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Bevacizumab salvage therapy following progression in high-grade glioma patients treated with VEGF receptor tyrosine kinase inhibitors

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Agents targeting the vascular endothelial growth factor (VEGF) pathway are being used with increasing frequency in patients with recurrent high-grade glioma. The effect of more than one antiangiogenic therapy given in succession has not been established. We reviewed the efficacy of bevacizumab, a VEGF-A monoclonal antibody, in patients who progressed following prior therapy with VEGF receptor tyrosine kinase inhibitors (R-TKi). Seventy-three patients with recurrent high-grade gliomas received VEGF R-TKi (cediranib, sorafenib, pazopanib, or sunitinib) as part of phase I or II clinical trials. Twenty-four of these patients with glioblastoma progressed and received bevacizumab-containing regimens immediately after R-TKi. Those who stopped R-TKi therapy for reasons other than disease progression, or received a treatment that did not include bevacizumab, were excluded from the analysis. The efficacy of bevacizumab-containing regimens in these 24 patients was evaluated. During R-TKi therapy, 6 of 24 patients (25%) had a partial response (PR) to treatment. The 6-month progression-free survival (APF6) was 16.7% and median time-to-progression (TTP) was 14.3 weeks. Grade III/IV toxicities were seen in 13 of 24 patients (54%). Subsequently with bevacizumab salvage therapy, 5 of 24 patients (21%) had a PR, the APF6 was 12.5%, and the median TTP was 8 weeks. Five of 24 patients had grade III/IV toxicities (21%). The median overall survival (OS) from the start of R-TKi therapy was 9.2 months (range: 2.8–34.1+), whereas the median OS after bevacizumab was 5.2 months (range: 1.3–28.9+). Bevacizumab retains modest activity in high-grade glioma patients who progress on R-TKi. However, the APF6 of 12.5% in this cohort of patients indicates that durable tumor control is not achieved for most patients.

Keywords: bevacizumab, recurrent glioblastoma, tyrosine kinase inhibitor, vascular endothelial growth factor.

High-grade gliomas are characterized by the presence of microvascular proliferation and necrosis and are associated with elevated levels of vascular endothelial growth factor (VEGF).[1] Even with optimal surgical resection, radiation, and standard chemotherapy, high-grade gliomas virtually always recur and median survival following recurrence is 7 months.[2,3] There is no standard therapy at recurrence, but the development of targeted molecular agents has resulted in promising therapeutic options.

The highly vascular nature of high-grade gliomas and the availability of molecular agents that inhibit the VEGF pathway have made angiogenesis inhibition an attractive therapeutic target for these tumors.[4,5] Currently, there are two clinically available mechanisms of VEGF inhibition.[6] One is through ligand sequestration, in which a monoclonal antibody such as bevacizumab[7] or a soluble decoy receptor such as aflibercept (VEGF-Trap)[8] binds circulating VEGF and prevents it from binding to the VEGF receptor. The other is by a small molecular inhibition of the VEGF receptor

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tyrosine kinase. Small molecule receptor tyrosine kinase inhibitors (R-TKis) selectively bind to the intracellular domain of a given receptor and inhibit the downstream effects mediated by that receptor tyrosine kinase. All VEGF R-TKis used clinically have activity at VEGFR-2, which inhibits angiogenesis, as well as at a variety of other potentially important targets such as VEGFR-1, VEGFR-3, platelet-derived growth factor receptor (PDGFR), and cKit.[9,10]

Recent phase II randomized studies have measured responses to bevacizumab, a humanized monoclonal antibody that binds to circulating VEGF-A, given alone or in combination with irinotecan for recurrent high-grade glioma.[11–13] For glioblastoma (GBM) patients, bevacizumab at recurrence resulted in radiographic response rates of 26%–61%, 6-month progression-free survival (APF6) rates of 20%–50%, and a median overall survival (OS) of 9 months.[11–13] These results are an improvement over historical data for GBM at recurrence (APF6 16%; median OS 7 months)[2,3] but unfortunately for most patients, survival is still limited and there is a need for more effective therapies.

Several phase I and II clinical trials using VEGF R-TKis have been conducted in recent years. Cediranib, a pan-VEGF R-TKi with additional activity against PDGFR and cKit, has demonstrated activity in a phase II trial of recurrent GBM, with radiographic responses in over 50% of patients and a median OS of 7.5 months.[14,15] These findings provided the basis for a phase III trial of cediranib alone or in combination with lomustine.

