CASE SERIES

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Bevacizumab for acute neurologic deterioration in patients with glioblastoma

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Practice Points

- Glioblastoma (GBM) is not only universally fatal, but can also cause significant neurological dysfunction as a result of the tumor location and peritumoral edema.
- Bevacizumab has been approved for recurrent malignant glioma; however, treatment is usually restricted to the outpatient setting where patients' performance status is typically acceptable for treatment.
- GBM patients hospitalized for acute neurological dysfunction due to large masses and/or significant peritumoral edema often require placement in a rehabilitation facility and may not make it to the outpatient setting to receive therapy.
- Bevacizumab has demonstrated improvement in neurological function and decreased corticosteroid requirement, making it an attractive therapy for severely debilitated patients.
- Bevacizumab may provide a therapy with which to rescue these patients so they may continue outpatient treatment and avoid prolonged admissions.
- In this retrospective study, nine GBM patients were treated with a single dose of bevacizumab while admitted for severe acute neurological deterioration. Patients with large tumors and significant edema responded and were able to resume outpatient therapy with significant reductions in steroid requirements.
- Bevacizumab may offer an alternative approach to rescue debilitated GBM patients who may otherwise not be considered for therapy owing to their poor functional status.

SUMMARY **Aim:** Glioblastoma causes neurologic dysfunction owing to the tumor's location and peritumoral edema. Bevacizumab improves symptoms and steroid dependence, and may rescue glioblastoma patients hospitalized for acute neurologic dysfunction, allowing them to return home for outpatient treatment. **Materials & methods:** We carried out a retrospective review of glioblastoma patients with severe neurologic dysfunction who received bevacizumab as inpatients. **Results:** Nine patients (median age: 51 years; median Karnofsky Performance Status [KPS]: 40%) received one dose of bevacizumab while admitted for neurologic deterioration. Seven patients were treated at recurrence, two at

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diagnosis. Six patients clinically improved and continued outpatient treatment, while five decreased/discontinued dexamethasone. **Conclusion:** Single bevacizumab treatment administered to naive hospitalized patients with glioblastoma improves function and quality of life through avoidance of prolonged hospitalization and rehabilitation admissions, and decreased dexamethasone administration.

Glioblastoma (GBM) is the most common brain cancer, affecting nearly 10,000 people annually in the USA. Despite improvements in therapy, GBM remains fatal, with a current median survival of 15–20 months from diagnosis [1,2]. In addition to the poor prognosis, many patients suffer neurological disability and poor quality of life. Neurological impairment is a direct consequence of the cancer itself and its associated peritumoral edema. Many patients with GBM take glucocorticoids to reduce brain edema, which improves function, but they suffer many deleterious side effects that compromise quality of life.

Bevacizumab (Avastin®, Roche, Basel, Switzerland), a monoclonal antibody that binds to the VEGF-A protein, has been approved for recurrent GBM. US FDA approval was based on radiographic response, not survival advantage; although the median survival of 8 months after recurrence is longer than what has been reported for any other agent administered as salvage therapy [3,4]. In addition, bevacizumab trials also demonstrated that patients benefit from an antiedema effect of the drug through vascular normalization, with a reduction in corticosteroid requirement. A recent Phase II study of newly diagnosed GBM patients treated with bevacizumab in addition to standard radiation and temozolomide suggested that the most functionally impaired patients benefited the most from this therapy [2].

Many patients with a large enhancing GBM have compromised neurological function, and may require hospital admission or placement in a skilled facility because of their disability. These patients, who represent the most impaired subgroup, may receive optimal benefit from bevacizumab therapy. However, there are no data on the speed of clinical improvement after bevacizumab administration or on whether it can substantially reverse neurologic deficits to allow the patient to return home instead of being transferred to another inpatient facility that will not administer bevacizumab. Furthermore, physical therapy alone is unlikely to improve a severely impaired patient's condition without treatment that directly addresses their disease. Therefore,

such a patient, particularly at recurrence, may never regain adequate function to qualify for further therapy, including bevacizumab. We sought to review our GBM inpatients treated with a single dose of bevacizumab to describe their outcomes, and determine whether inpatient bevacizumab administration can improve function sufficiently for patients to continue receiving treatment in an outpatient setting.

