) were treated with bevacizumab and carboplatin, cpt-11, or etoposide. Follow-up MRI scans were obtained 2 to 6 weeks after initiation of treatment. Contrast-enhancing tumor shrank in 7 patients, with reductions evident in as little as 2 weeks after initiation of therapy. Treatment seemed more effective for heterogeneously enhancing tumor compared with solidly enhancing tumor.

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Bevacizumab is a monoclonal antibody that neutralizes vascular endothelial growth factor (VEGF), the key mediator of tumor angiogenesis. VEGF impacts endothelial cell permeability, activation, survival, proliferation, invasion and migration, all of which play a role in tumor progression. In combination with chemotherapy, bevacizumab may improve survival in patients with metastatic colorectal cancer, breast cancer, and lung cancer.[1] Malignant gliomas express VEGF receptors,[2] and glioblastoma cell lines have been shown to secrete VEGF.[3] Therefore, we assessed the early imaging effects of bevacizumab coupled with etoposide, carboplatin, or cpt-11 on recurrent malignant (Grade III and Grade IV) gliomas using contrast-enhanced MRI.

Methods. A total of 21 patients with recurrent gliomas have been treated with bevacizumab and chemotherapy at UCLA. These patients were selected from the UCLA neuro-oncology clinic database of patients with gliomas, which includes data regarding patient treatment and outcome and other variables. All patients participating in this database, including those treated with bevacizumab in the current study, have signed institutional review board consent. To accurately describe the early MRI features related to the treatment of bevacizumab and chemotherapy, we performed a retrospective analysis with the following inclusion criteria: recurrent Grade III or Grade IV malignant gliomas, baseline MRI obtained within 14 days of initiating treatment, stable or decreasing steroid dose within 10 days of baseline MRI, no increase in steroid dose during treatment from baseline MRI, failed previous radiation and chemotherapy, evidence of tumor progression at least 4 weeks beyond completion of previous radiation, and signed institutional review board approved consent. Of the 21 patients, 14 met the above criteria. Of the 7 excluded patients, 4 had increasing steroid dose, 2 lacked recent baseline scans, and 1 was excluded because of neurologic progression and lack of follow-up scan.

Histologic diagnosis was based on the modified World Health Organization classification system. MRI scans were read by a neuroradiologist (W.B.P.) blinded to patient outcome. Pretreatment and early posttreatment scans were analyzed to determine the change (if any) in enhancing and nonenhancing tumor and edema. MRI sequences were acquired on a 1.5-T scanner and included sagittal T1-weighted, axial T1-weighted, T2-weighted fast spin-echo, proton density and gadolinium diethylenetriamine penta-aceticacid (Omniscan, Amersham Health, Princeton, NJ, 10 to 20 mL) enhanced axial and coronal T1-weighted images. Follow-up scans were classified as follows: progressive disease—increase in maximal dimension of tumor by 25% or more; mixed progressive disease—one region of tumor increased by 25% or more and another, noncontiguous region of tumor decreased by 50% or more; stable disease—reduction in maximal tumor dimension by less than 50% or increased in dimension by less than 25%; and partial response—decreased in maximal tumor dimension by at least 50%.

Results. Magnetic resonance images from 14 patients with histologically proven malignant gliomas were analyzed. Patient demographics, tumor type, and treatment response at first follow-up imaging are summarized in the table. Seven patients had a partial response, 3 had stable disease, 3 had mixed progressive disease, and 1 had progressive disease. Of the patients with stable disease, edema was decreased even when tumor size was unchanged. Reductions in the amount of enhancing tumor and peritumoral edema were apparent as early as 18 days after the start of therapy. In patients with glioblastoma multiforme (GBM), 4 of 10 showed a partial response, and 3 of 4 of the patients with Grade III gliomas (anaplastic astrocytoma and anaplastic oligodendroglioma) had a partial response. All responders showed changes on their first follow-up scan (18 to 41 days after initiation of treatment; figure 1). Seven patients were excluded based on the criteria detailed in the Methods. Of these patients, 4 of 7 showed a partial response, a rate similar to that of the included patients.