The optimal treatment for patients who fail VEGF R-TKi is unknown. Some of these patients opt for conventional salvage chemotherapy with known modest activity, but increasingly, patients are being treated with bevacizumab-containing regimens. The value of bevacizumab therapy in these patients is not known. In this pilot retrospective study, we reviewed our experience of patients with GBMs treated with VEGF R-TKi who then received salvage therapy with a bevacizumab-containing regimen.

Methods

We retrospectively reviewed all patients who received a small molecule TKi of the VEGFR (cediranib, sorafenib, sunitinib, or pazopanib) at our institutions as part of a phase I or II clinical trial for recurrent high-grade glioma. Seventy-three cases were identified. All the cases had a pathological diagnosis of anaplastic astrocytoma or GBM and had been treated with radiation and temozolomide according to the Stupp regimen.[16] They then had radiographic evidence of progressive disease (PD) by the Macdonald criteria[17] prior to clinical trial enrollment.

Among the R-TKi trials included (Table 1), there were both single-agent trials (sorafenib, cediranib, and sunitinib) and trials in which the VEGF R-TKi was combined with other molecularly targeted agents directed against EGFR (pazopanib/lapatinib and sorafenib/erlotinib) or mTOR (sorafenib/temsirolimus). One trial combined cediranib with the alkylating agent lomustine. All the TKis considered block VEGFR-2, as well as several other potentially relevant receptors. Sorafenib has activity at VEGFR-2, VEGFR-3, and PDGFR-β. Cediranib and pazopanib both act at VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, and cKit. Sunitinib has activity at VEGFR-2, PDGFR-α, PDGFR-β, and cKit.

Table 1. TKi trials

	Number of patients
Single agent	
Phase I	
Sorafenib	2
Phase II	
Cediranib	9
Sunitinib	1
Combination therapy	
Phase I	
Pazopanib + lapatinib	4
Cediranib + lomustine	1
Phase II	
Sorafenib + temsirolimus	3
Sorafenib + erlotinib	4

Of the 73 cases reviewed, 49 were excluded. The most common reasons for exclusion were discontinuation of TKi therapy due to grade IV toxicity ($n = 11$), treatment with a salvage therapy that did not contain bevacizumab ($n = 10$), or no additional therapy was given ($n = 10$). Of the remaining cases excluded, 6 received bevacizumab prior to treatment with R-TKi, 6 remained on TKi therapy without progression, and one developed leptomeningeal disease. Five cases had insufficient follow-up information.

The 24 cases included in this study all had pathologically confirmed GBM prior to treatment with antiangiogenic therapy. Each also had radiographic evidence of disease progression on R-TKi therapy as determined by the Macdonald criteria and received a bevacizumab-containing salvage regimen (Table 2) immediately after they had progressed. In these cases, survival, radiographic response, and toxicity of therapy were assessed.

Best radiographic response was determined by measuring the maximal cross-sectional area of the enhancing abnormality according to the Macdonald criteria[17] for partial response (PR) (at least a 50% decrease in the maximal cross-sectional area of the enhancing abnormality), PD (a 25% or greater increase in the maximal cross-sectional area of the enhancing abnormality), or stable disease (those in which the change was not large enough to meet criteria for PR or PD). Additional enhancing abnormalities or clear clinical deterioration were also considered evidence of progressive disease. Brain MRIs done every 4–8 weeks during treatment were compared with the pretreatment baseline scan, and all radiographic responses were assessed by a single investigator and corroborated by a second blinded review. There

Table 2. Patient characteristics

Male	17
Female	7
Median age	52 (19–73)
Number of prior therapies	
One	16
Two	8
Median initial Karnofsky performance status	80 (70–100)
Degree of surgical resection	
Biopsy	8
Subtotal resection	11
Gross total resection	5
Bevacizumab salvage regimen	
Plus irinotecan	20
Alone	2
Plus other chemotherapy (carboplatin and temozolomide)	2

was a 90% concordance between the reviewers, and discrepancies were adjudicated by a third reviewer.

Toxicities and adverse events of treatment were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Grade III toxicities of R-TKi therapy are reported. Any patients with grade IV toxicities on R-TKi therapy came off study due to toxicity and were therefore not included. Grade III or greater toxicities and adverse events during bevacizumab therapy are also reported.