Materials & methods

This is a Memorial Sloan-Kettering Internal Review Board approved, single-institution, retrospective case series. Neurology service admission records were crossreferenced with a pharmacy database and we reviewed all patients with GBM who were admitted to the neurology service between 2007 and 2011, and received bevacizumab infusion during their admission. Patients were included in our analysis if the reason for admission was significant neurological deterioration necessitating hospitalization as a direct consequence of tumor growth. Patients were excluded if the reason for admission was minor neurological dysfunction (i.e., symptoms that did not necessitate prolonged admission or inpatient physical therapy), seizures occurring without progression of tumor, deep venous thrombosis or thromboembolic complications, or non-neurological symptoms. We only included patients who were neurologically debilitated and required inpatient care. Outcomes analyzed included the ability to return to a clinic for continuation of outpatient bevacizumab with or without chemotherapy, dexamethasone dose adjustments, clinical response description, progression-free survival (PFS) and overall survival from the date of bevacizumab administration. The neurological assessments of these patients were reviewed and their clinical responses were tabulated as either improved, stable or worse. The designation of improved was given when the physician recorded an improvement or reversal in neurological function with improved Karnofsky Performance Status (KPS). Progression was determined via radiographic and clinical findings as per Response Assessment in Neuro-Oncology Criteria (RANO) criteria.

Results

From January 2007 to January 2011, 498 patients were admitted to our neurology service for a total of 1330 admissions. We identified nine patients who were admitted for neurological deterioration and received bevacizumab during their admission (Table 1). In all of those patients, a single dose of bevacizumab at 10 mg/kg was administered. Seven patients were treated for recurrent GBM and two were treated for newly diagnosed disease. Eight patients had pathologically confirmed GBM and one had a brainstem glioma that was not sampled. All nine patients were men with a median age at bevacizumab treatment of 52 years (range: 21–77 years) and a median KPS of 40 (range: 30–50). Seven patients were bevacizumab naive and two had received prior antiangiogenic treatment (one bevacizumab and one aflibercept). Seven patients had large enhancing masses with surrounding edema demonstrated on fluid-attenuated inversion recovery images (Figure 1); one patient had primarily leptomeningeal tumor; and one patient had a nonenhancing brainstem tumor with subependymal enhancement.

Of the seven patients treated for recurrence, five returned to the outpatient clinic for continuation of bevacizumab and two currently remain on bevacizumab. Of the two patients treated at recurrence who did not respond, one had a brainstem glioma and one had previously failed antiangiogenic therapy with aflibercept. All five patients who continued therapy reported clinical improvement; the two who did not resume outpatient therapy reported stable neurological symptoms. Of the five patients who continued outpatient therapy, two discontinued dexamethasone completely, two reduced the dose by 50% and one remained on the same pretreatment dose. For the seven recurrent patients, the median PFS was 16.4 weeks (range: 3.1–29.3 weeks) and the median overall survival was 21.3 weeks (range: 3.1–29.3 weeks) from the time of inpatient administration of bevacizumab (Figure 2). Five patients have died, including the two nonresponders.

Both patients treated at initial diagnosis had large enhancing tumors with surrounding edema and mass effect. One patient responded and resumed outpatient bevacizumab with radiation and temozolomide; this patient was alive and progression free while still receiving bevacizumab 13.4 weeks from initiation of

Table 1. Patient characteristics and results.

Patient	Pathology	KPS	Recurrences (n)	Continuation of outpatient treatment	Clinical response to inpatient bevacizumab	Dexamethasone response (mg)	Bevacizumab regimen (mg/kg)	Bevacizumab doses (n)	PFS from first inpatient dose (weeks)	OS from first inpatient dose (weeks)	OS from diagnosis (months)
1	GBM	50	1	Yes	Improved	20 to 4/day	10 q2 + TMZ	14+	29.3+	29.3+	67.1+
2	GBM	50	1	Yes	Improved	8/day to none	10 q2 + TMZ	5	16.4	21.3	14.8
3	GBM	40	1	Yes	Improved	30 to 16/day	10 q2 + TMZ	6	21.6	24.1	16.2
4	GBM	30	1	Yes	Improved	16/day to none	10 q2 + TMZ	5 [†]	12.4+	12.4+	7.2+
5	Brainstem glioma	40	1	No	Stable	No change	10 q2 + TMZ	1	3.1	3.1	6
6	GBM	40	3	No	Stable	No change	10 q2 alone	2	5.3	5.3	11.7
7	GBM	50	1	Yes	Improved	No change	10 q2 alone	5 [†]	10.6	10.6	13.8
8	GBM	30	0	Yes	Improved	24 to 4/day	10 q2 + TMZ	6+	13.7+	13.7+	4.1+
9	GBM	30	0	No	Died of disease	No change	10 mg + TMZ + RT	1	1.1	1.1	0.5

[†]Patient stopped bevacizumab due to toxicity.

GBM: Glioblastoma multiforme; KPS: Karnofsky Performance Status; OS: Overall survival; PFS: Progression-free survival; q2: Every 2 weeks; RT: Radiotherapy; TMZ: Temozolomide.