Three patients who were classified as having "mixed progressive disease" had a mixed response in which some tumor portions shrank dramatically whereas others enlarged after treatment. Interestingly, the heterogeneous and necrotic appearing portions of the tumor improved, whereas more solidly enhancing portions of the tumor increased in size (figure 2).

One patient with a recurrent anaplastic oligodendroglioma had a lobar hemorrhage 5 weeks after initiating therapy and subsequently died. Of the 14 patients included in this study, 4 have died: 2 with GBM and 2 with Grade III gliomas. The average time since treatment began for the alive patients is 140 days (range 120 to 177 days). The patients who died survived an average of 116 days (range 61 to 159 days) after the start of therapy. Of the 4 patients who died, 2 had mixed progressive disease and the other 2 had a partial response.

Discussion. Necrosis results in blood–brain barrier breakdown, which leads to enhancement and

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Table *Patient demographics and response to treatment*

Age, y	Sex	Diagnosis	Recurrence	Chemotherapy	Interval	Result
35	F	AO	2	Cpt-11	45	Mix PD
71	F	GBM	2	Carboplatin	35	PD
28	M	GBM	3	Carboplatin	22	Mixed PD
27	M	GBM	5	Etoposide	37	Mixed PD
41	M	GBM	3	Cpt-11	28	SD
50	M	AO	6	Cpt-11	21	PR
35	M	GBM	4	Cpt-11	27	PR
55	M	GBM	2	Cpt-11	45	PR
37	F	AO	1	Cpt-11	27	PR
64	M	GBM	1	Cpt-11	18	PR
37	M	GBM	3	Cpt-11	41	SD
61	F	GBM	1	Cpt-11	36	PR
44	F	GBM	2	Cpt-11	42	SD
40	F	AA	2	Cpt-11	41	PR

Interval = time in days between initiation of therapy and first follow-up MRI scan; AO = anaplastic oligodendroglioma; PD = progressive disease; GBM = glioblastoma multiforme; SD = stable disease; PR = partial response; AA = anaplastic astrocytoma.

edema.[4] We found that in several patients treated with bevacizumab/chemotherapy, areas of necrotic-appearing tumor demonstrated a response, whereas solid areas of tumor continued to grow. Solid tumors, particularly those with areas of hypoxia, are often the most resistant to conventional treatment.[5] There may be differences in the requirement of tumor endothelium for VEGF receptor stimulation between solid and necrotic areas of tumor.

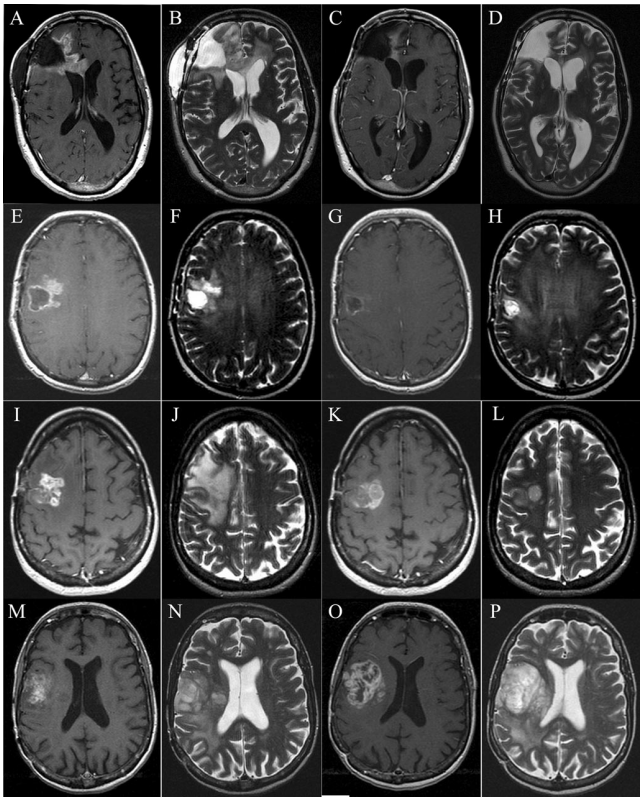

Figure 1. Initial (first two columns) and follow-up (last two columns) T1-weighted enhanced and T2-weighted scans (each row represents a different patient). In the top two cases (A through D; E through H), there is less tumor and edema after treatment, consistent with a partial response. The third case (I through L) shows minimal decrease in enhancing tumor but a near complete resolution of edema. The last case demonstrates progressive disease (M through P).