Statistical Methods

Median time-to-progression (TTP) and OS were estimated by the Kaplan–Meier method. TTP was measured in weeks from the therapy start date (R-TKi or bevacizumab) to the date of the brain MRI demonstrating progressive disease. OS was measured in months from the therapy start date to the date of death (available in 23 of the 24 patients). The adjusted APF6 is defined as the percentage of patients who achieved APF6 from the initiation of a given therapy and is reported for R-TKi and bevacizumab separately. For comparisons between radiographic responders and nonresponders, Fisher's exact test was used to compare the rates of APF6 and the log-rank test was used to compare survival curves. All tests were 2-sided, and statistical analyses were performed with the use of SAS software (version 9.2; SAS Institute, Cary, North Carolina).

Results

Patient Characteristics

There were 17 men and 7 women enrolled in this study (Table 2). The median age was 52 (19–73) years, and the median Karnofsky performance status prior to treatment with R-TKi was 80 (70–100). Treatment with the VEGF R-TKi was for first recurrence of disease in 16 of 24 (67%) of the cases and the second recurrence in the remaining 8 of 24 (33%). Twenty-one out of 24 patients had primary GBM, and the remaining 3 of 24 (12%) had histologically confirmed secondary GBM. R-TKi therapy included sorafenib in 9 patients, cediranib in 10 patients, pazopanib in 4 patients, and sunitinib in 1 patient. All patients were subsequently treated with bevacizumab either alone 2 of 24 patients (8.3%) or in combination with a chemotherapeutic agent (irinotecan 20 of 24 [83.3%], carboplatin 1 of 24 [4.2%], or temozolomide 1 of 24 [4.2%]).

Outcomes

Radiographic response, APF6, and OS are reported by specific therapy in Table 3. Median TTP was 14.3 (range: 3.9–94) weeks during R-TKi therapy and 8 (range: 0.4–125.9+) weeks during bevacizumab salvage therapy. Median OS was 9.2 (range: 2.8–34.1+) months from the initiation of R-TKi therapy and 5.2 (range: 1.3–28.9+) months from the initiation of bevacizumab. The APF6 was 16.7% with R-TKi therapy and 12.5% with bevacizumab. None of the patients who received bevacizumab alone achieved APF6. The median OS was 5.2 months for the bevacizumab plus chemotherapy subgroup and 1.5 months for the 2 patients who received bevacizumab alone (log-rank test, $P = .3225$). The median OS from the date of initial surgery was 24.5 (range: 12.6–63.0) months. Of the 4 patients who achieved APF6 on R-TKi therapy, none achieved APF6 on bevacizumab. Conversely, of the 3 patients who achieved APF6 on bevacizumab, none achieved APF6 on R-TKi therapy.

Radiographic Response

Radiographic PR was seen in 6 of 24 patients (25%) during R-TKi therapy and 5 of 24 (21%) during bevacizumab therapy. Stable disease as best response was present in 11 of 24 (46%) of patients during R-TKi therapy and 14 of 24 (58%) during bevacizumab therapy. There were no radiographic complete responses.

During R-TKi therapy, 50% of the radiographic responders (CR and PR) achieved greater than APF6,

Table 3. Radiographic response and survival outcome by specific therapy

	Radiographic PR (%)	APF6 (%)	Median OS (mos)
VEGFR-2 TKi			
Sorafenib (9)	11	22	9.9
Cediranib (10)	50	20	9.4
Pazopanib (4)	0	0	6.0
Sunitinib (1)	0	0	9.2
Bevacizumab salvage therapy			
Bevacizumab + chemo (22)	19	14	5.2
Bevacizumab alone (2)	50	0	1.5

whereas only 5.5% of nonresponders (SD and PD) achieved greater than APF6 (Fisher's exact test, $P = .0353$). However, median survival from the start of R-TKi therapy was similar in both groups (11.3 months in responders vs 7.8 months in nonresponders, log-rank test, $P = .1865$). During bevacizumab therapy, 20% of radiographic responders achieved APF6, compared with 10% in radiographic nonresponders (Fisher's exact test, $P = .5212$). Median survival from the start of bevacizumab therapy was similar between those who had a radiographic response and those that did not (6.0 vs 5.2 months, respectively, log-rank test, $P = .1962$).

Although the MacDonald criteria were used to define radiographic response in this study, we also retrospectively reviewed T2/FLAIR images in patients determined to have PR or SD by the MacDonald criteria. Prior retrospective studies have noted that a subset of patients treated with bevacizumab develop enlarging regions of abnormal hyperintensity on T2-weighted or FLAIR images without concordant findings on postgadolinium sequences.[18,19] These areas of T2/FLAIR hyperintensity may represent nonenhancing tumor infiltration with decreased tumor vascularity. In reviewing the available scans from 15 patients during TKi therapy, there were 2 patients who developed a prominent T2/FLAIR hyperintense (nonenhancing) pattern of disease recurrence prior to progression of enhancing disease by the MacDonald criteria. The MRI scans of 13 patients with either PR or SD during bevacizumab therapy revealed 1 patient with a similar nonenhancing pattern of progression several weeks prior to the development of increased enhancement.