Figure 1. MRI T₁-weighted postgadolinium images of three patients demonstrating the imaging characteristics of those who responded to therapy.

bevacizumab therapy. One patient died 8 days after infusion, secondary to progressive tumor; this patient had had a 3-month interval from initial clinical presentation to diagnosis with an enlarging mass and probably irreversible neurological injury.

Bevacizumab was generally well tolerated. No grade 5 toxicity occurred. One patient discontinued bevacizumab due to pulmonary embolus (Common Terminology Criteria for Adverse Events 4, grade 3 thromboembolic event) 2 months after the initiation of therapy. No other grade 3 or 4 toxicities attributable to bevacizumab occurred in these patients.

Discussion

GBM growth depends on angiogenesis to support tumor expansion, and a major pathway of vascular growth is supported by VEGF-A and its receptor VEGFR-2. GBM cells have been shown to secrete VEGF-A and upregulate VEGFR-2 as a primary means of supporting neoangiogenesis. Bevacizumab is a monoclonal antibody that binds to VEGF-A, rendering it inactive and blocking tumor neovascularization. In addition, VEGF blockade leads to normalization of the existing blood vessels, with a subsequent decrease in peritumoral edema.

Bevacizumab prolonged the 6-month PFS from 10–15% to 29–50% in patients with recurrent disease, leading to an accelerated FDA approval for bevacizumab alone [3,5–9]. In addition, in the BRAIN study, 16 out of 86 patients on dexamethasone were able to discontinue the steroid completely, and an additional 33 had a sustained reduction in corticosteroid use after bevacizumab administration, reducing exposure to steroids and their associated complications.

A retrospective review of patients with recurrent GBM only demonstrated a benefit for those patients in the worst condition [10]. Furthermore, 54% of the bevacizumab-treated patients were able to decrease their dexamethasone dosage and 18% discontinued it altogether, which was much better than in the control group where only 33% were able to reduce their dose [10]. Patients treated with bevacizumab also maintained their functional status for twice as long as control patients (median: 252 v 120 days; $p = 0.006$). Although a Phase II study of bevacizumab added to radiotherapy and temozolomide

Figure 2. Overall survival from initiation of bevacizumab therapy.

in newly diagnosed patients with GBM did not improve overall survival from historical controls who received bevacizumab at recurrence, a subset analysis demonstrated benefit with upfront bevacizumab in those patients with the worst prognostic factors [2]. These results are similar to those seen in a Phase II study of cediranib, an oral VEGFR inhibitor, in patients with recurrent GBM [11].

Given these data, we sought to determine whether a single dose of bevacizumab could rapidly improve neurological function in those patients so compromised that they required inpatient care to a point that they could continue outpatient treatment. Six out of our nine patients had a clinical improvement and could continue bevacizumab, and five could reduce or discontinue steroids. These patients had large enhancing tumors with significant peritumoral edema. None of the three patients who did not respond to bevacizumab could reduce their dexamethasone dose. Two patients with recurrent disease did not respond. One had a brainstem glioma, a disease that has not been shown to have a response to bevacizumab and the other had failed prior anti-VEGF therapy with aflibercept [12]. The newly diagnosed patient who did not respond had such a rapidly progressing disease that he died shortly after bevacizumab administration, making assessment impossible.

Our small series of patients is limited by the inherent selection bias regarding those who were given bevacizumab, the small sample size and the lack of historical control data, as well as the lack of an inpatient control group not receiving bevacizumab. Therefore, our experience is anecdotal. Additional limitations include the additional concomitant therapy that may also have been beneficial; although this unlikely given the rapid reversal of mass effect and edema. Despite the limitations of this study, these data suggest that some of the most debilitated patients may

be able to avoid placement in a facility with the judicious inpatient use of a single dose of bevacizumab. Patients most likely to benefit from bevacizumab have features similar to those who benefit in the outpatient setting. Providing bevacizumab to such patients often improves neurological function and the cost of administration of bevacizumab to inpatients may be offset by the ability to then discharge the patient. More rigorous research should be performed in order to balance the median PFS and cost of bevacizumab versus the cost of continued inpatient care – whether this involves hospitalization or inpatient rehabilitation – in this sick population.

Conclusion & future perspective

This case series challenges the traditional oncologic view of withholding chemotherapy from severely debilitated patients with low KPS/Eastern Cooperative Oncology Group scores. However, bevacizumab may reverse the neurological deficits of GBM patients suffering from a high tumor burden and edema. This topic deserves further study to determine the role of bevacizumab in the acute management of debilitated patients with GBM.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

Financial & competing interests disclosure

A Omuro serves on the advisory board for Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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