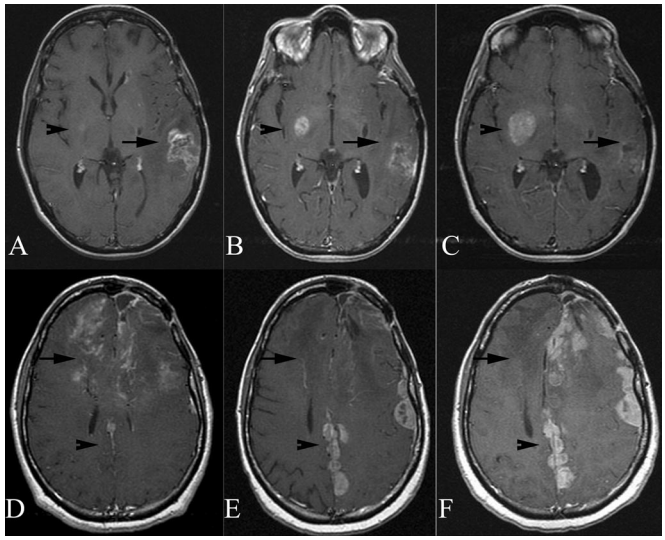

Figure 2. Initial (A and D) and two follow-up scans (B and E; C and F) on two patients demonstrating mixed progressive disease. Note that the heterogeneously enhancing tumor component (arrow) regresses, but the solidly enhancing component (arrow head) continues to grow in both of these patients. Image (B) is 49 days and image (C) is 99 days after treatment initiation. Image (E) is 49 days and image (F) is 78 days after treatment initiation.

Reduction in edema was striking in some cases. Even when enhancing tumor size was stable, marked reduction in edema was noted. This effect on edema is not surprising because VEGF is a potent mediator of vascular permeability.[1] Interestingly, brain edema was not decreased in an animal model of bacterial meningitis after bevacizumab treatment,[6] suggesting there is some degree of specificity for this effect. It has been hypothesized that increased vascular permeability may support tumor growth by "transforming the normally antiangiogenic stroma of normal tissues into a proangiogenic environment."[1] Therefore, reduction in peritumoral edema, by itself, may inhibit tumor growth. This is supported by clinical data showing that peritumoral edema in patients with high-grade gliomas correlates with poorer survival.[7]

Bevacizumab has been associated with bleeding, including CNS hemorrhage.[8] Brain tumors also increase the risk of intracranial hemorrhage. One patient of 21 treated to date at UCLA had intracranial hemorrhage and died during the subsequent hospital stay.

The high percentage of patients who showed an imaging response to bevacizumab/chemotherapy in the current study is remarkable. The typical response rate in recurrent GBM using chemotherapy

alone is 5% to 10%.[9] Given the limitations of our relatively small sample size, we found an imaging response rate of 50%. This response is seen using an antibody whose inhibition of VEGF activity presumably takes place on the luminal side of the vasculature.[1] However, there is some evidence that activation of the VEGF receptor on tumor cells promotes growth, and it has been found that glioblastoma cells express VEGF receptor in vitro.[2] Therefore, it is possible that treatment with bevacizumab interferes with an autocrine loop and thereby has a direct effect on glioma cells as well.

The speed of the response was also notable, with reduction in tumor enhancement and edema apparent by as few as 18 days after initiation of therapy. Such a quick response is uncommon in recurrent malignant glioma when using chemotherapy alone. It may be that detectable changes occur in even less time. In a mouse tumor model, vascular changes were apparent hours after bevacizumab treatment.[10] Future studies are required to determine the exact time course of the response to bevacizumab/chemotherapy treatment in patients with malignant gliomas.

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