Adverse Events

The grade III toxicities during R-TKi therapy were largely hematologic and varied by drug. Two patients had grade III hypertension and 1 had hand-foot syndrome on cediranib. As discussed in the Methods section, patients with grade IV toxicities on R-TKi therapy were not included in this study because they were taken off R-TKi therapy for a reason other than progression. During bevacizumab therapy, there were no grade III hematologic toxicities. Treatment was discontinued due to bowel perforation (grade III) in 2 patients (8%) and pulmonary embolism (grade IV) in 2 patients (8%). One patient (4%) had interrupted bevacizumab therapy due to a vascular necrosis of the femoral head (grade IV). Three of the 4 patients who discontinued bevacizumab due to adverse events had stable disease at the time of discontinuation.

Discussion

There is increasing interest in the use of VEGF R-TKi for the treatment of high-grade gliomas. Some agents such as cediranib, a potent pan-VEGFR inhibitor, appear to have activity producing response rates in excess of 50% and APF6 of approximately 26%.[14,15] Other VEGFR inhibitors under investigation in high-grade gliomas include sorafenib,[9] sunitinib, pazopanib, vandetanib, and XL184.[10] Although certain VEGF R-TKi therapies have demonstrated some activity, patients inevitably progress. The optimal treatment following progression on VEGF R-TKi therapy is unclear.

In this study, we evaluated the efficacy of bevacizumab, alone or in combination with a chemotherapeutic agent, in patients who progress on a VEGF R-TKi. The administration of bevacizumab produced radiographic responses in 21% of patients, but very few had sustained benefit (median survival 5.2 months, APF6 12.5%). Those that responded to bevacizumab after failing R-TKi therapy may have had tumors that were susceptible to angiogenesis inhibition, but for reasons of dosing or delivery did not effectively inhibit the VEGF pathway with the R-TKi. Alternatively, the benefit seen in responders may have been due to the effect of the accompanying chemotherapeutic agent such as irinotecan, which has modest activity in recurrent glioma.[20] In patients who responded to R-TKi therapy initially, yet progressed on bevacizumab, perhaps continuous exposure to VEGF pathway inhibitors resulted in acquired resistance to VEGF inhibition,[6] possibly through upregulation of other angiogenic factors such as basic fibroblast growth factor (b-FGF), ephrins, and stromal-derived factor-1α (SDF-1α), increased pericyte coverage, mobilization of bone marrow precursors, or adoption of a more invasive phenotype associated with vessel co-option.[18,21,22]

The population analyzed included various R-TKis, given alone or in combination with chemotherapeutic agents, and the results vary somewhat between each of the drugs. For example, the majority (83%) of radiographic responders during TKi therapy received cediranib, and all the patients who achieved APF6 during R-TKi therapy received either sorafenib or cediranib. The 24 cases reviewed were a selected group, in that they were able to tolerate TKi therapy, and had a clinical and functional status that was sufficient for them to receive multiple salvage therapies. This selection process likely resulted in under-representation of toxicities and a longer OS than that was seen for the population as a whole.

Salvage therapy with bevacizumab was associated with a few instances of grade III/IV nonhematologic adverse events, with a rate of thrombotic complications (8%) comparable to other studies of bevacizumab/irinotecan at recurrence (10%–12%).[11,13] The rate of gastrointestinal perforation (8%) was slightly higher than similar populations studied (0%–2.5%).[11,13,23] The administration of successive anti-VEGF targeted therapies in this small population did not appear to be associated with cumulative toxicities above what has been seen in trials of bevacizumab/irinotecan at first recurrence.

In conclusion, treatment of patients with high-grade gliomas who progress on VEGF R-TKi with bevacizumab-containing regimens produce only modest benefits. Alternative strategies are needed to improve the effectiveness of VEGF R-TKis and salvage therapies for patients who progress on these agents.

A more complete understanding of the mechanisms of resistance to VEGF R-TKis will be crucial in developing more effective therapies. Potentially, the combination of agents targeting VEGFR-2 with agents targeting resistance pathways (such as b-FGF or SDF-1α, or inhibiting vessel cooption and invasion) may lead to more promising results.

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